Full-Body Biomechanical Characterization of Children with Hypermobile Ehlers-Danlos Syndrome During Gait and Activities of Daily Living

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FULL-BODY BIOMECHANICAL CHARACTERIZATION OF CHILDREN WITH HYPERMOBILE EHLERS-DANLOS SYNDROME DURING GAIT AND ACTIVITIES OF DAILY LIVING

by

Anahita Qashqai

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ABSTRACT

FULL-BODY BIOMECHANICAL CHARACTERIZATION OF CHILDREN WITH HYPERMOBILE EHLERS-DANLOS SYNDROME DURING GAIT AND ACTIVITIES OF DAILY LIVING

by

Anahita Qashqai

The University of Wisconsin-Milwaukee, 2022
Under the Supervision of Professor Brooke Slavens

Hypermobile Ehlers-Danlos syndrome (hEDS) is an inherited connective tissue disorder, often under-diagnosed, and presenting with frequent chronic pain and severe musculoskeletal symptoms that can drastically reduce the quality of life during one’s life span. While there are limited quantitative approaches in the literature on adult movements, the biomechanics of movements during activities of daily living (ADLs) in children have not been investigated comprehensively. Therefore, the primary purpose of this dissertation was to characterize the biomechanics of the musculoskeletal system and investigate the biomechanics of hEDS by quantifying joint dynamics and muscle activations during ADLs and gait in the pediatric population. A major clinical concern is joint instability, with the highest incidences occurring in the shoulder (Chapter 2), hip, knee, and ankle (Chapters 3-5). This instability can lead to the development of pain and pathologies in children with hEDS. As a result, these joints are the focus of this dissertation with an aim to characterize the biomechanics of hEDS in children.

Chapter 2 investigates three-dimensional (3-D) shoulder complex kinematics during ADLs and shoulder active range of motion. The results indicated significant differences in shoulder joint ranges of motion compared to typically developing children (TD) during daily activities, such as reaching across the body and reaching to a back pocket; and active range of motion during
shoulder flexion, abduction, scaption, and extension. Finally, a potential clinical assessment was proposed to calculate reachable workspace, which may ultimately help clinicians plan more accurate individualized treatments and rehabilitation strategies.

The primary focus of Chapter 3 was characterizing the lower extremity joints during gait in children with hEDS compared to TD children. Ankle joint results revealed significant differences in all three planes of motion during gait in children with hEDS. Moreover, the knee power results indicated less absorption during late stance and early swing phases.

Chapter 4 investigated gait patterns during speed changes in hEDS and TD. The results demonstrated alterations in pelvis, hip, knee, and ankle joint kinematics differing from TD children. These changes may be related to previously reported proprioception deficits, reduced muscle strength, and balance impairments.

In chapter 5, as another potential tool to elucidate the findings of differences in gait, seven machine learning models were applied to classify hEDS gait dynamics. This was done by inspecting the time-series joint kinematics and the important features of the classifiers. Radial basis function support vector machine and fully connected neural networks with a three-layer depth exhibited promising results in distinguishing between hEDS and TD gait kinematics. Analyzing movement patterns in children with hEDS to improve diagnosis, mobility, and musculoskeletal pain management may lead to more effective rehabilitation therapies and pain management strategies leading to an enhanced quality of life in the patient.
I would like to dedicate this work:

To all the children who participated in this study with their kind hearts and big smiles for a better, happier future with less suffering and pain

To my husband, Matt, for his endless support and love

To my lovely mother and father, Zahra and Ibrahim, my beloved brother Abbas

To dearest my mother in-law Diane, father in-law Steve, and brother in-law Nick, who were my second family and supported me in my PhD Journey
TABLE OF CONTENTS

LIST OF FIGURES .............................................................................................................. xi

LIST OF TABLES ................................................................................................................ xiv

ACKNOWLEDGEMENTS ...................................................................................................... xvi

Chapter 1: Introduction and Literature Review ...................................................................... 1

1.1 Background .................................................................................................................... 1

1.1.1 Definition ................................................................................................................ 1

1.1.2 Rare Diseases, Diagnosis and Treatment................................................................. 3

1.1.3 Progression of Joint Hypermobility Symptoms ...................................................... 4

1.2 Musculoskeletal System Deficits .................................................................................. 5

1.2.1 Pain and musculoskeletal symptoms ..................................................................... 6

1.2.2 Fatigue and musculoskeletal symptoms ................................................................. 7

1.3 Shoulder Complex in Individuals with hEDS .............................................................. 8

1.3.1 Alteration in Shoulder Biomechanics ................................................................. 9

1.4 Lower Extremity Joints in hEDS ............................................................................... 11

1.4.1 Pathological Gait Mechanisms .......................................................................... 11

1.4.1.1 Deformity ....................................................................................................... 11

1.4.1.2 Muscle weakness ......................................................................................... 11

1.4.1.3 Sensory loss ................................................................................................. 12

1.4.1.4 Pain ............................................................................................................ 12
1.4.1.5 Impaired motor control ................................................................. 13
1.4.2 Gait Dynamics in the Presence of Hypermobility .......................... 13
1.4.3 Muscle activation in hEDS during gait .......................................... 17
1.4.4 Change of the Speed in Gait Analysis .......................................... 18
1.5 Statistical Parametric Mapping in biomechanics .............................. 19
1.6 Summary of the Research Problem .................................................. 20
1.7 Research Aims .................................................................................. 20
1.7.1 Specific Aim 1 .............................................................................. 20
1.7.2 Specific Aim 2 .............................................................................. 20
1.7.3 Specific Aim 3 .............................................................................. 21
1.7.4 Specific Aim 4 .............................................................................. 21

Chapter 2: Quantification of Shoulder Joint Kinematics in Children with hEDS Compared to Typically Developing Children During Activities of Daily Living and Active Range of Motion 22

2.1 Introduction ...................................................................................... 22
2.2 Methods ............................................................................................ 26
2.2.1 Participants .................................................................................. 26
2.2.2 Data Collection Protocol ............................................................... 28
2.2.3 Data Processing and Statistical Analysis ....................................... 31
2.3 Results ............................................................................................... 35
2.3.1 Shoulder Kinematics During Activities of Daily Living ......... 35
2.3.2 Shoulder Kinematics During Active Range of Motion ............ 41
2.3.3 Scapulohumeral Rhythm ............................................................... 46
2.3.4 Three-Dimensional Arm Workspace ................................................................. 47

2.4 Discussion .............................................................................................................. 48

Chapter 3: Evaluation of Lower Extremity Joint Dynamics and Muscle Activations During Self-Selected Walking: Comparison of Children with Hypermobile Ehlers-Danlos Syndrome and Typically Developing Children ................................................................. 51

3.1 Introduction .......................................................................................................... 51

3.2 Methods .................................................................................................................... 54

3.2.1 Participants ........................................................................................................ 54

3.2.2 Data Collection Protocol .................................................................................... 55

3.2.3 Data Processing and Statistical Analysis ............................................................... 58

3.3 Results ..................................................................................................................... 63

3.3.1 Spatio-Temporal Parameters ............................................................................. 63

3.3.2 Lower Extremity Angles, Moments, and Powers .................................................. 65

3.3.3 Lower Extremity Muscle Activations During Gait ............................................... 73

3.4 Discussion .............................................................................................................. 75

Chapter 4: Comparison of Joint Dynamics Alterations During Different Walking Speeds in Children with hEDS and Typically Developing Children ................................................................. 78

4.1 Introduction .......................................................................................................... 78

4.2 Methods .................................................................................................................... 80

4.2.1 Participants ........................................................................................................ 80

4.2.2 Data Collection Protocol .................................................................................... 82

4.2.3 Data Processing and Statistical Analysis ............................................................... 83
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3</td>
<td>Results</td>
<td>85</td>
</tr>
<tr>
<td>4.4</td>
<td>Discussion</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>Application of Machine Learning to Classify Gait Patterns of Children with Hypermobile Ehlers-Danlos Syndrome and Typically Developing Children</td>
<td>98</td>
</tr>
<tr>
<td>5.1</td>
<td>Introduction</td>
<td>98</td>
</tr>
<tr>
<td>5.2</td>
<td>Methods</td>
<td>102</td>
</tr>
<tr>
<td>5.2.1</td>
<td>Participants</td>
<td>102</td>
</tr>
<tr>
<td>5.2.2</td>
<td>Data Processing and Machine Learning Models</td>
<td>104</td>
</tr>
<tr>
<td>5.3</td>
<td>Results</td>
<td>107</td>
</tr>
<tr>
<td>5.4</td>
<td>Discussion</td>
<td>110</td>
</tr>
<tr>
<td>6</td>
<td>Summary and Conclusions</td>
<td>112</td>
</tr>
<tr>
<td>6.1</td>
<td>Summary of Findings</td>
<td>112</td>
</tr>
<tr>
<td>6.1.1</td>
<td>Specific Aim 1</td>
<td>112</td>
</tr>
<tr>
<td>6.1.2</td>
<td>Specific Aim 2</td>
<td>113</td>
</tr>
<tr>
<td>6.1.3</td>
<td>Specific Aim 3</td>
<td>113</td>
</tr>
<tr>
<td>6.1.4</td>
<td>Specific Aim 4</td>
<td>114</td>
</tr>
<tr>
<td>6.2</td>
<td>Study Limitations and Challenges</td>
<td>114</td>
</tr>
<tr>
<td>6.3</td>
<td>Future Directions and Recommended Clinical Implications</td>
<td>115</td>
</tr>
<tr>
<td>6.4</td>
<td>Concluding Remarks</td>
<td>117</td>
</tr>
<tr>
<td>7</td>
<td>Appendix</td>
<td>148</td>
</tr>
<tr>
<td>7.1</td>
<td>Shoulder Kinematics During AROM</td>
<td>148</td>
</tr>
</tbody>
</table>
7.1.1 Shoulder Kinematics During Flexion ................................................................. 148
7.1.2 Shoulder Kinematics During Scaption.............................................................. 149
7.1.3 Shoulder Kinematics During Abduction........................................................... 150
7.1.4 Shoulder Kinematics During Abduction........................................................... 151
7.2 Scapulohumeral Rhythm for Reaching Across the Body Task ............................... 152
7.3 KAD for Gait Analysis ............................................................................................. 153
7.4 Ankle Angles in Frontal Plane ............................................................................... 154
7.5 Summary Results for different speeds .................................................................... 156
LIST OF FIGURES

Figure 2.1: Marker locations for the established inverse kinematics model........................................ 28
Figure 2.2: Full body marker set in anterior and posterior anatomic positions. ............................... 28
Figure 2.3: Activities of daily living tasks.......................................................................................... 30
Figure 2.4: Active range of motion tasks.......................................................................................... 31
Figure 2.5: The overlaid inverse dynamics model on the representative participant ....................... 32
Figure 2.6: Range of motion group average during ADLs in SC joint............................................... 35
Figure 2.7: Range of motion group average during ADLs in AC, GH, and ST joints ...................... 36
Figure 2.8: 3-D group average profiles of SC, AC, GH, and ST joints during reaching across... 37
Figure 2.9: 3-D group average profiles of SC, AC, GH, and ST joints during combing .................. 38
Figure 2.10: 3-D group average profiles of SC, AC, GH, and ST joints during reaching............... 39
Figure 2.11: 3-D group average profiles of SC, AC, GH, and ST joints during drinking............... 40
Figure 2.12: Range of motion group averages during AROM in SC joint........................................ 41
Figure 2.13: Range of motion group average during AROM in AC, GH, and ST joints ............... 42
Figure 2.14: Scapulohumeral rhythm in the coronal plane............................................................... 46
Figure 2.15: Reachable workspace for subject 18 ............................................................................ 48
Figure 3.1: General coordinate system in laboratory................................................................. 56
Figure 3.2: Representation of a subject with Newington-Helen Hayes marker set.................. 58
Figure 3.3: Direction and coordinate of gait kinematic variables.................................................. 61
Figure 3.4: Distribution of spatio-temporal measures between hEDS and TD ......................... 64
Figure 3.5: Foot progression angle during the gait cycle............................................................... 65
Figure 3.6: 3-D ankle rotations during the gait cycle.. ................................................................. 66
Figure 3.7: Ankle joint moment and power during the gait cycle.. ............................................ 67
Figure 3.8: 3-D knee rotations during the gait cycle. .......................................................... 68
Figure 3.9: Knee joint moments and power during the gait cycle ..................................... 69
Figure 3.10: 3-D hip rotations during the gait cycle ............................................................ 70
Figure 3.11: Hip joint moments and power during the gait cycle .................................... 71
Figure 3.12: 3-D pelvis rotations during the gait cycle ......................................................... 72
Figure 3.13: Muscle activation duration the gait cycle for TA, MG, ST, and RF ................ 74
Figure 4.1: Walking speed across three speeds in hEDS and TD groups ......................... 85
Figure 4.2: Box plots of spatio-temporal measures among different speeds .................... 87
Figure 4.3: Ankle sagittal angle in three speeds in hEDS and TD .................................... 88
Figure 4.4: Repeated measure (RM) ANOVA SnPM{t} for ankle joint in hEDS ............... 88
Figure 4.5: Repeated measure (RM) ANOVA SnPM{t} for ankle joint in TD .................. 89
Figure 4.6: Knee flexion and extension in 3 speeds in hEDS and TD ............................... 90
Figure 4.7: Repeated measure (RM) ANOVA SnPM{t} for knee joint in hEDS ............... 90
Figure 4.8: Repeated measure (RM) ANOVA SnPM{t} for knee joint in TD ................. 91
Figure 4.9: Hip flexion and extension in 3 speeds in hEDS and TD ................................. 92
Figure 4.10: Repeated measure (RM) ANOVA SnPM{t} (a) for hip joint in hEDS .......... 92
Figure 4.11: Repeated measure (RM) ANOVA SnPM{t} for hip joint in TD ................. 93
Figure 4.12: Pelvic tilt in 3 speeds in hEDS and TD ......................................................... 94
Figure 4.13: Repeated measure (RM) ANOVA SnPM{t} for pelvis angles in hEDS .......... 94
Figure 4.14: Repeated measure (RM) ANOVA SnPM{t} for pelvis angles in TD .......... 95
Figure 5.1: Normalized concatenated ankle angles of children with hEDS ................. 105
Figure 5.2: ROC curves for linear, polynomial, gaussian, and RBF SVMs ...................... 108
Figure 5.3: RF ROC classifier results ............................................................................. 109
Figure 5.4: KNN classifier ROC.......................................................... 109

Figure 7.1: 3-D group average in SC, AC, GH, and ST joints during shoulder flexion........ 148
Figure 7.2: 3-D group average in SC, AC, GH, and ST joints during shoulder scaption........ 149
Figure 7.3: 3-D group average in SC, AC, GH, and ST joints during shoulder abduction ...... 150
Figure 7.4: 3-D group average in SC, AC, GH, and ST joints during shoulder extension....... 151
Figure 7.5: Scapulohumeral Rhythm in sagittal plane............................................... 152
Figure 7.6: Representation of KAD on the participant during the static trial...................... 153
Figure 7.7: Ankle frontal angle in three speeds in hEDS and TD. .................................... 154
LIST OF TABLES

Table 2.1: Demographics of children with hEDS/HSD .......................................................... 26
Table 2.2: Demographics of TD Children .................................................................................. 27
Table 2.3: Marker locations and body segments for the upper extremity model ..................... 29
Table 2.4: Four shoulder complex motion in three planes of motion ..................................... 32
Table 2.5: ROM and peak group averages for the shoulder in the coronal plane ..................... 43
Table 2.6: ROM and peak group averages for the shoulder in the transverse plane .................. 44
Table 2.7: ROM and peak group averages for the shoulder in the sagittal plane ...................... 45
Table 2.8: Linear regression models for the SHR in coronal .................................................. 47
Table 3.1: Demographics of children with hEDS/HSD .......................................................... 54
Table 3.2: Demographics of TD children .................................................................................. 55
Table 3.3: Marker locations and body segments for lower extremity plug-in gait model .......... 59
Table 3.4: Definition of four lower extremity articulations angles ........................................... 60
Table 3.5: Spatiotemporal Parameter for hEDS and TD ......................................................... 63
Table 3.6: Summary of significant different results during free walking .................................. 73
Table 3.7: EMG mean and SD for relative and absolute maximum amplitude of muscle ........... 74
Table 4.1: Demographics of children with hEDS/HSD .......................................................... 81
Table 4.2: Demographics of children with TD ...................................................................... 82
Table 4.3: Spatio-temporal parameters in hEDS and TD during three different speeds .......... 85
Table 4.4: p-values for post hoc analysis of different gait speeds in hEDS and TD group ........... 86
Table 5.1 Demographics of children with hEDS/HSD .......................................................... 103
Table 5.2: Demographics of TD children ............................................................................... 104
Table 5.3: ML classifier results .............................................................................................. 110
Table 7.1: Summary of RM ANOVA SnPM results of joint angle. ........................................... 156
Table 7.2: Summary of Post-hoc analysis for RM ANOVA SnPM results.............................. 156
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Chapter 1: Introduction and Literature Review

1.1 Background

1.1.1 Definition

Despite many individuals with hypermobility having no symptoms or disability, there are a group of hypermobility spectrum disorders (HSDs) that develop pain and musculoskeletal symptoms such as Ehlers-Danlos syndrome (EDS). EDS is a heterogeneous group of rare heritable connective tissue disorders (HCTDs) comprising approximately 13 subtypes [2]. An estimated 1 in 5,000-20,000 people have EDS [3, 4]. Affected individuals have overlapping phenotypes of abnormally soft, extensible skin that often heals poorly in association with joint hypermobility, subluxation, and instability, believed to be rooted in a disruption of normal collagen function [5].

The hypermobile type of EDS (hEDS) is the most prevalent type, but is often under-diagnosed, forming a continuum with benign hypermobility syndrome [6]. Recently, HSDs have been combined into one single continuous spectrum ranging from asymptomatic generalized joint hypermobility, to the hypermobility type of the hEDS or joint hypermobility syndrome (JHS) [2, 7]. However, there are still debates and conflicts in the field about whether or not these historically different syndromes should be merged as a unique identity [8]. One of the reasons for this unresolved debate stems from the fact that hEDS does not have an accurate diagnosis due to the unidentified casual gene [9]. This diagnostic dilemma leads to the need for more quantitative approaches to diagnose hEDS in both adults and pediatrics.

The prominent clinical characteristic of hEDS is joint hypermobility, which is caused by the change in the structure of joints’ connective tissues, such as ligaments and tendons [10]. Laxity of
tendons and ligaments has been reported to be the major determinant for musculoskeletal complaints [11, 12]. Plus, these differences could lead to aberrant joint functions. Chronic pain, compensation movements, fatigue, and muscle weakness are a few results of this alteration in the upper and lower extremity joints [13].

There is inconsistency in the literature as to what defines hypermobility, but these individuals generally have an excessive range of joint motion. Additionally, there are many significant heritable connective tissue disorders associated with hypermobility, and up to 50% of affected individuals reported related pain [14, 15]. Younger individuals, specifically children, generally tend towards a hypermobile state, with joint instability commonly leading to frequent dislocations and a predisposition of their joints to developing osteoarthritis.

Joint laxity and instability were reported in over 60% of the pediatric population [16]. Studies reported that as patients mature, they may no longer show overt joint hypermobility but present to their physicians with various musculoskeletal complaints, making diagnosis more difficult [17]. However, collective consensus on the pattern of these alterations and their possible short and long-term effects on children's health is still limited. [18].

