CURRICULUM VITAE

Kelly Eleanor Rock, PT, DPT
Board-Certified Clinical Specialist in Pediatric Physical Therapy (PCS)
PhD Candidate and Graduate Research Assistant
Department of Physical Therapy and Rehabilitation Science (PTRS)
University of Maryland School of Medicine
University of Maryland, Baltimore (UMB)

DATE: December 6, 2022

CONTACT INFORMATION

Business Address: Department of Physical Therapy and Rehabilitation Science
100 Penn Street, Room 201
Baltimore, MD 21201
Email: kellyrock422@gmail.com

EDUCATION

2007	BS	Ithaca College, Ithaca, NY - Clinical Science/Physical Therapy Minor: Recreation
2008	MSPT	Ithaca College, Ithaca, NY - Physical Therapy
2008	DPT	Ithaca College, Ithaca, NY - Physical Therapy
2022	PhD	University of Maryland School of Medicine, UMB Physical Rehabilitation Science Baltimore, MD Advisor: Victoria Marchese, PT, PhD Dissertation Title: "Skeletal muscle properties, gross motor performance, and quality of life in survivors of childhood hematologic and oncologic health conditions" Degree Conferral Date: December 2022

POST-GRADUATE EDUCATION AND TRAINING

2008-2009	Leadership Education in Neurodevelopmental and other Related Disabilities (LEND) – Physical Therapy Fellow University of Rochester, Rochester, NY Mentor: Karen Nolan, PT, DPT

HONORS AND AWARDS

2020-2021	National Institute of Health (NIH) Pre-doctoral Ruth L. Kirschstein National Service Award (NRSA) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Interdisciplinary Training Program (T32) in Muscle Biology (T32AR007592-24)
2021	APTA Oncology Outstanding Research Award – Poster Presentation for "Muscle and Mobility in Adolescent Survivors of Childhood Bone Tumors: Exploring a Functional Strengthening Intervention" from the

	American Physical Therapy Association, Academy of Oncologic Physical Therapy
2022	UMB Graduate Student Association Travel Fellowship Award ($300)
2022	APTA Academy of Cardiovascular and Pulmonary Physical Therapy Best Poster Award at the 2022 Combined Sections Meeting for "Reliability of Assessing Diaphragm Thickness Via B-Mode Ultrasound in Healthy Children and Adolescents"

EMPLOYMENT HISTORY

2009	Pediatric Physical Therapy Services, Rochester, NY – Physical Therapist
2009-2018	Children's National Health System, Washington, DC – Physical Therapist
2011-2021	Johns Hopkins Hospital, Pediatric Team, Baltimore, MD – Per Diem Physical Therapist
2018-present	Children's National Health System, Washington, DC – Per Diem Physical Therapist
2018-present	University of Medicine School of Medicine – Graduate Research Assistant

PROFESSIONAL CERTIFICATIONS

2007-present	American Heart Association, BLS for Healthcare Providers (CPR & AED)
2015	American Physical Therapy Association, Certified Clinical Instructor
2016-present	American Board of Physical Therapy Specialties, Certified Pediatric Clinical Specialist (PCS)

PHYSICAL THERAPY LICENSURE

2009-2021	District of Columbia (active)
2010-2021	Maryland (active)
2008-2010	New York (inactive)
2009-2010	Pennsylvania (inactive)
2011-2018	Virginia (inactive)

CLINICAL ACTIVITIES

Clinical Expertise

Pediatric Physical Therapy
Oncologic/Hematologic Physical Therapy
Musculoskeletal Tumors
Orthopedics/Sports Rehabilitation
Kinesiotape Techniques
Splinting Fabrication

Scope of Clinical Practice

Outpatient pediatric physical therapy practice
Acute care pediatric physical therapy practice
Early Intervention
Multidisciplinary rounds and practice
Physical Therapy Liaison – Hematology, Oncology, Bone Marrow Transplant

Clinical Instructor – 5 full-time graduate physical therapy students:
Ashley Speights - Duke University; Christina Lacci - Boston University; Martha Baron - University of Maryland School of Medicine; Kristen Papaloukas - Merrymount University; and Brittney Jorgensen -George Washington University
Clinical Mentor – 3 on-boarding staff:
Micheala Lewis, Justine Belschner, and Rebecca Manning

Clinical Enterprise
Multidisciplinary Sarcoma Clinic
Sickle Cell Integrated Clinic

PROFESSIONAL ORGANIZATION MEMBERSHIPS

2006-present American Physical Therapy Association (APTA), Member
2006-present APTA State Member (Current: MD)
2006-present APTA Academy of Pediatric Physical Therapy
2009-present APTA Academy of Oncologic Physical Therapy
2020-present American Congress of Rehabilitation Medicine (ACRM) Pediatric Oncology Task Force

ADMINISTRATIVE SERVICE

Institutional Service
2018-2021 Primary Representative, Student Government Association, UMB
2019-2021 Secondary Representative, Student Advisory Council, UMB
2019 Member, GPILS/OPS Award Committee, UMB
2019-2021 Member, UMB Graduate Research Conference Planning Committee
2019-present Big Sibling, Big Sibling Mentor Program, UMB
2020-present Grant Reviewer, Dr. Gladys E. Wadsworth Physical Therapy Research Fund Committee
2020-present Member, PTRS Internal Data and Safety Monitoring Board (IDSMB) Committee

Local and National Service
2013-2