Patients with hEDS have significant comorbidities associated with functional anomalies presenting as complex pain, dysautonomia, chronic fatigue, anxiety, and sleep dysfunction [19]. The symptoms range from isolated familial joint hypermobility to extreme multisystem disorder, which significantly impacts the daily quality of life [20, 21]. Many studies showed that for patients with hEDS “moderate to severe pain is an everyday occurrence” [21, 22]. However, the exact sources of pain that affect the quality of life are unknown. This lowered quality of life can also be compounded by the fact that a diagnosis of hEDS may exist as an “invisible disability.” Invisible
disabilities occur in individuals with conditions, illnesses, and structural or biomechanical anomalies that are life-limiting but not readily discernible to others [23].

1.1.2 Rare Diseases, Diagnosis and Treatment

Although rare diseases affect small numbers of patients, they are estimated to collectively affect about 350 million patients; This number is more than nearly twice total number of cancer and AIDS patients [24]. Even though there have been attempts in recent decades, particularly following the orphan law [25], to find therapeutics for rare diseases, the majority of rare diseases, including Ehlers Danlos Syndrome, still lack specific treatments [26].

There are at least 7,000 recognized rare diseases worldwide and the prevalence of Americans living with rare disease has been reported to be between 25-30 million in 2017 [27]. Each country has different criteria and definitions for a rare disease. World Health Organization (WHO) has defined a rare disease in the United States as a condition that affects fewer than 200,000 people based on the Orphan Drug Act of 1983 [27]. It is described by the European Union as affecting less than 1 in 2,000 persons. [28]. While individual diseases might be rare, the total number of people with rare disease is comparable to other diseases, such as diabetes as a major public health concern in the United States. In 2017, American Diabetes Association reported 30.3 million people with diabetes with direct ($237 billion) and indirect ($90 billion) costs [29]. On the other hand, the economic cost of the combined 379 rare diseases reached nearly $1 trillion in the U.S. in 2019, surpassing cost estimates for many chronic diseases [30]. This fast makes rare disease not only a global health concern, but also an economic burden.

The challenges of diagnosis and treatment in rare disease including EDS has been repeatedly addressed by different organizations and research groups [31-35]. 2014 WHO report on rare genetic diseases stated, “For many rare diseases, basic knowledge, like the cause of the disease,
pathophysiology, semiology, natural course of the disease and epidemiological data are limited or worse, missing. This significantly hampers the ability to both diagnose and treat these diseases” [29]. In a survey by European Organization for Rare Diseases [28], several aspects of diagnosis were compared for eight rare mobility diseases such as EDS. It was discovered that 25% of patients waited between 5 and 30 years from early symptoms until confirmatory diagnosis, and 40% of them first received an erroneous diagnosis that subsequently led to unnecessary medical interventions, such as surgery. In addition, Pacey et al. emphasized on effective management that requires engagement of a multidisciplinary team in the most severely affected patients of hypermobility [36].

1.1.3 Progression of Joint Hypermobility Symptoms

Joint hypermobility has a dynamic nature, and age plays a crucial role in determining its frequency and implication [37]. Much of what is known about the biomechanics of EDS in existing literature is based on adults. The previous studies showed that the frequency and intensity of joint hypermobility decreases with age, however, the extent of results have been variable in different research studies [38]. Also, there has been discrepancies and differences in terms of sex. Jansson et al. [39] reported that the male population showed a gradual decrease with increase in age. On the other hand, the female population showed increased hypermobility around 16–18 years age. The exact reason for this rise in frequency of joint hypermobility in 15-year-old females remains unclear.

In a more recent longitudinal study on 101 children with JHS/hEDS from 6 to 17 years old [40], functional impairments, quality of life, connective tissue laxity, muscular function, postural control, and musculoskeletal and multi-systemic complaints were measured at three time points over the course of three years. Their results indicated that children with a high prevalence of multi-systemic complaints and poor postural control, as well as high levels of pain and fatigue at baseline,
are more likely to have a worsening functional impairment trajectory and, as a result, should be given therapeutic priority. These results showed that it is crucial for children to go through helpful treatment plans to prevent possible progression of symptoms such as chronic pain.

1.2 Musculoskeletal System Deficits

Musculoskeletal deficits are often observed in children with hEDS. These deficits can result in a significant change in a child’s gait pattern. The excessive joint ranges of motion and the connective tissue disorders associated with hEDS are largely the cause of musculoskeletal joint instability. Joint instability, which has the highest incidence in the shoulder, hip, knee, and ankle, is a major clinical concern as it can lead to the development of pain and many pathologies [16, 36]. A recent study on pediatric musculoskeletal conditions in EDS reported that the knee was the most common site of the presenting problem, followed by the back and shoulder [16]. The only significant relationship of the patient and location of the presenting problem’s difference between girls and boys was that the back and hip were more likely to have issues in females than males. They also reported that lower extremity muscle weakness reduced physical function, and decreased endurance was observed in women with hEDS [41].

Pain is the symptom by which patients most often encounter the disease and complain [15]. The shoulder has been one of the frequently reported pain areas in hEDS, and it has been associated with shoulder instability, often resulting in subluxation, dislocation, and pain [42, 43]. At the elbow, both lateral and medial humeral epicondylitis are common, and the degree of hyperextension of the elbow could gradually increase over time [44]. Wrist pain is also a common complaint but can be treated successfully with surgery if the diagnosis can be made precisely [45, 46]. Radial tunnel syndrome and weak grip strength are also found in EDS patients [47]. According to the previous studies and clinical experience, the worst pain was most often located in the lower
limbs [21, 48-50]. Ankle with 66.7% of dislocation was the most commonly affected, followed by the knee (28.6%) [51]. Generally, joint hypermobility has been proposed as a risk factor for injuries and chronic pain to the ankle, knee, and hip joints [52, 53].

One of the primary clinical features of hEDS is recurrent joint dislocation, which is common and affects two-thirds of people with hEDS [51]. The most frequently dislocated joint is the ankle, followed by the knee, and the shoulder joint [51]. Another clinical feature is the presence of osteoarthritis. A significant association has been identified between joint hypermobility and osteoarthritis, where 60% of those diagnosed with hEDS develop osteoarthritis [6].

The casual relationship of hypermobility and musculoskeletal symptoms is not yet fully understood. Studies reported that as patients mature, they may no longer show overt joint hypermobility but present to their physicians with various musculoskeletal complaints making diagnosis more difficult [17]. This diagnostic dilemma leads to the need for more quantitative approaches to diagnose and assess hEDS in both adults and pediatrics.

1.2.1 Pain and musculoskeletal symptoms

The main reason people with hEDS seek medical help is pain, and joint pain is one of the major diagnostic measures [54]. In addition, individuals with hEDS are vulnerable to many painful conditions: bruising and poor wound healing; frequent dislocations and/or subluxations; joint pain resulting from early-onset osteoarthritis; musculoskeletal pain; scoliosis; fibromyalgia; irritable bowel syndrome; migraines; and gum disease [48].

Greater flexibility has been associated with chronic pain in the hEDS population due to applying excessive strain on joints [55]. Pain may also result from joint hypermobility and instability. Studies have shown that recurrent and chronic musculoskeletal pain increases with age and the spectrum of musculoskeletal painful sensations becomes wider [48]. Arthralgias (joint pain) and
myalgias (muscle pain) are common pain symptoms in adult patients. As the patients age since childhood, these symptoms become persistent, more generalized, and develop migratory patterns [19, 56]. The complex mechanism of musculoskeletal pain triggering, distribution, and progression derive from various pathophysiologic processes related to the pain mechanism [57]. hEDS, like pathologies such as fibromyalgia, rheumatoid arthritis, and osteoarthritis, has a developmental pain pattern with different phases during the life span. In childhood and early stages of the disease, pain is nociceptive and limited to large and small joints [58]. An abnormal range of motion at the hypermobile joint can increase tensive stress on adjacent muscles and tendons resulting in change in nociceptive afferents [57]. The symptoms are reported to be an increased rate of upper limb subluxations, lower bone mass and advanced osteoarthrosis [59, 60]. These symptoms may be considered as degenerative consequences of mechanical stress on articular surfaces due to congenital capsuloligamentous laxity.

1.2.2 Fatigue and musculoskeletal symptoms

Fatigue is considered as one of the major determinants that can deteriorate the quality of life in persons with hEDS. Over 84% of patients with hEDS are severely fatigued [21]. Prevalence of chronic fatigue in hEDS is directly associated with age. Individuals with hEDS in the first or second decade of life reported a minimum of 28% incidents of daily pain, while 90% of adults over 40 years old reported daily pain experience [14]. Fatigue associated with muscle weakness can also severely affect the walking pattern in this population [61]. Five possible determinants were discussed as causes of fatigue: sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain severity [62]. Still, these combined factors only predicted 38% of the variance of fatigue severity. This result indicates that there are still several unknowns in the mechanism of fatigue in hEDS. Studies discussed that the impact of
fatigue is dramatically more than or equal to the impact of pain on the activities of daily living (ADLs) [21, 57]. One of the hypotheses was that hypermobile subjects lack of postural control and, therefore, require an increase in muscle activation to avoid falls, movement failures, and compensate for joint instability [42, 63, 64].

1.3 Shoulder Complex in Individuals with hEDS

The shoulder is the most frequent joint to be reported as having a high prevalence of instability, subluxation, dislocation, and chronic pain in patients with JHS/hEDS compared to a control group [48, 65, 66]. Furthermore, the patients reported that the pain prevents them from being socially active and limits their functional activities in daily life. Simple daily activities, such as putting on a jacket or reaching for a glass may cause shoulder subluxation/dislocation with subsequent pain [67]. Prominent features that have been reported were fatigue, aching, muscle weakness, and discomfort in the shoulder [21]. Furthermore, surgery has a high failure rate in patients with very loose shoulders, so it is critical to define alternative treatment interventions [47].

As one of the most highlighted symptoms of hEDS, joint hypermobility is connected to reported laxity in the shoulder complex [68]. In most of the studies, the widely variable range of normal laxity in the shoulder [69-71], makes it difficult to assess the excessive shoulder laxity by physical tests [72, 73]. The contribution of joint laxity and hypermobility in shoulder instability is still unknown. Muscle activation pattern, joint capsular structure, co-existence of other shoulder pathologies (e.g., severe loss of glenoid and humeral bone), proprioception deficits, and altered biomechanics of the shoulder are other important factors that also affect shoulder instability [9, 74-80].
1.3.1 Alteration in Shoulder Biomechanics

Shoulder complex motion and their muscular activations have not been investigated in patients with hEDS. Johnson et al., in one of the most important shoulder studies on hEDS, found that increased pain intensity was observed in patients with hEDS when compared to a control group [81]. Furthermore, the patients reported that this pain often prevents them from being active and limits their function in daily life. Other prominent features were fatigue, aching, muscle weakness, and shoulder discomfort. They reported shoulder instability affects both physical activity and their participation during ADLs. Simple daily activities, such as putting on a jacket or reaching for a glass may cause shoulder subluxation and pain.

There are inconsistent and sparse studies on the biomechanics of shoulder instability in the presence of joint hypermobility. During shoulder elevation, substantial motion also occurs at the sternoclavicular (SC) and acromioclavicular (AC) joints, contributing to scapulothoracic (ST) motion through mechanical coupling [82-84]. Although abnormal SC and AC movements are expected to occur in parallel with abnormal ST motion, most research on shoulder instability has focused on scapular motion and relative glenohumeral (GH) and ST joints’ kinematics.

In the hypermobility literature, there is an increasing appreciation that GH joint stability may be directly influenced by the relationship of the scapula to the thorax in elevation [85-87]. Based on the reports of scapular dysfunction in HSDs [88-90], aberrant scapular kinematics can be expected during various shoulder movements. Scapular dysfunction may occur due to muscle imbalance/weakness or as a response to shoulder instability [91]. Ozaki et al. [91] reported decreased scapular abduction and excessive GH translation with shoulder elevation in subjects with multidirectional shoulder instability (MDI) using radiographic methods for the first time. Later, a few investigations have compared subjects with MDI to control subjects during arm
elevation [80, 92-96]. These results identified significantly less scapular upward rotation and altered scapulohumeral rhythm (SHR) in the subjects with GH instability.

A possible explanation is that reductions in scapular upward rotation in individuals with shoulder instability may represent a negative compensation and contribute to inferior GH joint instability [92]. Ogston et al. [92] reported that differences between the MDI and control group progressively increased throughout elevation; the largest difference was during the last phase of motion. Conversely, one study reported lesser scapular upward rotation contribution early in the ROM during arm elevation, whereas later with a greater scapular contribution [96]. Also, significantly greater internal rotation was observed in patients with shoulder instability which is believed to mechanically reduce anterior stability [80, 92]. Further investigation is required in individuals with shoulder instability and hypermobility to better understand the compensatory and biomechanical consequences of the scapular kinematics [97].

Previous studies suggested that alterations in scapular kinematics could be linked with a dysfunctional pattern of muscular coordination. Although abnormal scapular kinematics is believed to be related to shoulder dysfunction [98], there is sparse evidence on aberrant SHR and shoulder muscle activation patterns in subjects with hypermobility. Moreover, the widely variable range of normal laxity in the shoulder [69-71] makes the physical tests difficult to assess the excessive shoulder laxity, which leads to shoulder instability [72, 73]. The contribution of joint laxity and hypermobility in shoulder instability is still unknown.
1.4 Lower Extremity Joints in hEDS

Results from several studies have shown altered gait kinematics and kinetics in the ankle, knee, and hip joints in adults with hEDS [17, 99-104]. Although the literature shows differences in gait patterns of hypermobile and healthy individuals, these differences are not consistent [105]. Abnormalities in connective tissues in the hEDS/JHS can cause multiple abnormalities in various systems, especially the musculoskeletal system, which can affect the pattern of walking.

1.4.1 Pathological Gait Mechanisms

Gait analysis can provide important information regarding the cooperation of the musculoskeletal system with neurological functions. Causes of gait impairments may be categorized into five functional categories; deformity, muscle weakness, sensory loss, pain, and motor control impairment [106]. Possible hEDS gait pathologies will be discussed in all five categories.

1.4.1.1 Deformity

The deformity occurs when a connective tissue does not provide sufficient passive mobility. Any movement results from the cooperation of connective tissue components such as muscles, ligaments, or the joint capsule. Although most of the studies concentrated on contracture as the only example of deformity [107, 108], hypermobility, as a result of the loose connective tissues, could also cause deformity [109]. Individuals with hypermobile EDS (hEDS) commonly report foot pain mainly caused by foot deformity, such as flat foot and hallux valgus [110]. In addition, foot deformities may lead to abnormal walking patterns, which may be a contributing factor to poor balance [111].

1.4.1.2 Muscle weakness

Insufficient muscle strength could also lead to changes in the walking pattern. Patients with muscle weakness may modify the timing of muscle action to avoid threatening postures and induce
protective alignment during stance [100]. Moreover, primary muscle involvement in EDS can be expected based on altered interactions between muscle cells and extracellular matrix molecules, of which collagen is an important component [112, 113]. One study showed that while muscle mass was similar between hEDS and a control group, the hEDS group clearly showed lower extremity muscle weakness, as evidenced by reduced muscle strength, reduced endurance, and diminished functional performance [41]. So, the muscle weakness may be due to muscle dysfunction rather than muscle atrophy, in which altered force transmission due to abnormalities in muscle extracellular matrix composition may be an important factor.

1.4.1.3 Sensory loss

Impaired proprioception could impair the patient’s understanding of the position of lower extremity joints, segments, and ground contact [114]. Due to this impairment of information, a person might not know when it is the right time to lock the knee or hit the ground to emphasize the moment of contact. The most direct effect would be on the patients' walking speed [115]. To walk more safely, they would decrease their walking speed and usually widen their stride length. This hesitation could also have other influences on some of the mechanisms of gait and lead to, for instance, an overly flexed knee or inverted foot [116].

1.4.1.4 Pain

It has been reported that the main source of the pain is excessive tissue tension. Also, the physiological reactions to deformity and muscle weakness could cause pain during walking. However, the source of the pain in patients with hEDS is different. The correlation of fatigue and pain together can change the gait pattern in an individual with EDS [21, 117]. Fatigue is a frequent and clinically relevant problem in hEDS that drastically affects the quality of life [62]. This study showed that pain associated with fatigue is more often observed (84%) in the hypermobility type
of Ehlers Danlos compared to other subtypes in walking [21]. The most common presenting features in this patient group are joint pain followed by coordination problems and reduced joint movement range [118].

1.4.1.5 Impaired motor control

Proprioceptive deficits and difficulties in motor skills have been demonstrated in children with hEDS [119]. This study showed that the origin of these musculoskeletal deficits is found in the compromised structural integrity of connective tissue [39, 120]. It could be a significant challenge for individuals with hEDS to activate a certain muscle group in different gait phases. Multiple studies consistently showed that knee joint proprioception was observed to be significantly worse in children with hEDS compared to healthy controls [119, 121, 122]. However, the reasons for the identified deficits in motor control and proprioception are not known.

1.4.2 Gait Dynamics in the Presence of Hypermobility

Walking is the most frequently reported problematic activity of daily living [123, 124]. In addition, chronic pain in lower extremity joints is the most common symptom of hEDS, which may be caused by excessive strain on the joints during different movements. People with hEDS frequently complain about their modifications or restrictions to activities to avoid recurrent injury and pain. Therefore, three-dimensional (3-D) gait analysis has been investigated in patients with hypermobility. However, the results of these studies are not consistent, and there is no collective understanding of gait dynamics in children with hEDS. Moreover, according to a recent review and gait analysis evaluation in individuals with hypermobility, research on the hEDS group had poor or moderate reliability. [125].

Many clinicians consider JHS and hEDS to represent the same phenotypic group of patients that can be differentiated from other HCTDs but not distinguished from each other [8, 126].
Furthermore, lacking a subtle clinical and genetic diagnosis affected the quality of life in parallel to the poor or wrong diagnosis and treatment procedures. In this study, JHS and hEDS were considered as the same phenotype and will continue using “hEDS”. It also has been claimed that clinicians serve this population better by uniting the two diagnostic labels [8].

Although limited biomechanics research of hEDS joint mobility has been focused primarily on walking [17, 63, 99-101, 127-131], there is no conclusive evidence that hypermobile gait varies from normal walking in a consistent pattern. In addition, the association of joint pain, as one of the most important symptoms, and gait pattern has not been addressed in previous gait studies [125].

The following section will review the literature on gait analysis in JHS and hEDS, which is sparse and inconsistent.

Galli et al. as one of the pioneers in gait analysis in hEDS, has found altered gait patterns in adults [17]. Their results showed a lower anterior step length, reduced ankle dorsiflexion during stance and swing phases, and reduced plantar flexion position at initial contact. They also found no abnormalities present on frontal and transversal planes.

Bates et al. investigated the reliability of motion capture in individuals with hEDS [105]. They concluded that 3-D gait kinematic parameters are reproducible in a hypermobile population after examining intra- and inter-session reliability of gait data in adults with hypermobility and healthy adults and that joint laxity does not affect the variability of their kinematic gait analysis measures. This study suggested that motion analysis can be a valuable tool in therapeutic settings for determining how a patient moves.

Nikolajsen et al. concluded that the walking pattern in children with generalized joint hypermobility (GJH) was the same as healthy children [131]. However, different knee and hip sagittal peak moments were observed. Lower peak knee abductor moments and peak hip abductor
moments were observed in the hypermobility group. In general, decreased ankle and knee joint moments in the sagittal plane were significantly different in the hEDS group compared to the healthy group.

Rigoldi et al. considered two groups with Down syndrome and hEDS because of the presence of ligament laxity and difficulties in force transmission in both groups [99]. Toe-walking, abnormal gait, and delayed walking have been reported for this group of patients. Increases in both passive and active range of movement during walking were also reported. This study showed greater knee extension and reduced knee flexion compared to healthy children. This finding may indicate that the active range of motion (AROM) is more limited than the passive range of motion because of pain, muscle weakness, and fear of self-injury.

One of the first studies on lower extremity muscle-tendon properties [132] investigated torque, angle, and electromyography (EMG) simultaneously recorded during slow stretch to the onset of pain. The results demonstrated a significantly larger maximal joint angle in the hEDS patients in comparison to the control group due to the lack of neurophysiologic response at the end range needed to protect the joints. They suggested that this response is important to understand when designing subsequent physical therapy and interventions.

Fatoye et al. had the same result as Rigodi et al. [99] for the increased knee extension and reduced knee flexion in children with JHS. Peak ankle plantar flexion, peak knee flexion loading response, peak knee extension and peak knee flexion swing were calculated [63]. They showed that knee flexion during loading response increases with higher walking speed. Because the knee range of motion depends on walking speed, having a wide range of speeds in gait analysis would help better understand the gait patterns.
Following the results from [99], Roumbaut et al. suggested that muscle weakness could be a reason for this reduction in knee flexion [41]. Furthermore, it may be due to the significantly higher pain perception that children with hEDS have compared to healthy children. The pain could also be a major reason that the patient’s compensations act to decrease the shear force in the knee and to decrease the compressive force from quadriceps. They also concluded that impaired proprioception could cause the patients to move their segments and joints outside of their standard and normal range of motion [133].

Celleti et al. on the study of adults with hEDS investigated the possible relationship between the intensity of fatigue and primary gait pattern. Compared to a control group, they found a significant difference in ankle power generation and absorption [127]. They suggested that fatigue in adults with hEDS, could be why these individuals must produce more force or power during their walking. They compared muscle activation, joint angles, and spatiotemporal parameters during gait, and isometric strength between participants with EDS (hypermobility and classical subtypes) and healthy adults [134].

Robbins et al. compared lower extremity inter-segmental coordination amplitude and variability during gait between patients with EDS and healthy adults [104]. They found out that patients with EDS had more variability between gait trials in lower limb motor coordination than healthy adults, which could be related to impaired proprioception, reduced strength, pain, or slower gait. Another limitation of this study was that they mixed hEDS and the classical subtype into one group and compared it to healthy adults. They also reported that gait speed was significantly higher in the control group, which could change the gait dynamics. However, they didn’t normalize their results by speed. So, it was not clear whether the difference between the two groups was because of
gait pattern or the speed. They also used the same cohort as their previous 2019 paper on gait [134].

One of the most recent studies in 2020 on gait dynamics of adults with hEDS showed a reduction in walking speed, stride length, and step length [102]. Moreover, kinematics results indicated decreased knee flexion, hip extensor moment, and knee power generation and absorption. They concluded that the JHS group walked more slowly with a kinematic stiffening pattern, and no hypermobility was observed during gait. They suggested that the observed stiffening pattern could be a strategy to avoid pain and improve balance. Impairments in moment and power generation could be related to several symptomatic and etiological factors in JHS.

In 2021, Bates et al. compared sagittal kinematics and kinetics of gait and stair climbing between hypermobile and non-hypermobile adults [135]. They showed no significant difference between the kinematics in GJH and JHS compared to healthy adults. This finding contrasted with the previous findings from Galli and Rigoldi et al., which showed the differences in gait kinematics [17, 99, 131].

1.4.3 Muscle activation in hEDS during gait

Previous studies showed altered muscle activations during gait compared to healthy individuals in patients with EDS. A recent study showed the isometric strength differences in hEDS and the classical subtype of EDS [134]. Also, higher activation of the rectus femoris, more prolonged gluteus medius activation, and lower medial gastrocnemius activation were observed. While there were similarities in joint angles, the EDS group had slower gait speed, shorter stride length, and a greater percentage of time in stance. They concluded that the muscle activation and spatiotemporal parameters were altered during gait in patients with EDS [134].
Another study’s results demonstrate considerably reduced quadriceps and hamstrings muscle strength and muscle strength endurance in hEDS patients compared to healthy subjects, resulting in poorer functional performance and impaired physical function [41]. Motor coordination and joint stability have been linked to the co-contraction of agonist and antagonist muscles. Co-activation is defined as agonist and antagonist muscles identified as prime movers or stabilizers. Also, previous studies suggested that alteration of co-activation could lead to an abnormal movement [136]. Co-activation, one of the four causes of inefficient gait [136], plays an important role in developing motor skills in young children. This finding parallels another report that lower extremity muscle weakness, reduced physical function, and decreased endurance were observed in women with hEDS [41].

1.4.4 Change of the Speed in Gait Analysis

The influence of gait speed on the gait characterization is undeniable. Previous research has shown that spatio-temporal parameters, joint angles, ground reaction forces (GRF), moments and powers at the joints and EMG are significantly related to the walking speed in typically developing (TD) children [137]. Fatoye et al. showed that the knee range of motion is dependent on the speed of walking; having a wide range of speed in gait analysis would help in better understanding gait patterns [63]. While previous research on individuals with hEDS and JHS suggested the necessity of studies on different gait speeds, to date, there have been no studies on gait investigating different speeds in hEDS or JHS.

Multiple studies reported that speed is the primary parameter in dynamic gait analysis, not age [138, 139]. In EMG analysis, the signal's magnitude changed, but the pattern of muscle activation had drastic alteration as well [137]. With respect to the importance of speed, prior research on gait, especially pathologic gait analysis, focused on a single self-selected speed to report gait metrics.
Speed is not only a critical contributor to gait dynamics characterization; it is also a key stability determinant [140]. For example, an increased EMG amplitude during fast speed compared to free speed may indicate balance and stability issues in individuals with hEDS.

1.5 Statistical Parametric Mapping in biomechanics

Joint kinematic and kinetic data during a movement cycle is considered a 1-dimensional (1-D) data since it changes during a certain time. However, classical biomechanics literature often analyzes the data with a discrete approach and reduces the original dimensional of the data to zero dimension (0-D). For instance, for comparing knee flexion angle in a patient and control group, the peak values of the curve would be compared.

Statistical Parametric Mapping (SPM) uses random field theory to make statistical inferences regarding registered (normalized) sets of 1-D measurements [141]. The application of SPM in biomechanics was initially developed to analyze cerebral blood flow in 3-D [142], but it has been validated on biomechanical data since 2008 [143]. SPM has a variety of scientific measures. In addition, it is highly generalized and flexible, and it permits field-wide and spatiotemporally specialized hypothesis testing. Therefore, it has been widely used in biomechanics recently [144].

A classic biomechanical approach, which uses discrete analysis, has multiple disadvantages and can cause misinterpretation of the results, especially when there is a borderline effect. In fact, if one’s hypothesis pertains to 1-D trajectories, then objectivity obliges one to employ a 1-D model of randomness. In the example of investigating the differences in the knee joint, it is inappropriate to test the hypothesis in 0-D model of randomness.
1.6 Summary of the Research Problem

hEDS has been considered a progressive disorder that deteriorates functional movement and augments chronic pain during an individual’s lifespan. Further, the relationship between quantitative joint kinematics, joint kinetics, strength, and quality of life is unknown. An important question is whether these complications in the musculoskeletal system affect joint dynamics in children.

1.7 Research Aims

This study aimed to characterize hEDS by quantifying motion and muscle activations during activities of daily living (ADLs). Four specific aims were executed for this study:

1.7.1 Specific Aim 1

To quantify the joint kinematics of the shoulder in children with hEDS compared to TD children during activities of daily living and shoulder active range of motions.

Shoulder kinematics in children with hEDS were characterized. Motion analysis was used to evaluate ADLs, including reaching across the body, reaching to a back pocket, combing hair, and drinking. SC, AC, GH, and ST joint kinematics were also quantified in 3-D. The main goal was to advance the understanding of shoulder biomechanics in the presence of joint hypermobility in children with hEDS.

1.7.2 Specific Aim 2

To evaluate joint dynamics and muscle co-activations of the lower extremity during self-selected walking.

The kinematic and kinetic metrics in three planes of motion and muscle activations during walking were evaluated. Parameters were calculated by the inverse dynamics method using position data from motion capture (Vicon Motion Systems, Oxford, UK) and GRFs from force plates (©
Advanced Mechanical Technology, Inc., Watertown, MA). Amplitude and on-off timing were calculated from the EMG signals. Since joint instability has been connected to the ratio of agonist and antagonist muscles’ activation, muscle co-contraction was investigated. For this purpose, two groups of muscles in the lower extremity were considered: rectus femoris vs. semitendinosus and tibialis anterior vs. medial gastrocnemius.

1.7.3 Specific Aim 3

To compare changes in joint dynamics during different walking speeds in children with hEDS compared to TD children

The main goal was to investigate the gait pattern changes among different walking speeds in children with hEDS compared to TD children. Since speed amplifies gait alterations, free self-selected, fast, and slow gait speeds were calculated to evaluate the effect of speed on gait metrics. It was hypothesized that children with hEDS have a different change in the gait pattern, especially in knee and ankle sagittal angles.

1.7.4 Specific Aim 4

To use machine learning to classify children with hEDS and TD based on gait dynamics.

Machine learning models were developed to predict a class (0: TD, 1: hEDS) based on time-continuous (time-series) kinetic and kinematic data. The classification was carried out by supervised machine learning models using support vector machine (SVM), random forest (RF), k-mean nearest neighbor (KNN), and fully connected neural networks (NN) classifiers. The main goal was to explore a deeper insight into clinical gait analysis.
2.1 Introduction

Coordinated movement of the arm is possible through the contribution of four joint articulations such as the SC, AC, ST, and GH joints. The shoulder is the most frequent joint to be reported having a high prevalence of instability, subluxation, dislocation, and chronic pain in patients with JHS and hEDS [48, 65, 66]. Furthermore, it has been reported that pain prevents individuals with hEDS from being socially active and limits their functional activities in daily life. Simple daily activities, such as putting on a jacket or reaching for a glass, may cause shoulder subluxation/dislocation with subsequent pain [67]. Prominent features that have been reported were fatigue, aching, muscle weakness, and discomfort of the shoulder [21]. Furthermore, because surgery has a significant failure probability in individuals with excessively lax shoulders, it is necessary to establish alternate therapy strategies [47].

As one of the most highlighted symptoms of hEDS, joint hypermobility is connected to reported laxity in hEDS shoulder complex in literature. In most studies, the wide variable range of normal laxity in the shoulder [68-70] makes it difficult for physical tests to assess the excessive shoulder laxity, leading to shoulder instability [72, 73]. The contribution of joint laxity and hypermobility to shoulder instability is still unknown. Muscle activation pattern, joint capsular structure, coexistence of other shoulder pathologies (e.g., severe loss of glenoid and humeral bone), proprioception deficits, and altered shoulder biomechanics are other important factors that also affect shoulder instability [9, 74-80].
There is a large gap in the literature and a lack of knowledge on how shoulder complex movements differ between children with hEDS and TD children. Johnson et al., in a recent study on the shoulder in adults with hEDS, found out that increased pain intensity was observed compared to a control group [81]. To the author’s knowledge, 3-D shoulder complex motion has not been investigated in children with hEDS during ADLs.

Scapular motion and its movement pattern play an essential role in GH elevation. During arm elevation, the scapula rotates upwardly and internally accompanying by posterior tilt [145]. The orientation of the scapula relative to the thorax and the position of the scapula on the thorax are used to describe 3-D ST motion [146]. For instance, the primary purpose of clavicle rotation in SC joint is to place the scapula in an optimal position to accept the head of the humerus [145]. Therefore, understanding this relation between ST and GH joints can elucidate possible abnormal shoulder elevation.

It should be emphasized that the ST joint is not a typical joint by definition and does not have the standard characteristics of a joint. This articulation of the scapula and the thorax depends mainly on the integrity of the AC and SC joints. Significant motion occurs at the SC and AC joints during shoulder elevation, contributing to ST motion through mechanical coupling. As a result, aberrant SC and AC motion is predicted when ST motion is abnormal. The scapula’s position is critical for appropriate shoulder function because it offers a stable base, especially in GH elevation. Therefore, it is essential to analyze SC and AC kinematics when investigating ST and GH movements [145].

There are inconsistent and sparse studies on the biomechanics of shoulder instability in the presence of joint hypermobility. During shoulder elevation, the substantial motion also occurs at the SC and AC joints, contributing to ST motion through mechanical coupling [82-84]. Although abnormal SC and AC movements are expected to occur in parallel with abnormal ST motion, most
research on shoulder instability has focused on scapular motion and relative GH and ST joint
kinematics.

In the hypermobility literature, there is an increasing appreciation that GH joint stability may be
directly influenced by the relationship of the scapula to the thorax in elevation [85-87]. Based on
the reports of scapular dysfunction in HSD, such as hEDS and JHS [88-90], aberrant scapular
kinematics can be expected during various shoulder movements. Scapular dysfunction may occur
due to muscle imbalance/weakness or as a response to shoulder instability [91]. Ozaki et al. [91]
reported decreased scapular abduction and excessive GH translation with shoulder elevation in
subjects with MDI using radiographic methods for the first time. Later, several investigations have
compared subjects with MDI to control subjects during elevation of the arm [80, 92-96]. SHR is
the kinematic interaction between scapula rotation and humerus elevation, vital in functional
movement. These results identified significantly less scapular upward rotation and altered SHR in
the subjects with GH instability.

A possible explanation for this alteration is that reductions in scapular upward rotation may
represent a negative compensation and contribute to inferior GH joint instability [92]. Ogston et
al. [92] reported that differences between individuals within the MDI and control groups
progressively increased throughout elevation; the largest difference was during the last phase of
motion. Conversely, one study reported lesser scapular upward rotation contribution early in the
range of motion (ROM) during arm elevation, whereas later with a greater scapular contribution
[96]. Also, significantly greater internal rotation was observed in patients with shoulder instability
which is believed to mechanically reduce anterior stability [80, 92]. Further investigation is
required in individuals with shoulder instability and hypermobility to better understand the
compensatory and biomechanical consequences of the scapular kinematics [97].
The central aim was to quantify the joint kinematics of the shoulder in children with hEDS/HSD compared to a TD group of children during ADLs and shoulder AROM. Based on the literature on shoulder instability [98, 147, 148], it was hypothesized that scapular upward rotation (that includes elevation) is less in children with hEDS compared to TD children. Second, it was hypothesized that the SC and AC range of motion is higher in those with hEDS than in the TD group during elevation. Third, it was hypothesized that reachable workspace based on the hand trajectories was higher in the hEDS group during 3-D AROM compared to the TD group. Lastly, it was expected that the range of motion during shoulder elevation in GH joint angle was higher than in those with hEDS compared to the TD group.

The short-term goal of this chapter was to define and characterize 3-D shoulder kinematics in children with hEDS compared to TD children. The finding may advance the understanding of shoulder biomechanics in the presence of hypermobility and musculoskeletal symptoms. The long-term goal of this research may reveal potential targets to prevent or treat shoulder pathologies in hEDS.
2.2 Methods

2.2.1 Participants

In total, twenty-one (21) children with hEDS/HSD were recruited by the Genetics Center of Children’s Wisconsin. The specific diagnosis and demographics are listed in Table 2.1 (All hEDS/HSD participants were white). Ten children were diagnosed with hEDS, four with HSD, and five did not have a clear phenotype for HSD or hEDS, therefore, considered hEDS/HSD. Nineteen (19) TD children were recruited from the community with no prior history of shoulder hypermobility or injury (Table 2.2; all TD children were not Hispanic or Latino). The Beighton

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Table 2.1: Demographics of children with hEDS/HSD

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<tr>
<th>Subject</th>
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<th>Age</th>
<th>BMI</th>
<th>Gender</th>
<th>Ethnicity</th>
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N= 19

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score, as a generalized measure of hypermobility, was obtained in TD children [149]. All TD children showed Beighton scores less than four, indicating normal ROM.

Table 2.2: Demographics of TD Children

<table>
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2.2.2 Data Collection Protocol

The present study was conducted in the University of Wisconsin-Milwaukee (UWM) Mobility Laboratory located at UWM Innovation Campus and was approved by the University’s Institutional Review Board separately for hEDS and TD groups. Assent and/or consent were obtained at the first testing visit, prior to any study activities. Subject 8 did not complete all the shoulder tasks and was not included in the analyses. Subject-specific measurements were taken using a caliper, including the anterior-posterior elbow diameter and hand thickness at the third metacarpal joint for the right and left sides. The marker names and locations are described in Figure 2.1 and Table 2.3. All markers were placed by the student PI (Anahita Qashqai). Twenty-seven passive reflective markers of 14 mm diameter were placed bilaterally on bony landmarks (Figure 2.2).
The tasks were ADLs, those being combing, drinking, reaching across, and reaching to back pocket (Figure 2.3), and AROM comprising shoulder elevation during flexion, abduction, extension, scaption, and shoulder internal and external rotation in 0 and 90 degrees of abduction (Figure 2.4). All the tasks started and ended at the same position while the arm was fully extended on their side. The subject repeated each task for a total of 5 trials and paused momentarily in between trials. Then, the subject was instructed to bring the filled water bottle to their mouth and bring the arm back down to the starting position. For the reaching across the body task, the subjects were instructed to reach across their body with their dominant hand to touch the side of the opposite arm, approximately around the insertion point of the deltoid muscles on the humerus.

The tasks were typical motions of daily living and did not increase the risk of subluxation above what is routinely encountered daily. However, subjects were asked to inform the research team if such a dislocation or subluxation were to occur during the data collection. One incident of

Table 2.3: Marker locations and body segments for the upper extremity model. Scapula, upper arm, forearm, and hand markers were placed on right and left sides.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Segment</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRN</td>
<td>Thorax</td>
<td>Xiphoid Process; most inferior portion of the sternum</td>
</tr>
<tr>
<td>IJ</td>
<td>Thorax</td>
<td>Suprasternal Notch; between sternal clavicular heads</td>
</tr>
<tr>
<td>SPC7</td>
<td>Thorax</td>
<td>Spinal Process C7; most prominent spinous process of the spine posteriorly</td>
</tr>
<tr>
<td>TS</td>
<td>Scapula</td>
<td>Trigonum Spinae</td>
</tr>
<tr>
<td>AA</td>
<td>Scapula</td>
<td>Acromial Angle</td>
</tr>
<tr>
<td>SS</td>
<td>Scapula</td>
<td>Scapular Spine; 1/2 between TS and AA</td>
</tr>
<tr>
<td>IA</td>
<td>Scapula</td>
<td>Inferior Angle</td>
</tr>
<tr>
<td>AC</td>
<td>Scapula</td>
<td>Acromion</td>
</tr>
<tr>
<td>CP</td>
<td>Scapula</td>
<td>Coracoid Process</td>
</tr>
<tr>
<td>HUM</td>
<td>Upper Arm</td>
<td>Lateral aspect of humerus; straight line from acromion to lateral humeral epicondyle</td>
</tr>
<tr>
<td>OLC</td>
<td>Upper Arm</td>
<td>Olecranon</td>
</tr>
<tr>
<td>ULN</td>
<td>Forearm</td>
<td>Ulnar Styloid</td>
</tr>
<tr>
<td>RAD</td>
<td>Forearm</td>
<td>Radial Styloid</td>
</tr>
<tr>
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<td>Hand</td>
<td>Third Metacarpal</td>
</tr>
<tr>
<td>M5</td>
<td>Hand</td>
<td>Fifth Metacarpal</td>
</tr>
</tbody>
</table>
subluxation in subject 19 was reported during the shoulder abduction task. Subject 19 decided to continue the data collection since it was painless and was a recurring situation for the participant.

Figure 2.3: Activities of daily living tasks. Combing, drinking, reaching back pocket, and reaching across the body were performed 5 times by each participant.
2.2.3 Data Processing and Statistical Analysis

Marker trajectories were labeled, and all gaps were filled based on the standard methods, such as Spline in Vicon Nexus software. Final marker positions were filtered using a Woltring filter with MSE equal to 20 [150], and the data was transferred to MATLAB software using C3D files of each task.

Figure 2.4: Active range of motion tasks. Shoulder flexion, scaption, abduction, and extension during arm elevation, and rotation with 0 and 90° abducted arm were performed 5 times by each participant.
2.2.3.1 Shoulder Complex joint angles

A customized bilateral upper extremity model comprised of eleven segments, including the thorax, clavicles, and scapulae (Figure 2.5), was used [151]. The joints of interest were three-degree-of-freedom AC, GH, and ST joints; and two-degree-of-freedom SC.

Figure 2.5: (A) The overlaid on the representative participant during drinking task, (B) the custom inverse kinematics model in Vicon software.

GH, AC, SC, and ST joints (Table 2.4) were quantified over time from the beginning to the end of each task. The beginning and end of the tasks were detected based on the least velocity of either right and left olecranon or hand markers. The customized inverse kinematics model was used to calculate the joint angles [151]. The time was normalized to 100% for the whole cycle of each task based on the detected start and end frames. Segment coordinate systems (SCS) were determined

Table 2.4: Four shoulder complex motion in three planes of motion and each rotation

<table>
<thead>
<tr>
<th>SC (YXZ)</th>
<th>AC and ST (YXZ)</th>
<th>GH (ZXY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation (+)/depression (-)</td>
<td>Upward (+)/downward (-) rotation</td>
<td>Flexion (+)/Extension (-)</td>
</tr>
<tr>
<td>Protraction (+)/Retraction (-)</td>
<td>Internal (+)/External (-) Rotation</td>
<td>Internal (+)/External (-) Rotation</td>
</tr>
<tr>
<td>Axial rotation of clavicular*</td>
<td>Anterior (+)/Posterior (-) Tilt</td>
<td>Anterior (+)/Posterior (-) Tilt</td>
</tr>
</tbody>
</table>

* Axial rotation of clavicular in sagittal plane was not calculated due to the inability of clavicle axial rotation detection without in vivo methods
for each segment. The joint angles were calculated by the relative motion between two adjacent SCS, distal relative to proximal. The SCS followed the right-hand rule with the positive Y-axis as the flexion/extension axis, the X-axis as the abduction/adduction axis, and the Z-axis as the internal/external rotation axis. For left shoulder measures, it is recommended to mirror the raw position data with respect to the sagittal plane (z = -z). Then, all definitions for right arm shoulders are applicable [152].

Scapular rotation is defined as the orientation of the scapula relative to the thorax. Upward and downward rotation, external and internal rotation, and posterior and anterior tilt are motions in coronal, transverse, and sagittal planes of motion, respectively. It should be noted that the axial rotation of the clavicle cannot be measured through non-invasive palpation methods.

Group averages and standard deviations were computed for the peak and ROM values for each of the shoulder complex joints in the coronal plane, transverse, and sagittal planes. Wilcoxon signed-rank tests were used to compare results between hEDS and TD groups for ROM and peak values (p-value = 0.05).

2.2.3.2 Scapulohumeral Rhythm

The SHR was calculated by quantifying the ratio of the GH joint angle to ST joint angle during arm elevation, using a recently modified method [153, 154]. Therefore, the SHR was defined as the ratio of the GH movement to the ST upward rotation during arm elevation. The tasks that involved considerable shoulder elevation were analyzed for the SHR except for rotation tasks. Linear regression was used to model the SHR as the coefficient for each group was calculated. Adjusted R² and p-values were calculated for each model.
2.2.3.3 Reachable Workspace During Active Range of Motion

Five trials of AROM tasks for the dominant arm were selected to obtain hand positions. Filtered hand trajectories were used to calculate the workspace during AROM for shoulder flexion, scaption, abduction, and extension. MATLAB software was used to prepare the data and develop alpha shape algorithms. AROMs were reshaped and concatenated for each task and averaged for each subject individually. The critical alpha-shapes were analyzed by the “All-Points” method using MATLAB software’s “Critical Alpha” function, which included all the points that were created by the hand movement [155]. Finally, a nonconvex region was determined by a bounding area of critical alpha-shapes.

The mean final error was calculated for each subject’s trial. The workspace boundaries were determined by the parameters of the alpha shapes by the least-squares fitting to the captured hand trajectories to create alpha-shape geometries [156, 157]. The total surface area of each alpha-shape was determined as the sum of surface patches across the quadrants and was further normalized with respect to the surface area of a unit hemisphere for each subject (by dividing it by $2\pi R^2$, where $R$ corresponds to the radius of the fitted alpha-shape). Finally, the reachable workspace was calculated by the relative surface area representing the portion of the unit hemisphere covered by the hand movement. So, the final reachable workspace was analyzed as the relative surface area (RSA) that lay between 0 and 1 and was compared between the group averages.
2.3 Results

2.3.1 Shoulder Kinematics During Activities of Daily Living

In the coronal plane, SC ROM in hEDS was significantly lower in reaching across (hEDS: 14.0 ± 5.8; TD: 18.01 ± 7.8; p-value = 0.03) and higher reaching back (hEDS: 21.6 ± 8.5; TD: 16.8 ± 7.2; p-value = 0.02) compared to TD (Figure 2.7). In the transverse plane, GH ROM in hEDS was significantly higher in reaching across (hEDS: 119.6 ± 25.0; TD: 105.2 ± 26.6; p-value = 0.03) compared to TD. In the same transverse plane and task, ST ROM (hEDS: 18.6 ± 5.0; TD: 23.5 ± 6.0; p-value = 0.02) indicated lower value in hEDS compared to TD (Figure 2.7). Average ROM from 0-100% of reaching across the body (Figure 2.8), combing (Figure 2.9), reaching to back pocket (Figure 2.10), and drinking (Figure 2.11) were also plotted below.

![Graphs showing SC Down/Upward Rotation and SC Pro/Retraction ROM](image)

Figure 2.6: Range of motion group average and SD in SC joint during combing (C), drinking (D), reaching across the body (R-A) and reaching to back pocket (R-B) tasks. Red and blue indicates the hEDS and TD group respectively. SC ROM was significantly different in coronal plane during reach.
Figure 2.7: Range of motion group average and SD in AC, GH, and ST joints during combing (C), drinking (D), reaching across the body (R-A) and reaching to a back pocket (R-B) tasks in three planes of motion. Red and blue indicates the hEDS and TD group respectively. GH ROM (p-value=0.03), and ST ROM (p-value=0.02) in the transverse plane indicated significant differences between hEDS and TD in the reach across task.
Figure 2.8: 3-D group average profiles of SC, AC, GH, and ST joints during reaching across the body task in children with hEDS (Mean: Red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
Figure 2.9: 3-D group average profiles of SC, AC, GH, and ST joints during combing task in children with hEDS (Mean: Red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
Figure 2.10: 3-D group average profiles of SC, AC, GH, and ST joints during reaching back pocket task in children with hEDS (Mean: red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
Figure 2.11: 3-D group average profiles of SC, AC, GH, and ST joints during drinking task in children with hEDS (Mean: Red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
2.3.2 Shoulder Kinematics During Active Range of Motion

The results in SC joint during AROM indicated that during shoulder extension in hEDS (26.4 ± 11.0) was significantly higher compared to TD (14.1 ± 10.2; p-value < 0.001) ROM in coronal plane (Figure 2.12). During shoulder flexion, GH in ROM in transverse plane (hEDS: 160 ± 29.3; TD: 127.2 ± 59.1) and ST in sagittal plane (hEDS: 28.0 ± 8.5; TD: 14.3 ± 7.6) were significantly increased in hEDS (p-values < 0.001). Furthermore, during shoulder abduction, AC ROM (hEDS: 38.9 ± 8.6; TD: 28.0 ± 4.9; p-value < 0.001) and ST (hEDS: 52.3 ± 14.1; TD: 43.5 ± 12.1; p-value = 0.02) in transverse plane, ST (hEDS: 33.8 ± 11.3; TD: 20.8 ± 6.8; p-value < 0.001) in sagittal plane were significantly increased in children with hEDS. Finally, during shoulder extension, ST (hEDS: 14.8 ± 5.6; TD: 11.7 ± 1.4 ; p-value = 0.03) in coronal plane showed significant difference between hEDS and TD (ROM and peak values for all the tasks in coronal (Table 2.5), transverse (Table 2.6), and sagittal (Table 2.7) plane are shown in pages 43-45). 3-D group average profiles of SC, AC, GH, and ST joints during AROM can be found in chapter 7 (Appendix).

Figure 2.12: Range of motion group averages and SD in SC joint shoulder flexion (Flx), scaption (SCP), abduction (ABD) and extension (EXT). Red and blue indicates the hEDS and TD group respectively. SC ROM was significantly different in coronal plane during extension (p-value<0.001)
Figure 2.13: Range of motion group average in AC, GH, and ST joints during shoulder flexion (Flx), scaption (SCP), abduction (ABD) and extension (EXT) tasks in three planes of motion. During shoulder flexion GH in transverse plane and ST in sagittal plane were significantly different. During shoulder abduction, AC and ST in transverse plane, ST (p-value=0.00) in sagittal plane indicated significant differences. During shoulder extension, ST (p-value=0.03) in coronal plane showed significant difference.
Table 2.5: ROM and peak group averages (±1 SD) for each shoulder complex articulations in the coronal plane in hEDS and TD.

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Table 2.6: ROM and peak group averages (±1 SD) for each shoulder complex articulations in the transverse plane in hEDS and TD.

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Table 2.7: ROM and peak group averages (±1 SD) for each shoulder complex articulations in the sagittal plane in hEDS and TD.

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2.3.3 Scapulohumeral Rhythm

Multiple linear regressions between GH elevation and ST upward rotation were calculated for different tasks in the coronal plane (Table 2.8). The coefficients of each model indicated the ratio of GH elevation with respect to ST upward rotation (Figure 2.14). Adjusted $R^2$ results showed higher than 90% and strong correlation between dependent and independent variables for all regressions, except reaching back ($R^2=64$; moderate correlation) and shoulder extension ($R^2=79$; 

**Scapulohumeral Rhythm in the Coronal Plane**

![Figure 2.14: (A) Scapulohumeral rhythm as the relative angle of GH elevation to ST upward rotation (B) and GH flexion to ST posterior tilt (C) during shoulder scaption. Red line shows the linear regression of hEDS, and blue indicates TD group. Both regressions show:](image)

- **hEDS**: $+1.23x + 38.65$ ($R^2 = 0.94$)  
  (Equation 2-1)
- **TD**: $0.92x + 17.95$ ($R^2 = 0.97$)  
  (Equation 2-2)
moderate/strong correlation). The SHR in hEDS was 23% higher in children with hEDS compared to TD children (Table 2.8). Higher SHR indicates that the ratio of GH elevation to ST upward rotation is 1.23:1 in hEDS and 0.92:1 in TD during elevation. SHR during drinking in both groups was 1.52 in hEDS and 1.24 in TD, respectively. Except for reaching back, all the movement indicated less scapular upward rotation compared to GH in hEDS vs. TD (higher SHR).

### 2.3.4 Three-Dimensional Arm Workspace

| Plane of motion                    | SHR~Coeff × \(
\frac{GH}{ST}\) + intercept |
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<td>hEDS: +1.52x + 43.32, Adjusted (R^2) = 0.99</td>
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</tr>
<tr>
<td>Shoulder Flexion</td>
<td>hEDS: +1.13x + 19.87, Adjusted (R^2) = 0.98</td>
</tr>
<tr>
<td>Shoulder Extension</td>
<td>hEDS: −0.79x + 10.95, Adjusted (R^2) = 0.79</td>
</tr>
</tbody>
</table>

Table 2.8: Linear regression models for the SHR in coronal plane during the tasks that contains shoulder elevation. Negative coefficient in reach back and shoulder extension indicates the anterior tilt in scapula.

Ten children with hEDS and 18 TD children were analyzed to calculate the concatenated matrix of flexion, scaption, abduction, and extension (3×404) for five trials per task. Relative surface area (RSA) for hEDS and TD was calculated separately. The results indicated greater RSA for hEDS (0.79 ± 0.21) compared to TD (0.65 ± 0.28) children (Figure 2.15). Therefore, children with hEDS indicated a greater reachable workspace during AROM in shoulder elevation.
Discussion

In this chapter, it was demonstrated that the 3-D kinematics of the shoulder complex, including SC, AC, GH, and ST, during the ADLs of combing, drinking, reaching to back pocket, and reaching across, and during AROM, such as shoulder elevation during flexion, abduction, extension, scaption, and shoulder internal and external rotation in 0 and 90 degrees of abduction. The SHR and reachable workspace were analyzed to investigate the possible limitation of shoulder function during different activities.

A significantly different pattern in SC, GH, and ST was observed during reaching across the body and reaching to back pocket tasks. Also, the results revealed an increased ROM in AC joint during all the ADL tasks, which may have influenced the significant changes observed in SC, GH, and ST. During shoulder elevation, motions at the SC and AC joints contribute to ST motion through mechanical coupling. Therefore, any alteration in those two joints would affect the ST joint and eventually GH elevation [158, 159].

Figure 2.15: Reachable workspace for subject 18 as an example based on the hand trajectories (mm). The table shows the average and standard deviation of relative surface areas (RSA) for hEDS and TD groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>RSA [0,1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>hEDS</td>
<td>0.79 (0.21)</td>
</tr>
<tr>
<td>TD</td>
<td>0.65 (0.28)</td>
</tr>
</tbody>
</table>
Reaching across and combing tasks required the most ROM contribution from all joints. Results for combing and drinking showed no significant difference between TD and hEDS. However, that does not mean the same shoulder pattern in both groups. Some studies showed that even small kinematic differences in scapular kinematics can be associated with shoulder malfunction and decreased subacromial clearance [160-162]. Due to the limited studies on shoulder kinematics in children with hEDS, the results of this study could not be thoroughly compared with current literature. However, excessive GH extension reduced ST rotation and increased AC ROM was in line with previous studies on adults with hypermobility [94, 163].

The SHR results indicated higher SHR in hEDS, indicating higher GH elevation than ST upward rotation than TD (Table 2.8). According to these results, except for the combing task, the hypothesis for aim 1 can be partially accepted that the hEDS group shows less scapular rotation during GH elevation than TD. This difference may indicate scapular dysfunction due to muscle imbalance or weakness or a response to shoulder instability in children with hEDS [91]. Lastly, results from AROM tasks showed increased reachable workspace in hEDS compared to the TD group. Higher observed relative surface area might cause further shoulder pathologies due to excessive ROM affecting joint articulations and their surrounding connective tissues [164].

This study has several limitations that should be considered in interpreting the results. First, gimble lock (GL) is one of the drawbacks of using rotation sequences to calculate joint angles, making it challenging to obtain an accurate interpretation of shoulder angles [165, 166]. One of the limitations of this study was to exclude the trials with GL, which may have influenced the final comparison between the two groups.

Second, the participants self-selected the velocity in all tasks in ADL and AROM. Although this would help to understand the nature of the individual movement pattern, it may make it difficult
to interpret and average the results for each group. For instance, some participants elevated their arms during combing while having GH extended, and others had their GH closer to flexion in the sagittal plane (Figure 2.9). Therefore, caution should be considered while interpreting the tasks, and note that differences are rooted in an individual’s preferred method of executing the task.

Lastly, some of the combing trials had higher ROM during elevation than the maximum AROM tasks such as shoulder flexion, abduction, and scaption. Since the range of motion tasks were not constrained and self-selected, higher values in ADLs may indicate that the hEDS group could reach a higher range of motion under different circumstances. For future studies, it would be helpful to also look at the passive range of motion in each plane of elevation to better understand the possible excessive ROM in hEDS.

This chapter aimed to characterize shoulder complex kinematics differences in the hEDS and TD groups. Different movement patterns were observed, specifically in SC, AC, and ST joints during elevation. Previous studies showed significantly lower shoulder function, increased pain intensity, and reduced physical activities in hEDS compared with controls [81]. These findings could provide new insights into characteristics of hEDS shoulder function and help the clinicians investigate more accurate and effective rehabilitation and physical therapy exercises aligned with the nature of shoulder function in this group.
Chapter 3: Evaluation of Lower Extremity Joint Dynamics and Muscle Activations During Self-Selected Walking: Comparison of Children with Hypermobile Ehlers-Danlos Syndrome and Typically Developing Children

3.1 Introduction

Clinicians and researchers have utilized gait analysis to characterize pathological walking, integrating joint kinematics, kinetics, and muscle activations to understand deficits in the musculoskeletal system. In complex gait disorders, quantifying altered walking patterns in children with lower extremity deficiencies enables us to identify gait abnormalities and compensatory mechanisms to prevent future or current injuries and pain. Individuals with hEDS frequently complain about their modifications or restrictions to activities such as walking to avoid recurrent injury and pain [15, 50, 58, 167]. 3-D gait analysis has previously been used to evaluate joint dynamic patterns in individuals with hypermobility [17, 63, 99-102, 131, 134, 168, 169]. However, the results of these studies are not consistent, and they do not come to a collective understanding of walking patterns in the presence of hypermobility. Moreover, according to a recent review and gait analysis evaluation in individuals with hypermobility, research on the hEDS group had poor or moderate reliability in reported gait results [125].

While some studies have shown significant differences in gait kinematics and kinetics [17, 101, 128], others reported no significant differences in joint dynamics between the EDS and healthy groups [102, 135, 169]. Lower gait speed, shorter strides, and a greater percentage of time in stance were also observed [134]. It should be noted that the majority of studies focused on adults with hEDS, and there is limited literature on gait biomechanics of children with JHS or hEDS.
Increased knee extension and reduced knee flexion in children with JHS have been reported in two studies [63, 99]. Knee flexion during loading response increases with higher walking speed was also discussed. Following the results from [99], Roumbaut et al. suggested that muscle weakness could be a reason for this reduction in knee flexion [41]. Furthermore, it may be due to the significantly higher pain perception that children with hEDS have compared to healthy children. Impaired proprioception could also cause the patients to move their segments and joints outside of their standard and normal range of motion [133].

In 2021, Bates et al. compared sagittal kinematics and kinetics of gait and stair climbing between hypermobile and noon-hypermobile adults [135]. They showed no significant difference between the kinematics in GJH and JHS compared to healthy adults in the sagittal plane. This finding contrasted with the previous studies [17, 99, 131].

Alteration in lower extremity muscle activation and strength has been reported in the literature for individuals with hypermobility [61, 132, 134, 168, 170, 171]. The primary causality of this alteration is still unknown; however, some studies reported the deficits in force transmission through the muscles due to ligament laxity [132, 170, 172]. For the first time, a study showed significant different muscle-tendon units in hEDS patients [132], which may also affect the result of kinematic and kinetic equilibrium in lower extremity joints during walking.

In a recent and one of the first studies on lower extremity muscle activation patterns in adults with hEDS, the principal component of muscles indicated higher muscle activity for rectus femoris, lower for medial gastrocnemius, and no significant difference in tibialis anterior and hamstring muscles [134]. Results from EMG analysis in children with hEDS indicated increased muscle coactivation compared to healthy individuals [131, 171]. Compared to healthy adults, a decrease in muscle strength in the hamstrings and quadriceps has been observed in patients with hEDS over
time [168]. Significantly less muscle strength in the knee extensor and flexor muscles was reported for adult women with hEDS. Moreover, muscle fatigue and pain were reported, especially in ankle and knee joints [132]. While there are limited studies on the quantification of muscle activity in adults with hEDS, to the author’s knowledge, a comprehensive study of muscle activations is still lacking in children with hEDS during walking.

Although limited biomechanics research of hEDS joint mobility has been focused primarily on walking [17, 63, 99-101, 127-131], there is no conclusive evidence that hypermobile gait varies from normal walking in a consistent pattern. In addition, the association of joint pain (as one of the most important symptoms) and gait pattern has not been addressed in hypermobile gait studies [125]. In general, limited 3-D kinematics and kinetics analysis, and muscle activation strength and duration measures, specifically in the pediatric population, showed a need to characterize mentioned parameters in children with hEDS during gait. The first hypothesis was that the gait pattern of ankle and knee dynamics was significantly altered in children with hEDS compared to TD. Second, It was hypothesized that weakness and increased co-activation in the lower extremity muscle, especially in the hamstring and gastrocnemius, exist during walking. Finally, in the third hypothesis in this chapter, an altered pattern of hip angles was also expected in the sagittal plane due to compensatory movements.

To accomplish these aims and investigate the mentioned hypothesis, SPM was used to compare gait metrics between hEDS and TD children. Analyzing gait data by a discrete approach has been shown to possibly compromise the spatiotemporal integrity of the original fields [141, 173]. Nevertheless, SPM has been widely used in biomechanics healthy and pathological analysis and has shown promising results in understanding gait characteristics [173-179].
3.2 Methods

3.2.1 Participants

In total, twenty-one (21) children with hEDS/HSD were recruited by the Genetics Center of Children’s Wisconsin. The specific diagnosis and demographics are listed in Table 3.1. Nine children were diagnosed with hEDS, four with HSD, and five did not have an apparent phenotype for HSD or hEDS; therefore, they were considered hEDS/HSD. Nineteen (19) TD children were recruited with no prior history of lower extremity hypermobility, injury, or walking deficits (Table 3.2). The Beighton score, as a generalized measure of hypermobility, was obtained in TD children.

Table 3.1: Demographics of children with hEDS/HSD

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Age</th>
<th>BMI</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>#01</td>
<td>hEDS</td>
<td>16.4</td>
<td>27.6</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#02</td>
<td>hEDS</td>
<td>12.6</td>
<td>38.1</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#03*</td>
<td>hEDS</td>
<td>14.7</td>
<td>23.7</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#04</td>
<td>hEDS / HSD</td>
<td>11.6</td>
<td>22.4</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#05</td>
<td>hEDS</td>
<td>16.5</td>
<td>18.3</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#06</td>
<td>hEDS / HSD</td>
<td>17.2</td>
<td>19.9</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#07</td>
<td>hEDS / HSD</td>
<td>17.2</td>
<td>18.5</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#08</td>
<td>hEDS</td>
<td>9.4</td>
<td>16.6</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#09**</td>
<td>hEDS</td>
<td>8.0</td>
<td>N/A</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#10**</td>
<td>hEDS</td>
<td>12</td>
<td>N/A</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#11</td>
<td>HSD</td>
<td>14.8</td>
<td>17.8</td>
<td>M</td>
<td>Do not wish to report</td>
</tr>
<tr>
<td>#12</td>
<td>hEDS</td>
<td>15.0</td>
<td>23.2</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#13</td>
<td>HSD</td>
<td>15.1</td>
<td>29.7</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#14</td>
<td>HSD</td>
<td>12.1</td>
<td>20.2</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#15</td>
<td>HSD</td>
<td>16.4</td>
<td>18.8</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#16</td>
<td>hEDS</td>
<td>8.6</td>
<td>22.3</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#17</td>
<td>hEDS / HSD</td>
<td>16.2</td>
<td>19.0</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#18</td>
<td>hEDS</td>
<td>16.8</td>
<td>18.5</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#19</td>
<td>hEDS / HSD</td>
<td>15.0</td>
<td>18.4</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#20</td>
<td>hEDS</td>
<td>9.3</td>
<td>18.6</td>
<td>M</td>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>#21</td>
<td>hEDS</td>
<td>11.6</td>
<td>15.5</td>
<td>F</td>
<td>Hispanic or Latino</td>
</tr>
</tbody>
</table>

N= 18  hEDS: 9  HSD: 4  hEDS/HSD: 5  Mean: 13.6  SD: 3.1  Mean: 21.3  SD: 5.9  M: 5  F: 13  Hispanic: 2  Non-Hispanic: 15  N/A: 1
All TD children showed Beighton scores less than four, indicating normal ROM. Subject 8’s analysis was different from the rest of the TD children due to motor control impairments and did not meet the criteria for the control group. Therefore, subject 8 was excluded from the analysis and group averages.

### 3.2.2 Data Collection Protocol

The present study was conducted in the UWM Mobility laboratory located at the UWM Innovation Campus and was approved by the University’s Institutional Review Board separately for hEDS and TD. Assent and/or consent forms were obtained prior to any study activities at the first testing visit. Subject-specific measurements such as body weight, height, leg length, knee width, and ankle width were measured. Marker trajectories were captured via a 15-camera Vicon T-Series Motion Table.
Analysis System (Oxford Metric Group, Oxford, UK) at a 120 Hz sampling rate. An infrared wand was used to calibrate and sync all 15 cameras in the motion capture system to obtain a global coordinate system for data collection (Figure 3.1). Four force platforms (© Advanced Mechanical Technology, Inc., Watertown, MA) were used to collect GRFs and set to zero before data collection.

Newington-Helen Hayes marker set was applied to the subjects on their bony landmarks to capture lower body movements during gait [1]. A standardized placement protocol was followed, and to reduce human error [180], all markers were placed by the same person (Anahita Qashqai). Prior to the dynamic trials, a static trial was conducted with knee alignment devices (KADs) positioned on the knee to calculate joint centers and define the knee local coordinate system [181]. Previous

Figure 3.1: General coordinate system in laboratory; z-axis: pointed vertically while moving upward considered positive and downward negative. The global Z axis was defined perpendicular to the lab floor. x-axis and y-axis were perpendicular.
studies showed that using KAD would increase the accuracy of direct movement of the bone up to 40% due to less soft tissue lying between the patella marker and the bone [182]. Therefore, a patellar marker was used instead of a thigh marker.

Instructions were provided, and subjects were asked to walk at self-selected free speed. All children walked barefoot and with no assistive devices. Subjects were asked to walk along a 7 m walkway with four embedded force plates. The force plates were used to determine initial contact, and toe-off was determined using the method proposed by O’Connor et al. [183]. Various phases of the gait cycle, consisting of stance, swing, pre-swing, double support, and single support, were defined for the right and left legs. Simultaneously, muscle activity of the dominant side was passively recorded using 16-channel Delsys Tringo wireless EMG system at a sampling rate of 2000 Hz to investigate muscle firing patterns, including on/off timing, amplitude, and relative level of contraction. EMGs were recorded using a sensor with the four silver bar electrodes and an integrated amplifier. The subject’s skin was prepared using abrasive gel and cleaned using isopropyl alcohol to lower skin impedance. Lower extremity muscles of interest included Rectus Femoris (RF), Medial Hamstrings (MH), Medial Gastrocnemius (MG), and Tibialis Anterior (TA). EMG sensors were located on the belly of the muscles at a position distant from the innervation zones and the muscle-tendon interfaces, following the recommendations of [184].
Data Processing and Statistical Analysis

The Nexus 2.10.1 software was used to label and process the marker trajectories exported to MATLAB by a Vicon-Matlab interaction. A custom Matlab code was used to process, normalize, and evaluate gait metrics. The average walking speed for each trial was measured, and the trials were ranked based on the lowest difference from the average to control speed consistency for each subject. Each side's top five limb strides were selected, from foot strike to ipsilateral foot strike. The Vicon plug-in gait lower extremity model computed 3-D ankle, knee, hip, and pelvis joint angles. Throughout each task, all joint angles were calculated bilaterally in 3-D (sagittal, frontal, and transverse). All lower body angles were calculated in rotation order YXZ except for ankle angles, which are calculated in order YZX (Table 3.4).

Figure 3.2: Representation of a subject with Newington-Helen Hayes marker set [1]. Three-dimensional prospective of lower extremity static trial with KAD markers are shown. After the static trial, KADs were replaced with the knee markers on right and left sides. There
3.2.3.1 Lower Extremity Gait Measures

Walking speed was calculated based on the stride length divided by stride time in Vicon Software. Stride length was defined as the distance between the proximal end of the foot at the initial strike and the proximal end of the foot at the next consecutive ipsilateral initial contact (IC). Stride time was defined as the total time from IC to consecutive ipsilateral IC. Foot contacts events were computed using GRFs for each walking trial. If GRFs could not predict ICs, the lowest z position of heel, ankle, or toe markers was chosen.

Gap filling, Spline Fill, and Pattern Fill functions in Vicon Nexus were used to fill the marker trajectory gaps. After making sure all markers were labeled with no gaps, a Woltring filter [185] with a mean squared error of 10 was applied to the position data, which is standard filtering in
pediatric literature [186, 187]. In the next step, analog data such as GRFs were filtered with Butterworth low pass fourth-order (zero-lag) with a cut-off at 300 Hz [188]. Gait events were detected after filtering the analog data with the force threshold of 20. The second method to verify the initial contact was based on left or right toe, heel, and ankle markers. Finally, the dynamic plug-in gait model [181] was applied through Vicon Software to calculate joint dynamics in ankle, knee, hip, and pelvis (Figure 3.3). In the last step, subject model outputs were filtered using a low-pass digital fourth-order (zero-lag) with a cut-off at 6 Hz. The last filter is by default setup in Vicon Software, as recommended by Winter [189], to filter out signal noise above 6 Hz using a fourth-order filter with zero-lag.

Time series gait data was exported to Matlab software, where cropping the gait data for each stride was calculated. Data from each stride were normalized to 101 data points representing 0–100% of the gait cycle, with 0% representing initial contact (IC) and 100% representing IC of the same foot in the next stride. Kinetic parameters were normalized to each participant’s body weight to eliminate the weight bias.

3.2.3.2 EMG Analysis and parameter calculations

Raw EMG data was exported to Matlab software and resampled based on the motion data frequency. Signal to noise ratio was calculated for each trial [190]. The EMG were low pass filtered (cut-off = 5 Hz), rectified, and high pass filtered (cut-off = 500 Hz).
“On” muscle activation was defined based on the average value of EMG in a given window range around two standard deviations above resting EMG [191]. Low pass filtering was used over RMS due to the possible shifts in onset depending on the length of the time window for computing the moving averages [192, 193]. Each signal was also time normalized to the gait cycle. Separately, Onset/offset time instants are normalized with respect to gait cycle duration to provide mean activation intervals as a percentage of the gait cycle. Additionally, to measure the antagonist co-contraction ratio, the duration of co-activations were obtained between the rectus femoris (RF) and semitendinosus (ST), and tibialis anterior (TA) and medial gastrocnemius (MG).
3.2.3.3 Statistics Analysis

Matlab (The Mathworks Inc., Natick, M.A., 2021) Statistics and Machine Learning Toolbox was used for statistical analysis of spatio-temporal parameters. Shapiro–Wilk tests were applied to assess data normal distribution to apply the appropriate statistical testing for spatio-temporal parameters and EMG measures (Parametric vs. Non-parametric). SPM (SPM1d version 0.4) in MATLAB. Normality of the data was assessed with a build-in function in SPM. Kinematics and kinetics were analyzed using the spm1d Version 0.4 for the 1-D SPM analysis software package for Matlab [141]. A two-sample non-parametric Hotelling’s T2 test (SnPM{T2}) was applied to evaluate differences in joint angles, moments, and powers. Iterations of 10000 were used in all SnPM tests. As discussed in the introduction, the key con of SPM is that statistical findings are displayed in the original sample space and that no (possibly biased) parameterization approach is required.
3.3 Results

3.3.1 Spatio-Temporal Parameters

Based on the Shapiro-Wilk test, seven spatiotemporal parameters were quantified and checked for data normality. The mean and standard deviation for each variable were calculated. Results from the Shapiro-Wilk test indicated that cadence, walking speed, step time, and step width in the hEDS group were not normally distributed.

Table 3.5: Spatiotemporal Parameter for hEDS and TD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>hEDS</th>
<th>Typically Developing</th>
<th>Mann–Whitney U test</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Shapiro-Wilk test (p-value)</td>
<td>Mean (SD)</td>
<td>Shapiro-Wilk Test (p-value)</td>
</tr>
<tr>
<td>Cadence (step/min)</td>
<td>112.1 (22.42)</td>
<td>0.04*</td>
<td>119.87 (8.39)</td>
<td>0.98</td>
</tr>
<tr>
<td>Walking Speed (m/s)</td>
<td>1.20 (0.14)</td>
<td>0.01*</td>
<td>1.27 (0.16)</td>
<td>0.86</td>
</tr>
<tr>
<td>Step Time (s)</td>
<td>0.51 (0.05)</td>
<td>0.01*</td>
<td>0.50 (0.04)</td>
<td>0.47</td>
</tr>
<tr>
<td>Foot Off (%)</td>
<td>59.91 (1.80)</td>
<td>0.20</td>
<td>59.02 (1.18)</td>
<td>0.81</td>
</tr>
<tr>
<td>Opposite Foot Off (%)</td>
<td>50.72 (1.01)</td>
<td>0.068</td>
<td>50.33 (0.05)</td>
<td>0.98</td>
</tr>
<tr>
<td>Step Length (m)</td>
<td>0.61 (0.05)</td>
<td>0.31</td>
<td>0.64 (0.07)</td>
<td>0.64</td>
</tr>
<tr>
<td>Step Width (m)</td>
<td>0.10 (0.02)</td>
<td>0.03*</td>
<td>0.12 (0.03)</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Figure 3.4: Distribution of spatio-temporal measures between hEDS and TD; The range and number of outliers are shown below each bar plot. Red circles indicate 18 hEDS participants’ data, and blue circles shows TD children data. Cadence, walking speed, step time, foot off, opposite foot off, step length, and step width were analyzed between two groups separately.
3.3.2 Lower Extremity Angles, Moments, and Powers

Differences in joint angles, moments, and powers were not statistically significant between hEDS and TD children, except for the ankle angles in sagittal, frontal, and transverse planes. Foot progression results showed no significant results (Figure 3.5). However, more external rotation was observed in the hEDS group. The average ankle angle in the transverse plane in children with hEDS was shifted towards ankle adduction compared to TD children. The critical t-statistics = 2.300 was exceeded at time 59% (toe-off) with a probability value of p=0.044, indicating that hEDS had significantly greater ankle adduction in the transverse plane during toe-off and early swing than the TD children. SnPM results for ankle angle in the sagittal plane showed a significantly more plantarflexed position in hEDS at the beginning of the gait cycle. Lastly, comparisons between ankle joints in the frontal plane showed a more inverted angle in hEDS from 57% to 68% of the gait cycle, which is in the transition from stance to swing phase.

Figure 3.5: Foot progression angle during the gait cycle. Each line represents the average of trials within the corresponding group.
Ankle Joint Kinematics in Sagittal, Coronal, and Transverse Plane

Figure 3.6: 3-D ankle rotations during the gait cycle. Each line represents the average of trials within the corresponding group. SnPM indicated significant results in all planes of motion for ankle angle.
Ankle Joint Moment in Sagittal Plane and Ankle Power

Figure 3.7: Ankle joint moment and power. Sagittal plane joint moments are shown. Each line represents the average of trials within the corresponding group. No significant results were observed for ankle moment and power in hEDS compared to TD.
Knee Joint Kinematics in Sagittal, Coronal, and Transverse Plane

Figure 3.8: 3-D knee rotations during the gait cycle. Each line represents the average of trials within the corresponding group. SnPM indicated no significant results in all planes of motion for the knee joint.
Knee Joint Moments in Sagittal and Coronal Planes and Knee Power

Figure 3.9: Knee joint moments and power during the gait cycle. Results from coronal and sagittal plane are shown. Each line represents the average of trials within the corresponding group. Knee power was significantly greater in transition from stance to swing phase.
Figure 3.10: 3-D hip rotations during the gait cycle. Each line represents the average of trials within the corresponding group. SnPM indicated no significant results in all planes of motion for the hip joint.
Figure 3.11: Hip joint moments and power during the gait cycle. Coronal and sagittal planes are shown. Each line represents the average of trials within the corresponding group.
Pelvis Kinematics in Sagittal, Coronal, and Transverse Plane

Figure 3.12: 3-D pelvis rotations during the gait cycle. Each line represents the average of trials within the corresponding group. SnPM indicated no significant results in all planes of motion for the pelvis.
To sum up the kinematic and kinetic results, the ankle indicated significant results in all three planes of motion (Figure 3.6). In early stance, ankle plantar flexion increased in hEDS compared to TD (p-value = 0.01). In the frontal plane, at the end of stance and early swing, the ankle in the hEDS group indicated more inverted compared to TD (p-value < 0.001). Finally, during adduction/abduction, the ankle was significantly more adducted in hEDS (p-value = 0.04).

All of the moment and powers showed no significant differences between hEDS and TD except for knee power. Moreover, results from knee power indicated less absorption in the late stance and early swing in the hEDS group (Figure 3.9).

3.3.3 Lower Extremity Muscle Activations During Gait

To analyze duration of co-activation for TA/MG, their superimpositions were observed during early stance from 17.2 ± 4.1% to 19.2 ± 8.5% of gait cycle for TD, and from 23.5 ± 5.9% to 27.0 ± 4.6% of gait cycle for hEDS (Figure 3.13). Co-activation between semitendinosus and rectus femoris happened during three points in the gait cycle; early stance (hEDS: 0% to 18.3 ± 7.7%; TD: 0% to 16.2 ± 4.1%), and two points during the swing phase (hEDS: 70.9 ± 9.1% to 83.4 ± 6.7%, TD: 81.1 ± 5.9% to 86.2 ± 7.3%; hEDS: 97.4 ± 3.1% to 100.0 ± 0.0%, TD: 93.0 ± 4.1% to 100.0 ± 0.0%). hEDS showed significantly longer co-activation between ST and RF during the swing phase (p-value < 0.001).

All muscles indicated significantly higher relative max amplitude during walking in hEDS compared to TD (p-value < 0.001). However, in analyzing absolute max values, significantly less

<table>
<thead>
<tr>
<th>Significant Gait Measures</th>
<th>Gait Percentage (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle Plantar/Dorsi Flexion</td>
<td>8-13% (p-value=0.01)</td>
</tr>
<tr>
<td>Ankle Eversion/Inversion</td>
<td>67-68% (p-value&lt;0.001)</td>
</tr>
<tr>
<td>Ankle Adduction/Abduction</td>
<td>59-65% (p-value=0.04)</td>
</tr>
<tr>
<td>Knee Power</td>
<td>56-59% (p-value=0.01)</td>
</tr>
</tbody>
</table>
amplitude was observed, except for medial gastrocnemius (hEDS: 109.5 ± 75.2 µv; TD: 106.8 ± 42.8 µv).

Table 3.7: EMG mean and SD for relative and absolute maximum amplitude of muscle activations during 100% of gait cycle

<table>
<thead>
<tr>
<th>Muscles</th>
<th>Relative Max Amplitude (%)</th>
<th>Absolute Max Amplitude (µv)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hEDS</td>
<td>TD</td>
</tr>
<tr>
<td>Rectus Femoris</td>
<td>34.2 (17.6)</td>
<td>22.3 (10.9)</td>
</tr>
<tr>
<td>Semitendinosus</td>
<td>44.4 (19.3)</td>
<td>30.9 (12.1)</td>
</tr>
<tr>
<td>Medial Gastrocnemius</td>
<td>42.9 (27.3)</td>
<td>26.5 (13.8)</td>
</tr>
<tr>
<td>Tibialis Anterior</td>
<td>50.3 (13.4)</td>
<td>36.6 (14.7)</td>
</tr>
</tbody>
</table>

Figure 3.13: Muscle activation duration the gait cycle for TA, MG, ST, and RF. Dashed red and blue windows are showing the co-contraction window for agonist and antagonist muscles for hEDS and TD respectively.
3.4 Discussion

Potential differences in ankle biomechanics during walking were observed that may be related to ankle joint instability reported in the hEDS population. Although normalized muscle activation was higher in hEDS, the maximum amplitude of EMG was significantly lower across all the muscles. Higher relative activation and lower value of EMG amplitude may contribute to excessive fatigue reported in the hEDS population. Previous results suggested a positive and direct relationship between the occurrence and intensity of fatigue and muscle weakness in adults with EDS with musculoskeletal complaints [61, 62]. Future research should focus on the relationship between fatigue, muscle weakness, and objectively measured physical activity, preferably in a larger cohort of EDS patients. However, the association between EMG activation and fatigue in children with hEDS should be investigated in future studies.

There are certain limitations to the study that should be noted. The relatively rare prevalence of hEDS resulted in a smaller sample size. To maximize recruitment, the hEDS group had a large age range (8 to 18 years). It is unclear how gait changes as patients with hEDS age, which may have impacted the findings.

Due to the exploratory nature of this study, a power analysis was applied based on the effect sizes of all the measured metrics. Because of the lack of literature on children with hEDS, it was not feasible to calculate an accurate power. Another limitation was the difficulties of recruitment in this population. However, based on the data from the literature, a power analysis was done using G*Power software (3.1.9.7) on some of the joint kinematics and kinetics metrics [194]. Based on the effect size of 1.5 in the peak knee moment, a sample size of 8 per group at (a) 0.05, with 80% power (1- β) was calculated. Previously, a sample size of 7 was determined for the ankle power
absorption with an effect size of 1.72 and power of 82%. Peak hip extension with the effect size of 0.97 had 83% power and a sample size of 20 for each group.

In this study, non-parametric statistics were used to compare different measures between the two groups. The main difference is that non-parametric Probability Density Functions (PDF) generally do not make assumptions regarding the distribution from which data are drawn and instead build the test statistic PDF empirically, directly from experimental data. Moreover, non-parametric procedures are generally much slower because they build randomness models iteratively based on experimental data.

In the study protocol, the author had two rationales not to collect maximum voluntary contraction (MVC) for normalization [140]. First, for this population, where fatigue is a big issue, MVC testing on the day of data collection will affect the data quality. Secondly, maximum dynamic activation does not always happen with MVC. It may end up that the amplitude of the EMG during activity, especially at a fast speed, surpasses the normalized parameter and has more than 100% activation. The EMG signals were normalized to the subject’s fastest speed for these two specific reasons.

Another possible limitation was the presence of skin laxity and its effect on the accuracy of motion capture techniques to obtain markers’ positions. Bates et al. showed that, except for the pelvis, sagittal plane angles had the most reliable results in terms of variability [105]. This study suggests that sagittal plane joint angles indicated the most promise in differentiating between cohorts and measuring the change in gait following an intervention. As discussed in the introduction, the present studies were somewhat controversial, and there has been no general agreement on the alteration of gait patterns in children with hEDS. Understanding gait patterns in children with hEDS may identify contributors to joint instability during functional activities. These findings
could ultimately help prevent lower extremity injuries and better treatment planning. In addition, this study could fill the gap in the literature for understanding the gait pattern of hEDS in pediatrics.

In conclusion, three main takeaways of this chapter are summarized below:

1. Alteration in ankle angles in all three planes of motions while no other significant changes in the rest of the kinematic measures may be associated with a high prevalence of ankle pain and dislocation.

2. Knee power absorption was significantly lower in children with hEDS. Knee absorption has a key role in smoothing gait movements.

3. Higher relative activation of muscles and co-contractions in hEDS, while having significantly lower absolute values of EMG amplitude, may indicate muscle weakness.
Chapter 4: Comparison of Joint Dynamics Alterations During Different Walking Speeds in Children with hEDS and Typically Developing Children

4.1 Introduction

The influence of speed on gait characterization is undeniable. Previous research has shown that spatio-temporal parameters, joint angles, GRFs, moments and powers at the joints, and muscle activation patterns are significantly related to the walking speed [137, 140, 177, 195-197]. Multiple studies reported that speed is the primary parameter in the dynamic gait analysis, not age or sex [138, 139]. All three planes of motion have shown a significant change in kinematic and kinetic data with changes in speed [137]. In terms of muscle activity, the magnitude of the signal change and the pattern of muscle activation was also altered [198, 199].

In addition, speed should be considered not only as a key contributor to gait dynamics but also as a requirement for stability [140]. For example, an increase in EMG amplitude during fast walking compared to free speed walking can indicate the balance and stability issues in the patients [200]. On the other hand, reduced walking speed would result in changes in locomotor task demands, which may eventually lead to alterations in the muscle activity patterns that support body stability and balance during walking [140, 199]. However, given the significance of speed on walking pattern and stability, most studies, especially those pertaining to pathologic gait analysis, have focused on a single self-selected or free speed to report gait characteristics [53, 138, 181, 187, 189, 201-203].

A considerable amount of literature has been published on the significant effects of speed change on lower extremity joints, muscle coordination, and variation of joint angles and moments in
healthy children [137, 140, 178, 197-199, 204-206] and children with walking deficits [177, 195, 207-210]. Research on children with hEDS has been mostly limited to self-selected speed (i.e., free speed); however, it is critical to understand possible compensation strategies due to the coordination and stability deficits during speed changes [100]. One study showed an increased variation of spatio-temporal parameters in children with JHS at slower speeds compared to a control group [211]. In addition, proprioceptive deficits and difficulties in motor skills have been demonstrated in children with hEDS [119], which has been an important feature connected to the alteration of gait dynamics in various walking speeds [212].

Multiple studies consistently showed that knee joint proprioception was observed to be significantly worse in children with hEDS compared to the healthy control [119, 121, 122]. However, the reasons for the identified motor control and proprioception deficits are still not known. Fatoye et al. showed that the knee range of motion is dependent on the speed of walking in children with hypermobility syndrome and concluded that having a wide range of speed in gait analysis would help better the understanding of the gait pattern differences in this population [63]. While the previous research in hEDS and JHS suggested the necessity of studies on different gait speeds, to the author’s knowledge, there have been no comprehensive studies on gait dynamics investigating different speeds in children with hEDS.

Some studies suggested that proprioceptive impairments occur as a consequence of compromised structural integrity of connective tissue in individuals with hEDS [39, 120]. Additionally, the control deficit prevents patients from dictating the timing and intensity of muscle action, which can cause alteration in force transmission and musculoskeletal response in different gait phases [213]. In other words, it may be a significant challenge for a patient to activate a specific muscle group in different gait phases when changing the speed of walking.
The knee joint’s role during walking requires significant kinematic changes in case of speed alteration to accommodate the changes in spatio-temporal parameters and hip joint [214]. Increased knee extension and reduced knee flexion in children with JHS have been reported in two studies [63, 99]. They also discussed that knee flexion increases with higher walking speed during loading response. Therefore, it is likely that individuals with hypermobility have a different pattern during speed changes than the healthy population because of the knee deficits. Because the knee range of motion is dependent on the speed of walking, having a wide range of speed in gait analysis would help a better understanding of the gait patterns.

The central aim was to compare and characterize the joint dynamics changes during different walking speeds in children with hEDS to TD children. Since speed amplifies gait alterations, free self-selected, fast, and slow speeds during gait were obtained to evaluate the effect of speed on gait metrics. It was hypothesized that the children with hEDS have a different alteration in their gait pattern, especially in the knee and ankle angles, during slower and faster walking speeds compared to TD children.

4.2 Methods

4.2.1 Participants

Twenty-one (21) children with hEDS/HSD were recruited by the Genetics Center of Children’s Wisconsin. The specific diagnosis and demographics are listed in Table 4.1. Nine children were diagnosed with hEDS, four with HSD, and five did not have an apparent phenotype for HSD or hEDS; therefore, they were considered to be hEDS/HSD. Nineteen (19) TD children were recruited with no prior history of lower extremity hypermobility, injury, or any walking deficits (Table 4.2). The Beighton score, as a generalized measure of hypermobility, was obtained in TD children [149]. All TD children showed Beighton scores less than four, indicating normal ROM.
From the hEDS cohort, subjects 1 and 2 did not have fast-speed trials due to concerns for fatigue and pain. Subject 3 was excluded from the gait analysis due to losing the tibial marker on the dominant side. Finally, subjects 9 and 10 dropped out of the study due to severe health conditions after the first visit and were excluded. From the TD group, subject 8’s analysis was different from the rest of the TD children due to motor control impairments and did not meet the criteria for the control group.

Table 4.1: Demographics of children with hEDS/HSD.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Age</th>
<th>BMI</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>#01*</td>
<td>hEDS</td>
<td>16.4</td>
<td>27.6</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#02*</td>
<td>hEDS</td>
<td>12.6</td>
<td>38.1</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#03**</td>
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<td>14.7</td>
<td>23.7</td>
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<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#04</td>
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<td>22.4</td>
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</tr>
<tr>
<td>#05</td>
<td>hEDS</td>
<td>16.5</td>
<td>18.3</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#06</td>
<td>hEDS / HSD</td>
<td>17.2</td>
<td>19.9</td>
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</tr>
<tr>
<td>#07</td>
<td>hEDS / HSD</td>
<td>17.2</td>
<td>18.5</td>
<td>M</td>
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</tr>
<tr>
<td>#08</td>
<td>hEDS</td>
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<td>16.6</td>
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</tr>
<tr>
<td>#09***</td>
<td>hEDS</td>
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<tr>
<td>#10***</td>
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<td>N/A</td>
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<tr>
<td>#11</td>
<td>HSD</td>
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<td>17.8</td>
<td>M</td>
<td>Do not wish to report</td>
</tr>
<tr>
<td>#12</td>
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<td>15.0</td>
<td>23.2</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#13</td>
<td>HSD</td>
<td>15.1</td>
<td>29.7</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#14</td>
<td>HSD</td>
<td>12.1</td>
<td>20.2</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#15</td>
<td>HSD</td>
<td>16.4</td>
<td>18.8</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#16</td>
<td>hEDS</td>
<td>8.6</td>
<td>22.3</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#17</td>
<td>hEDS / HSD</td>
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<td>19.0</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#18</td>
<td>hEDS</td>
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<td>18.5</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
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<tr>
<td>#19</td>
<td>hEDS / HSD</td>
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<td>18.4</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#20</td>
<td>hEDS</td>
<td>9.3</td>
<td>18.6</td>
<td>M</td>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>#21</td>
<td>hEDS</td>
<td>11.6</td>
<td>15.5</td>
<td>F</td>
<td>Hispanic or Latino</td>
</tr>
</tbody>
</table>

N (Fast)= 16, hEDS: 9, Mean: 13.6, SD: 3.1, Hispanic: 2
N (Free)=18, HSD: 4, Mean: 21.3, SD: 5.9, Non-Hispanic: 15
N (Slow)=18, hEDS/HSD: 5, M: 5, F: 13, N/A: 1
4.2.2 Data Collection Protocol

Subjects were given verbal instruction for changes in walking speed and were not dictated with any metronome or device to keep a specific rhythm or speed. In addition, participants were given enough breaks between their different walking speed trials to reduce the effect of fatigue on their gait. Marker trajectories were captured via a 15-camera Vicon T-Series Motion Analysis System (Oxford Metric Group, Oxford, UK) at a 120 Hz sampling rate. After measuring anthropometric parameters required by the plug-in gait model, Newington-Helen Hayes marker set was applied to each subject on their bony landmarks to capture lower body movements during gait [1]. A standardized placement protocol was followed, and to reduce human error [180], all markers were
placed by the same person (Anahita Qashqai). Prior to the dynamic trials, a static trial was conducted with KADs positioned on the knee to calculate joint centers and define the knee local coordinate system [181].

All children walked barefoot and with no assistive devices. Subjects were asked to walk along a 7 m walkway with four force plates embedded. The force plates were used to determine initial contact, and toe-off was determined using the method proposed by O’Connor et al. [183]. First, instructions were provided, and subjects were asked to walk at free speed. Then, they were asked to walk as fast as possible, as if they were crossing the street in a hurry. Running trials were excluded from the analysis. Finally, participants were asked to walk slowly. When there were incidents of marker fall (more likely at higher speeds), the marker was replaced, and an additional static trial was captured to re-calibrate the subject.

4.2.3 Data Processing and Statistical Analysis

The Nexus 2.10.1 software was used to label and process the trajectories of each marker in the lower extremity, then exported to MATLAB by a Vicon-Matlab interaction code that was developed to calculate and export the 3-D gait variables. A Woltring filter [185] with a mean squared error of 10 was applied [186, 187]. Next, GRFs were filtered using a Butterworth low pass fourth-order (zero-lag) with a cut-off at 300 Hz [188]. Gait events were detected after filtering the analog data with the force threshold of 20. The second method to verify the initial contact was based on left and right toe, heel, and ankle markers. Finally, the dynamic plug-in gait model [181] was applied through Vicon Software to compute 3-D ankle, knee, hip, and pelvis joint angles. In the last step, subject model outputs were filtered using a low-pass digital fourth-order (zero-lag) with a cut-off at 6 Hz. This last filter is a default setup in Vicon Software used as Winter [189] recommended to filter out signal noise above 6 Hz using a fourth-order filter with zero-lag. All
lower body angles were calculated in rotation order YXZ except for ankle angles, which are calculated in order YZX. The five highest speed strides were selected for fast trials, and the lowest speed strides for slow trials. After selecting the trials for each participant, a customized Matlab code was used to process, time normalize, and evaluate gait metrics. A more detailed description of data acquisition and processing is given in chapter 3.

Matlab Statistics And Machine Learning Toolbox was used for statistical analysis. Histograms and Shapiro–Wilk tests were applied to assess normal data distribution. Kinematics, kinetics, and GRFs were analyzed using the spm1d Version 0.4 for the 1-D SPM analysis software package for Matlab [141]. Most variables did not have a normal distribution; therefore, non-parametric SPM analysis was used for all the comparisons. As it pertains to normality, parametric and non-parametric models have been validated to converge and have the same results [215].

Two separate repeated-measure Analysis of Variance (RM ANOVA) were used to analyze the effect of speed on each gait variable. Then, the F-statistic (SnPM \{F\}) was calculated at each point during the gait cycle. Next, three post-hoc two-tailed non-parametric t-statistics were calculated between each speed separately for the hEDS and TD groups. For these post-hoc comparisons, the SnPM{t} statistic was calculated for each between-speed comparison. (Fast vs. free, free vs. slow, fast vs. slow speed).
4.3 Results

Seven spatiotemporal parameters were quantified, and Kruskal–Wallis test was applied at different speeds to investigate the similarity of parameters. The Kruskal–Wallis test results indicated that except for step width and opposite foot contact, the rest of the spatio-temporal parameters were significantly different among all three speeds in hEDS and TD.

No spatio-temporal parameter was significantly different when comparing the two groups separately for each speed. While similar results were found between hEDS and TD spatio-temporal parameters across different speeds, there are some consistent differences in cadence, step time, and foot-off based on the walking speeds. Cadence indicated higher values in all three speeds in TD children. On the contrary, step time and foot-off values were increased in children with hEDS.

Table 4.3: Spatio-temporal parameters in hEDS and TD during three different speeds

<table>
<thead>
<tr>
<th>Parameters</th>
<th>hEDS</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast</td>
<td>Free</td>
</tr>
<tr>
<td>Cadence (step/min)</td>
<td>145.10 (28.5)</td>
<td>111.91 (22.1)</td>
</tr>
<tr>
<td>Walking Speed (m/s)</td>
<td>1.80 (0.20)</td>
<td>1.20 (0.15)</td>
</tr>
<tr>
<td>Step Time (s)</td>
<td>0.41 (0.04)</td>
<td>0.51 (0.05)</td>
</tr>
<tr>
<td>Foot Off (%)</td>
<td>57.61 (1.50)</td>
<td>59.46 (1.77)</td>
</tr>
<tr>
<td>Opposite Foot Off (%)</td>
<td>50.31 (0.76)</td>
<td>50.68 (1.03)</td>
</tr>
<tr>
<td>Step Length (m)</td>
<td>0.73 (0.11)</td>
<td>0.62 (0.06)</td>
</tr>
<tr>
<td>Step Width (m)</td>
<td>0.11 (0.02)</td>
<td>0.11 (0.02)</td>
</tr>
</tbody>
</table>
across fast, free, and slow speeds. In addition, the TD group showed a higher standard deviation in fast and slow speed, whereas hEDS indicated similar step width during increased and decreased speed change. Finally, a similar higher standard deviation was observed in opposite foot-off variables in hEDS and TD.

Results from RM ANOVA indicated significant changes in joint angle patterns across the different speeds. Speed changes significantly affected ankle plantar/dorsiflexion during walking. Post hoc analysis revealed significant differences in ankle angles during the transition of stance to swing and early-mid swing phase. Moreover, as the speed increased, ankle plantarflexion became significantly higher in late stance and push-off. The post-hoc results in the TD ankle pattern indicated significant results in push-off and early stance at the beginning of single-limb support across all speed changes. hEDS showed no significant differences in ankle plantarflexion in early stance between fast and free and free and slow speeds.
Figure 4.2: Box plots of spatio-temporal measures among different speeds between hEDS and TD; Red circles indicate 18 hEDS participants’ data (except for slow speed with 16 subjects), and blue circles shows TD children data. cadence, step time, foot off, opposite foot off, step length, and step width were analyzed among different speeds.
Figure 4.3: Ankle sagittal angle in three speeds in hEDS and TD. Blue, gray, and red lines are representing fast, free, and slow speed respectively. SD for each value is shown with shaded of the same color for each speed.

Figure 4.4: Repeated measure (RM) ANOVA SnPM(t) (a) and Post hoc analysis (b-d) in hEDS for (b) fast vs. free, (c) free vs. slow, and (d) fast vs. slow speeds. Significant differences were in transition of stance to swing, and early-mid swing phase in children with hEDS.
Figure 4.5: Repeated measure (RM) ANOVA SnPM(t) (a) and Post hoc analysis (b-d) in TD during walking speeds (b) fast vs. free, (c) free vs. slow, and (d) fast vs. slow for ankle angle in sagittal plane. The post hoc analysis indicated significant results in early stance and transition of stance to swing.
Figure 4.6: Knee flexion and extension in 3 speeds in hEDS and TD. Blue, gray, and red lines are representing fast, free, and slow speed respectively. SD for each value is shown with shaded of the same color for each speed.

Figure 4.7: Knee angle in sagittal plane. Repeated measure (RM) ANOVA SnPM{t} (a) and Post hoc analysis (b-d) in hEDS during walking speeds (b) fast vs. free, (c) free vs. slow, and (d) fast vs. slow. The post hoc analysis indicated significant results in early swing.
Figure 4.8: Repeated measure (RM) ANOVA SnPM(t) results for knee angles in TD children. (a) and Post hoc analysis (b-d) in TD during walking speeds (b) fast vs. free, (c) free vs. slow, and (d) fast vs. slow for knee angle in sagittal plane. The post hoc analysis indicated significant results in early stance for fast vs. slow and free vs. slow, in transition of stance to swing for all speed comparisons, and in late swing for fast vs. free and fast vs. slow speed comparisons.
Figure 4.9: Hip flexion and extension in 3 speeds in hEDS and TD. Blue, gray, and red lines are representing fast, free, and slow speed respectively. SD for each value is shown with shaded of the same color for each speed.

Figure 4.10: Repeated measure (RM) ANOVA SnPM {t} (a) and Post hoc analysis (b-d) in hEDS during walking speeds (b) fast vs. free, (c) free vs. slow, and (d) fast vs. slow for hip angle in sagittal plane. The post hoc analysis indicated significant results in early stance for fast vs. slow, and in transition of stance to swing for all speed comparisons.
Figure 4.11: Repeated measure (RM) ANOVA SnPM{$t$} (a) and Post hoc analysis (b-d) in TD during walking speeds (b) fast vs. free, (c) free vs. slow, and (d) fast vs. slow for hip angle in sagittal plane. The post hoc analysis indicated significant results in early stance, transition of stance to swing, and swing phase for fast vs. slow comparisons.
Figure 4.12: Pelvic tilt in 3 speeds in hEDS and TD. Blue, gray, and red lines are representing fast, free, and slow speed respectively. SD for each value is shown with shaded of the same color for each speed.

Figure 4.13: Repeated measure (RM) ANOVA SnPM\{t\} (a) and Post hoc analysis (b-d) in hEDS during walking speeds (b) fast vs. free, (c) free vs. slow, and (d) fast vs. slow for pelvis angles in sagittal plane. RM ANOVA and post hoc analysis indicated no significant differences in all speed for hEDS group.
The knee joint post-hoc analysis indicated significant results in early stance for fast vs. slow, and in transition from stance to swing for all speed comparisons (Figure 4.7). Similar to ankle, more kinematic pattern changes were observed in TD compared to hEDS across different speeds; Early stance for fast vs. slow, and free vs. slow in the transition of stance to swing for all speed comparisons, and in the late swing for fast vs. free and fast vs. slow speed comparisons.

Post-hoc SnPM analysis on the hip joint revealed significant results in early stance for fast vs. slow and transition from stance to swing for all speed comparisons in hEDS. The post hoc analysis for
TD indicated significant results in early stance, the transition of stance to swing, and swing phase for fast vs. slow comparisons. While there were no significant differences in pelvic tilt in hEDS across different speeds, the result of comparing fast and slow speed in TD children showed significant differences in mid-stance and swing.

4.4 Discussion

Joint angles and moments analysis during different walking speeds indicated different walking patterns in the hEDS and TD groups. In general, less significant results and changes in movement patterns were observed in children with hEDS. These results further support the central hypothesis on differences in walking pattern alteration across different speeds in children with hEDS. One reason why hEDS gait pattern has changed differently from TD may be related to proprioceptive deficits and difficulties in motor skills reported in this population [115, 119, 121]. The knee joint’s role during walking requires significant kinematic changes in case of speed alteration to accommodate the changes in spatio-temporal parameters and hip joint [214]. Indirect estimates of knee joint loading suggest that loads increase with walking speed [216]. Previous studies indicated impaired knee proprioception in adults [122, 217] and children [121] with hypermobility syndrome. Less knee joint pattern alteration in children with hEDS during faster speed may be due to the inability to compensate for extra applied forces on the knee joint. Previous research shows that during early-stance compressive tibiofemoral forces increased 52% as walking speed increased [205]. Moreover, faster walking resulted in greater compressive forces during weight acceptance and increased compressive and anterior/posterior tibiofemoral loading rates in addition to a greater abduction.

While increased knee extension and reduced knee flexion in children with JHS have been reported in two studies [63, 99], the results of this study revealed no significant differences in knee joint
kinematics (Chapter 3 results). However, significantly less knee power absorption was observed in hEDS in late stance. Future studies may investigate the knee joint pattern compensation during faster speed change and its association with the high occurrence of knee pain in children with hEDS. Clinicians should be aware of these identified deficits in children with hEDS and apply proprioceptive training and muscle strengthening with the concentration on knee and ankle joints. Therapies, such as an 8-week closed kinetic exercise program, improved proprioception, increased muscle strength, and reduced joint pain [217]. Moreover, several studies investigated the use of supportive splints [67], strength training [218], and simpler remedies like elastic bandages [219]. It should be emphasized that these findings cannot be extrapolated to all patients on the hypermobile spectrum disorder due to this group’s variability of musculoskeletal manifestations and complications. For instance, even in this study’s small cohort, two of the participants with hEDS, who were siblings, had different joint malfunctions, one in the upper extremity and the other presenting in the lower extremity. These results must be approached with caution and with respect to each individual patient’s medical history, especially when applied in clinics and for the patients’ treatment planning.

Understanding gait patterns in children with hEDS may identify contributors to joint instability during functional activities. These findings could ultimately help prevent lower extremity injuries and lead to better treatment planning. This study could fill the gap in the literature for understanding the gait pattern of hEDS in pediatrics.
Chapter 5: Application of Machine Learning to Classify Gait Patterns of Children with Hypermobile Ehlers-Danlos Syndrome and Typically Developing Children

5.1 Introduction

Machine learning (ML) enables us to design machines (algorithms) to learn from data and discover patterns according to this method’s nature [220]. One of the significant advantages of ML in science is that it is not required to have a complete knowledge of the system, and the ML model can still create predictions with high accuracy and precision. In many cases, in the steps of diagnosis and treatment, where the disease is too complicated, ML could be a valuable tool to discover the important aspects of the disease [221]. Historically, it is interesting that the concept of NN, as a popular ML model, was inspired by how neurons interact with each other and learn a task such as walking [222]. Using ML, the body movement can be analyzed in the same way that the body and brain learned it as a child.

Gait analysis can find information about multiple features of an individual’s musculoskeletal system. In clinical practice, specific gait metrics such as the spatio-temporal parameters (e.g., speed, step width) are used for disease diagnosis, rehabilitation progress monitoring, and physical therapy intervention [223]. Classical biomechanical gait analysis extracts single time-discrete variables (e.g., the range of motion in the ankle joint) from time-continuous variables (e.g., ankle joint angle-gait stride curve). However, a large amount of data is discarded in this approach. An objective approach to finding gait patterns of which metrics are key factors and not just significantly different is lacking [220]
Since the beginning of ML popularity, several studies have used ML for classification, prediction, and pattern recognition of a particular motion in healthy subjects and different pathologies. The application of ML in biomechanics and specifically gait analysis has been explored in most of the ML techniques [224]. Most gait studies applied supervised learning techniques to classify or predict walking patterns [225]. NN, Radial Basis Function (RBF), Ensembles methods (Bagging, Boosting, Random Forest), Decision Tree, K-Nearest Neighbor (KNN), and Support Vector Machine (SVM) are a few ML models that have been used in gait biomechanics [224-233].

Clinical gait analysis is how quantitative information is collected to help understand the causes of gait abnormalities to facilitate treatment decision-making best. Since 2012, there has been a great deal of interest in using Random Forest (RF) for classifications in different stages of treatment and different disorders within clinical gait analysis [234]. RF has been used to predict the likelihood of good outcomes from orthopedic surgeries or different treatment plans [235, 236]. Breiman et al. formalized this model for classification in 1984 [237] using decision trees as hierarchical learners consisting of an ensemble of binary decisions. Later, decision trees became very popular and widely used in numerous ML applications, such as biomechanics [238, 239]. The success story behind it may be due to several advantages they possess. For instance, they are intuitive, fast, and scalable to very large datasets [237].

Although the general method of applying the RF is the same, there are differences in execution, parameters, classes, and the goal. Several studies have been done using RF as a reliable classifier to be used in clinical decision-making [231, 234, 235, 240]. Schwartz et al. used RF for the first time in the clinical gait analysis of children with cerebral palsy to predict the outcome of the surgery of psoas lengthening by using the gait data [235]. Another advantage of using RF in gait
analysis is that with no formal distribution assumptions, RFs are non-parametric and can thus handle skewed and multi-modal data and categorical data that are ordinal or non-ordinal [241].

As a supervised ML technique, SVM has been popularly used in the classification of either conditions or patterns of walking and distinguishing between different patients within healthy groups [220, 225, 229, 242-247]. Furthermore, SVM is considered a powerful technique for general data classification and has been widely used to classify human motion patterns with accurate and precise results [229, 242, 248]. The advantage of SVM algorithms is that they can generate a classification result with limited data sets by minimizing structural and empirical risks [249]. Therefore, it would be a good choice in smaller sample sizes, which is a big issue in biomechanics. Several SVM techniques have been used to classify gait dynamics, such as kernel-based classifiers [250], transforming the input data into a high-dimensional space where classification is possible. In the case of non-linearity, the RBF kernel is usually the first reasonable choice as it can non-linearly map data into higher dimensional space.

With the popularity of ML in recent years, ML techniques have been successfully employed to help researchers in gait analysis for various patient groups such as stroke [240], Parkinson’s disease [251], cerebral palsy [252], and patients suffering from different functional gait disorders [253]. Although the ML techniques showed very successful results and high accuracy in SVM and deep learning, the secret of how that model decided a particular classification or regression problem remained unsolved. In other words, even if the underlying mathematical principles in these systems are comprehensible, it is still difficult to understand if meaningful patterns and dependencies were learned and what the classification model has learned. In addition, the black-box characteristics hide the artificial intelligence-based decisions to provide explanations.
In the ML field, interpretability is the ability to explain or present in understandable terms to a human [254]. Transparency is not needed for the model to predict; it is required for a human to understand how that model decided to predict in such a way. There is a demand for enhancing transparency in ML prediction models in clinical cases [220]. More transparency in the predictive models could help identify the features responsible for alterations in gait patterns. However, the trade-off between transparency and accuracy is always questionable [246]. Using ML to detect gait patterns in different pathologies has been exponentially developed and added to the body of this field. However, the black-box nature of these methods has made the interpretation of the gait data difficult. This interpretation could be a helpful tool for a clinician in the diagnosis and treatment process.

There are several advantages to using ML models in gait analysis. Loss of data used in studying gait with single time-discrete variables could hide important information since the nature of kinematics and kinetics data is continuous in a gait cycle. Moreover, the combination of variables cannot be evaluated in the former gait analysis. The use of ML in the study of gait analysis has been considered when attempting to solve this problem.

Due to extensive new datasets, the application of ML techniques is becoming increasingly popular in clinical biomechanics. The application of artificial NN and SVMs highlighted that gait patterns are unique to an individual person [223], exhibited natural changes within different time scales, and identified that grades of fatigue could be differentiated from human gait patterns. This advantage is significant for patients with hEDS since fatigue is one of the most critical challenges they encounter daily [127].

Gait analysis is a key assessment for clinicians and therapists in prognostics, diagnosis, treatment, and rehabilitation process, especially in neuro-musculoskeletal diseases [181]. Furthermore,
researchers have shown that ML algorithms could even diagnose diseases like dementia and diabetes before any significant clinical signs by physicians [255-257]. The main aim in this chapter was to classify hEDS and TD children based on their 3-D features using an ML classifier. It was hypothesized that the ML classifier would be able to distinguish between two hEDS and TD by analyzing ankle, knee, hip, and pelvis angles during walking.

5.2 Methods

5.2.1 Participants

In total, twenty-one (21) children with symptomatic hypermobility were recruited by the Genetics Center of Children’s Wisconsin. The specific diagnosis and demographics are listed in Table 5.1. Nine children were diagnosed with hEDS, four with HSD, and five did not have an apparent phenotype for HSD or hEDS; therefore, they were considered to be hEDS/HSD. Nineteen (19) TD children were recruited with no prior history of lower extremity hypermobility, injury, or walking deficit (Table 5.2). The present study was conducted in the UWM Mobility laboratory located at UWM Innovation Campus and was approved by the University’s Institutional Review Board separately for hEDS and TD children.
Table 5.1 Demographics of children with hEDS/HSD.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Age</th>
<th>BMI</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>#01</td>
<td>hEDS</td>
<td>16.4</td>
<td>27.6</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#02</td>
<td>hEDS</td>
<td>12.6</td>
<td>38.1</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#03*</td>
<td>hEDS</td>
<td>14.7</td>
<td>23.7</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#04</td>
<td>hEDS / HSD</td>
<td>11.6</td>
<td>22.4</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#05</td>
<td>hEDS</td>
<td>16.5</td>
<td>18.3</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#06</td>
<td>hEDS / HSD</td>
<td>17.2</td>
<td>19.9</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#07</td>
<td>hEDS / HSD</td>
<td>17.2</td>
<td>18.5</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#08</td>
<td>hEDS</td>
<td>9.4</td>
<td>16.6</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#09**</td>
<td>hEDS</td>
<td>8.0</td>
<td>N/A</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#10**</td>
<td>hEDS</td>
<td>12</td>
<td>N/A</td>
<td>M</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#11</td>
<td>HSD</td>
<td>14.8</td>
<td>17.8</td>
<td>M</td>
<td>Do not wish to report</td>
</tr>
<tr>
<td>#12</td>
<td>hEDS</td>
<td>15.0</td>
<td>23.2</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#13</td>
<td>HSD</td>
<td>15.1</td>
<td>29.7</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#14</td>
<td>HSD</td>
<td>12.1</td>
<td>20.2</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#15</td>
<td>HSD</td>
<td>16.4</td>
<td>18.8</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#16</td>
<td>hEDS</td>
<td>8.6</td>
<td>22.3</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#17</td>
<td>hEDS / HSD</td>
<td>16.2</td>
<td>19.0</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#18</td>
<td>hEDS</td>
<td>16.8</td>
<td>18.5</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#19</td>
<td>hEDS / HSD</td>
<td>15.0</td>
<td>18.4</td>
<td>F</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>#20</td>
<td>hEDS</td>
<td>9.3</td>
<td>18.6</td>
<td>M</td>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>#21</td>
<td>hEDS</td>
<td>11.6</td>
<td>15.5</td>
<td>F</td>
<td>Hispanic or Latino</td>
</tr>
</tbody>
</table>

N= 18  
hEDS: 9  
SD: 3.1  
Mean: 13.6  
hEDS/HSD: 5  
SD: 5.9  
Mean: 21.3  
HSD: 4  
SD: 3.1  
Mean: 13.6  
Hispanic: 2  
Non-Hispanic: 15  
M: 5  
F: 13  
N/A: 1
Table 5.2: Demographics of TD children.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>BMI</th>
<th>Gender</th>
<th>Race</th>
<th>Beighton Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>#01</td>
<td>13.4</td>
<td>31.2</td>
<td>M</td>
<td>White</td>
<td>1</td>
</tr>
<tr>
<td>#02</td>
<td>14.9</td>
<td>19.3</td>
<td>F</td>
<td>White</td>
<td>2</td>
</tr>
<tr>
<td>#03</td>
<td>8.3</td>
<td>17.3</td>
<td>F</td>
<td>White</td>
<td>1</td>
</tr>
<tr>
<td>#04</td>
<td>8.9</td>
<td>17.4</td>
<td>F</td>
<td>White</td>
<td>2</td>
</tr>
<tr>
<td>#05</td>
<td>15.5</td>
<td>18.3</td>
<td>F</td>
<td>White</td>
<td>2</td>
</tr>
<tr>
<td>#06</td>
<td>13.4</td>
<td>20.1</td>
<td>F</td>
<td>White</td>
<td>2</td>
</tr>
<tr>
<td>#07</td>
<td>11.0</td>
<td>21.3</td>
<td>F</td>
<td>White</td>
<td>1</td>
</tr>
<tr>
<td>#08*</td>
<td>13.1</td>
<td>16.0</td>
<td>M</td>
<td>White</td>
<td>0</td>
</tr>
<tr>
<td>#09</td>
<td>12.0</td>
<td>26.6</td>
<td>M</td>
<td>White</td>
<td>0</td>
</tr>
<tr>
<td>#10</td>
<td>10.9</td>
<td>17.4</td>
<td>M</td>
<td>Asian</td>
<td>2</td>
</tr>
<tr>
<td>#11</td>
<td>15.7</td>
<td>20.8</td>
<td>F</td>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td>#12</td>
<td>10.2</td>
<td>15.9</td>
<td>M</td>
<td>White</td>
<td>2</td>
</tr>
<tr>
<td>#13</td>
<td>11.8</td>
<td>20.9</td>
<td>F</td>
<td>White</td>
<td>0</td>
</tr>
<tr>
<td>#14</td>
<td>13.1</td>
<td>14.2</td>
<td>M</td>
<td>White</td>
<td>0</td>
</tr>
<tr>
<td>#15</td>
<td>10.2</td>
<td>18.1</td>
<td>F</td>
<td>White</td>
<td>0</td>
</tr>
<tr>
<td>#16</td>
<td>12.5</td>
<td>17.8</td>
<td>F</td>
<td>White</td>
<td>1</td>
</tr>
<tr>
<td>#17</td>
<td>13.7</td>
<td>19.6</td>
<td>M</td>
<td>White</td>
<td>0</td>
</tr>
<tr>
<td>#18</td>
<td>14.1</td>
<td>22.5</td>
<td>F</td>
<td>White</td>
<td>3</td>
</tr>
<tr>
<td>#19</td>
<td>16.0</td>
<td>23.0</td>
<td>M</td>
<td>White</td>
<td>1</td>
</tr>
</tbody>
</table>

N= 18
Mean: 12.6  Mean: 20.1  M: 7  White: 16  Mean: 1.1
SD: 2.3  SD: 4.0  F: 11  Asian: 2

5.2.2 Data Processing and Machine Learning Models

Marker trajectories were captured via a 15-camera Vicon T-Series Motion Analysis System (Oxford Metric Group, Oxford, UK) at a 120 Hz sampling rate. Instructions were provided, and the subjects were asked to walk at free speed. All children walked barefoot and with no assistive devices. The Nexus 2.10.1 software was used to label and process the marker trajectories exported to MATLAB by a Vicon-Matlab interaction. The Vicon plug-in-gait lower extremity model computed 3-D ankle, knee, hip, and pelvis joint angles. Finally, a customized Matlab code was used to process, normalize, and evaluate gait metrics.

For the database, 3-D time-series kinematics were used as features to compare hEDS and TD. A self-written script executed the first data processing steps within the software Matlab 2021a
(MathWorks, USA) after processing the joint angles in the Vicon software (Similar to chapter 3). Moreover, the data was evaluated for possible gimble lock incidents. For subject classification, an average of 50-60 strides per subject for either left or right were selected. The total number of strides was 1,023 for hEDS and 954 for TD.

Python 3.10.1 IDE for professional developers was used through PyCharm 2021.3.3. Keras, Tsklearn, Matplotlib, Numpy, and Pandas packages were used to pre-process the data, build ML models, and evaluate the final classification results. In the pre-processing phase, each variable was normalized to 101 data points, z-transformed, and scaled linearly to a range of −1 to 1 (Max-Min scaler [258]). Max-Min normalization to avoid that data with larger numeric ranges dominate the smaller numeric ranges. The z-transformation was applied for kinematic variables for each trial separately. 3-D joint angles were concatenated as a time series with the dimension of 1,212; Ankle (101×3) + Knee (101×3) + Hip (101×3) + Pelvis (101×3). An example of ankle angle concatenation is shown in Figure 5.1. Therefore, the overall matrix’s size was (1,023 × 1,212) for hEDS, and (954 × 1,212) for TD. Finally, the labels for hEDS and TD were added to be 1 and 0,

![Normalized concatenated ankle angles of children with hEDS in sagittal, frontal, and transverse planes of motion. Each value was normalized with Max-Min scaler and z-transformed for ML model input.](image)

Figure 5.1: Normalized concatenated ankle angles of children with hEDS in sagittal, frontal, and transverse planes of motion. Each value was normalized with Max-Min scaler and z-transformed for ML model input.
respectively and merged two Data frames. The final input size for ML model evaluation was (1,977 × 1,212).

Multiple SVM models (Linear, Polynomial, Gaussian, and RBF), a Sully connected NN, RF, and KNN classifiers were used to investigate the best model results for classification. Prediction accuracies were reported over two validation methods: a ten-fold cross-validation and a Leave-One-Out cross-validation technique. In ten-fold cross-validation, eight parts of the data was used for training, one part for the validation set, and the remaining part for testing. Validation set and loss values were checked for possible overfitting during training. The receiver operating characteristic (ROC) curve and confusion matrix was calculated to evaluate the classification results. ROC analysis generally selects optimal models and quantifies the accuracy of diagnostic tests [259]. Also, the area under the ROC curve (AUC), which is a representation of the classification performance, was utilized to assess the effectiveness of the SVM classifier.

Finally, for explaining the kernel and more complicated classifiers, the Layer-Wise Relevance Propagation Toolbox was used to explain the decision of the classifiers [260]. Averaged relevance for each of the 1,212 input values were calculated to explain which part of the data was more important to the classifier. Positive values indicated a positive effect on the classifier’s choice, while negative R values were an indication of the negative effect on the classifier’s accuracy.
5.3 Results

In this section different ML classifiers’ results and evaluations will be illustrated on hEDS and TD time-series gait features. Fully connected NN and RBF SVM had the highest accuracy of above 97%, with an AUC of 1. Only 2-3% of results had false-negative, and from 0.5-1% had false-positive results.

ROC curves for SVM model evaluations are shown in Figure 5.2. The results indicated that RBF SVM had the best accuracy of 97.2%, with an AUC of 1.0 among all the SVM classifiers. In the RF classifier, although the accuracy was 94.4%, the false negative for one subject was high Figure 5.3.

KNN had the lowest accuracy among all the classifiers Figure 5.4 with a 37.9% false-positive rate. The overall evaluation scores and model properties are shown in Table 5.3.
Figure 5.2: ROC curves for linear, polynomial, gaussian, and RBF SVMs; RBF had the best accuracy (97.2%) while linear SVM had the worst accuracy (76.4%).
Figure 5.3: RF ROC classifier results. Although the overall accuracy is 94.4%, model failed to classify hEDS correctly for some trials and had a high false-positive rate. Confusion matrix results indicated that 8.7% of the gait strides were wrongly classified as hEDS, whereas only 1.7% had a wrong label of TD where they belonged to the hEDS group.

Figure 5.4: KNN classifier ROC; the model classified hEDS and TD with an accuracy of 68.1%. Confusion matrix results indicated that 17.9% of the gait strides were wrongly classified as hEDS, whereas only 37.9% had a wrong label of TD where they belonged to the hEDS group.
Table 5.3: ML classifier results; Accuracy, AUC (area under curve of ROC), and important model features are shown below

<table>
<thead>
<tr>
<th>ML Classifiers</th>
<th>Accuracy</th>
<th>AUC</th>
<th>Model properties and Hyperparameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear SVM</td>
<td>76.4%</td>
<td>0.80</td>
<td>21.4% False Negative, 14.8 False positive</td>
</tr>
<tr>
<td>Polynomial SVM</td>
<td>79.1%</td>
<td>0.90</td>
<td>Quadratic 24.8% False Negative, 11.3 False positive</td>
</tr>
<tr>
<td>Gaussian SVM</td>
<td>90.3%</td>
<td>0.97</td>
<td>Kernel function: Gaussian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kernel scale: 140</td>
</tr>
<tr>
<td>RBF SVM</td>
<td>97.2%</td>
<td>1.0</td>
<td>Kernel function: Gaussian + regularization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kernel scale: 35</td>
</tr>
<tr>
<td>KNN</td>
<td>68.1%</td>
<td>0.84</td>
<td>Preset: Medium KNN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of neighbors: 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distance metric: Euclidean</td>
</tr>
<tr>
<td>RF</td>
<td>94.4%</td>
<td>0.92</td>
<td>Ensemble method: AdaBoost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum number of splits: 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of learners: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Learning rate: 0.1</td>
</tr>
<tr>
<td>Fully Connected NN</td>
<td>97.5</td>
<td>1.0</td>
<td>loss=binary_crossentropy</td>
</tr>
<tr>
<td>(Sequential)</td>
<td></td>
<td></td>
<td>optimizer=adam</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 Dense Layers with 2 relu and one sigmoid activation</td>
</tr>
</tbody>
</table>

5.4 Discussion

The results of the current chapter showed that hEDS and TD could be distinguished using ML classifiers. Linear and polynomial SVM and two layers NN models showed acceptable results. However, the performances of RBF SVM, RF, and three-layered NN models were superior compared to other classifiers. This result may indicate that due to the non-linear nature of gait variables, more robust ML models with non-linearity and regularization can have more precise and accurate outputs. Considering the computational cost, RBF and polynomial kernels need less time compared to the linear kernel in the same conditions. The RBF kernel is the most promising kernel function in this classification problem, and it may also provide better applicability to real-time system implementation.
To improve the overall accuracy of classification, a couple of pre-processing and hyperparameter tunings were implemented. GridSearchCV from Sklearn was used for the RF model to find the optimized number of trees. For the NN model, adding a layer of Relu helped the model to have higher accuracy. For the RBF model, adding the regularization constant helped the classifier to have a lower False-negative. It should be emphasized that the results could be further improved by optimizing the SVM classifier with the appropriate kernel function, regularization parameter (C), and the width ($\sigma$) of the RBF value that depends on the data characteristics.

ML classifiers such as RBF SVM have shown promising results and thus could be a powerful tool to identify deficits in children with hEDS during gait. As a final remark, it is also vital to mention that interpreting the ML model in clinical practice may cause confusion and lack of interpretability. Therefore, more customized explainable tools are required in gait analysis to practically use model outputs.
Chapter 6: Summary and Conclusions

This dissertation aimed to provide a comprehensive biomechanical characterization of the joint dynamics and muscle activations during ADLs and walking in children with hEDS. This research focused on the shoulder, ankle, knee, and hip as the most frequently reported joint instability and pain location complaints. Effective management of symptoms requires the engagement of a multidisciplinary team in the most severely affected individuals with hEDS [36]. This study’s multidisciplinary approach aimed to address the current gaps in knowledge of hEDS and investigate potential quantifying assessments to improve the diagnosis and treatment of children with hEDS. Furthermore, this study investigated novel techniques for characterizing the joint dynamics in children with hEDS and blends the multidisciplinary methods to assess the shoulder and lower body joints during different activities.

Children with a high prevalence of multi-systemic complaints and poor postural control, and high levels of pain and fatigue are more likely to have a worsening functional impairment trajectory and, as a result, should be given therapeutic priority [40]. Therefore, children must receive helpful treatment plans to prevent a possible progression of symptoms, such as chronic joint pain. Furthermore, studying movement analysis for children with hEDS to improve diagnosis, musculoskeletal mobility directly, and pain management can prevent future injuries and may lead to rehabilitation therapies and pain management techniques to improve quality of life.

6.1 Summary of Findings

6.1.1 Specific Aim 1

Specific aim 1 was to quantify the joint kinematics of the shoulder in children with hEDS compared to TD children during ADLs and shoulder AROMs. A significantly different pattern in SC, GH, and ST was observed during reaching across the body and reaching to back pocket tasks. Also, the
results revealed an increased ROM in AC joint during all ADL tasks, which may have influenced the significant changes observed in SC, GH, and ST. A greater reachable workspace was observed in children with hEDS compared to TD children during shoulder flexion, scaption, abduction, and extension. Increased reachable workspace may cause further shoulder pathologies due to excessive ROM affecting joint articulations and surrounding connective tissues. To the author’s knowledge, this is the first study to investigate the characteristics of the shoulder complex joint angles in this population.

6.1.2 Specific Aim 2
Chapter 3 evaluated joint dynamics and muscle activations of the lower extremity during a self-selected walking speed. These results indicated alterations in ankle angles which may be associated with a higher prevalence of ankle pain and dislocation. Additionally, knee power absorption has a key role in smoothing gait movements, and it was observed that children with hEDS had significantly lower knee power absorption than TD children. Finally, higher muscle activations and co-contractions in hEDS were observed, which may be associated with the reported fatigue in this population.

6.1.3 Specific Aim 3
Specific aim 3 compared changes in joint dynamics during different walking speeds in children with hEDS compared to TD children. Joint angles and moments indicated different walking patterns in the hEDS group compared to the TD group during different speeds. In general, children with hEDS tend to make fewer alterations in their gait patterns when changing speeds. Understanding gait patterns in children with hEDS during different walking speeds may identify contributors to joint instability and proprioception deficits.
6.1.4 Specific Aim 4

Specific aim 4 focused on using ML to classify children with hEDS and TD based on gait dynamics. According to chapter 5, the classification of gait measures in children with hEDS and TD by ML models indicated promising results with the highest accuracy of 97% for NN and RBF SVM models. This research was the first study to investigate whether ML can classify hEDS from a healthy group by modeling the 3-D joint angles during gait. hEDS shares multiple clinical manifestations with several other pathologies. This challenge causes confusion and uncertainty for clinicians, primarily physical and occupational therapists, in the treatment process. ML models can handle high-dimensional data and various factors and make decisions without explicitly understanding causes and relationships between several clinical features. Therefore, the ML technique will be a great tool to communicate with clinicians and interpret the data in a meaningful way.

6.2 Study Limitations and Challenges

The large standard deviations were observed in shoulder measures, such as ST axial rotation angle and SC rotation in the coronal plane in the shoulder complex, and gait measures, such as pelvic tilt across children with hEDS. These variances may be due to the heterogeneity of the subjects in terms of their clinical manifestations and age differences. It should be emphasized that the patient cohort consisted of twelve (12) children with hEDS, four (4) children with HSD, and five (5) children with hEDS/HSD. To compensate for this issue, a non-parametric SPM approach was used. The parametric analysis assumes that the data has a Gaussian (normal) distribution, and it is randomly distributed. Then it computes the mean and SD and applies them to the whole group. On the contrary, the non-parametric approach is generally not based on any specific distribution or prior assumption and is instead established by experimental data from the test. While analyzing
the time series data with a non-parametric approach does not resolve the high variance and heterogeneity issues, it may be able to help obtain more realistic and accurate results from the sample group.

The term hEDS was used in this dissertation. However, many clinicians consider JHS and hEDS to represent the same phenotypic group of patients that can be differentiated from other HCTDs but not distinguished from each other [8, 126]. Therefore, JHS and hEDS were considered as the same phenotype in this study, therefore “hEDS” was used for the purpose of this dissertation. It also has been claimed that clinicians serve this population better by uniting the two diagnostic labels [8]. However, this preference for terminology might change due to the future alteration of the classification of this syndrome.

6.3 Future Directions and Recommended Clinical Implications

hEDS is a progressive disorder that deteriorates functional movement and augments chronic pain during an individual’s lifespan. There is a limited knowledge of how this disorder progresses and affects individuals over time. Previous studies revealed a 28% incidence rate of daily pain reported by children with hEDS, while 90% of adults over 40 years old reported daily pain experiences [14]. To the author’s knowledge, the impact of age on musculoskeletal symptoms in the transition from childhood to adulthood is still unknown. The results from this study focused on children with hEDS, and interestingly, these gait dynamics results differ from the results reported in adults [102, 135]. Future studies can investigate the change of these symptoms and alterations during a patient’s lifespan and propose more prognostic approaches for children with hEDS.

The current evidence for the physical therapy assessment and management of JHS/hEDS is limited in size and quality [261]. In most clinical settings, more traditional ROM assessments have been obtained using goniometers or inclinometers [262]. Although motion capture systems could reveal
more information on the individual’s movement pattern, it is not accessible to all clinics and care
centers due to the high cost of this equipment. Previous findings revealed the feasibility of using a
Kinect depth camera to analyze reachable workspace using alpha-shape approach [157]. This study
reported promising results in using the reachable workspace as a potential method for assessing
patients with various neuromusculoskeletal conditions. In chapter 2, the feasibility of using a
reachable workspace for children with hEDS was examined. However, the reliability and
repeatability of reachable workspace measures by Kinect cameras need to be investigated in future
studies to establish it as a clinical assessment for individuals with hEDS. Considering the low cost
and availability of Kinect cameras compared to more expensive motion capture technology, this
method could be used to distinguish individuals with varying degrees of upper limb functional
impairments.

Despite the possible insights that ML can bring to HSDs and their complicated musculoskeletal
manifestations [263], there has been no study to apply ML techniques to the joint dynamics of
these individuals. One reason might be that the simpler classification models have low accuracy
but more transparency in interpreting the results. On the other hand, more complicated
classification methods can perform higher accuracy and more accurate predictions despite a higher
computational cost. Future work should examine the feasibility of using ML models to investigate
multiple combinations of clinical features, such as the shoulder instability measures and their
association with shoulder kinematics.

In summation, future research can investigate different treatment plans to establish successful
rehabilitation techniques to prevent pathologies associated with musculoskeletal complications in
hEDS to maximize the quality of life.
6.4 Concluding Remarks

EDS is an inherited pathology of connective tissue caused by a deficiency in protein synthesis [12]. These changes in connective tissue structures are responsible for several clinical manifestations. As discussed in the first chapter, from all 13 subtypes of EDS, hEDS is the only one without known causal mutation gene(s). Because of these unknown responsible genes, unavailable accurate diagnosis, and high variability in musculoskeletal symptoms, it is challenging to develop an efficient treatment plan for individuals with hEDS. Another important fact is that although diagnoses of hEDS/HSD have increased in recent decades, it has been estimated that 95% of individuals are undiagnosed [264]. That may be why some researchers and clinicians believe that hEDS is not considered a rare disease.

Based on the finding of this dissertation, a full-body assessment of the musculoskeletal system with an individualized therapy approach could elucidate the complexity of several clinical manifestations in hEDS and help clinicians make more accurate decisions in a patient’s treatment journey.
References


Chapter 7: Appendix

7.1 Shoulder Kinematics During AROM

7.1.1 Shoulder Kinematics During Flexion

Figure 7.1: 3-D group average profiles of SC, AC, GH, and ST joints during shoulder flexion in children with hEDS (Mean: red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
7.1.2 Shoulder Kinematics During Scaption

Figure 7.2: 3-D group average profiles of SC, AC, GH, and ST joints during shoulder scaption in children with hEDS (Mean: red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
Figure 7.3: 3-D group average profiles of SC, AC, GH, and ST joints during shoulder abduction in children with hEDS (Mean: red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
7.1.4 Shoulder Kinematics During Abduction

Figure 7.4: 3-D group average profiles of SC, AC, GH, and ST joints during shoulder extension in children with hEDS (Mean: red line; SD: Shaded red area) and typically developing children (Mean: blue line; SD: shaded blue area)
7.2 Scapulohumeral Rhythm for Reaching Across the Body Task

Figure 7.5: Scapulohumeral Rhythm as the relative angle of GH elevation to ST upward rotation (A) and GH flexion to ST posterior tilt (B) during reaching across. Red line shows the linear regression of hEDS, and blue indicates TD group.
7.3 KAD for Gait Analysis

Figure 7.6: Representation of KAD on the participant during the static trial
7.4 Ankle Angles in Frontal Plane

Figure 7.7: Ankle frontal angle in three speeds in hEDS and TD. Blue, gray, and red lines are representing fast, free, and slow speed respectively. SD for each value is shown with shaded of the same color for each speed.
TD Ankle Add/Abduction non-Parametric RM ANOVA and Post-hoc t-test

- RM ANOVA
  - $\alpha = 0.05$, $F^* = 4.822$, $p = 0.002$

- Fast vs. Slow
  - $\alpha = 0.05$, $t^* = 2.810$
  - $p = 0.011$

- Fast vs. Free
  - $\alpha = 0.05$, $t^* = 2.570$
  - $p = 0.009$

- Fast vs. Slow
  - $\alpha = 0.05$, $t^* = 2.661$
7.5 Summary Results for different speeds

Table 7.1: Summary of RM ANOVA SnPM results of joint angle differences comparison among fast, free, and slow speeds in the sagittal plane.

<table>
<thead>
<tr>
<th>Joint Angles</th>
<th>hEDS (%) gait cycle</th>
<th>TD (%) gait cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle Dorsi/Plantar Flexion</td>
<td>(8-19) / (42-62) / (68-79)</td>
<td>(4-32) / (43-63) / (64-66)</td>
</tr>
<tr>
<td>Knee Flx/Extension</td>
<td>(2-18) / (58-72)</td>
<td>(0-28) / (51-80) / (92-100)</td>
</tr>
<tr>
<td>Hip Flx/Extension</td>
<td>(1-19) / (35-54) / (70-100)</td>
<td>(42-50) / (75-81)</td>
</tr>
<tr>
<td>Pelvic Ant/Posterior Tilt</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 7.2: Summary of Post-hoc analysis for RM ANOVA SnPM results of lower extremity joint angle differences during different speed in the sagittal plane.

<table>
<thead>
<tr>
<th>Joint Angles</th>
<th>hEDS (% gait cycle)</th>
<th>TD (% gait cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast vs. Free</td>
<td>Free vs. Slow</td>
</tr>
<tr>
<td>Fast vs. Free</td>
<td>(47-59) / (68-77)</td>
<td>(55-63)</td>
</tr>
<tr>
<td>Free vs. Slow</td>
<td>(7-17) / (40-58)</td>
<td>(10-20) / (53-62)</td>
</tr>
<tr>
<td>Fast vs. slow</td>
<td>(59-65) / (94-100)</td>
<td>(1-27) / (52-80)</td>
</tr>
<tr>
<td>Ankle Dorsi/Plantar Flexion</td>
<td>(60-66)</td>
<td>(56-71)</td>
</tr>
<tr>
<td>Knee Flx/Extension</td>
<td>(60-66)</td>
<td>(56-71)</td>
</tr>
<tr>
<td>Hip Flx/Extension</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pelvic Ant/Posterior Tilt</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pelvic Ant/Posterior Tilt</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pelvic Ant/Posterior Tilt</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Gait Phases</td>
<td>Late stance and early swing</td>
<td>Late stance and early swing</td>
</tr>
<tr>
<td></td>
<td>Early stance, late stance, early swing, late swing</td>
<td>Early stance, late stance, early swing, mid swing</td>
</tr>
</tbody>
</table>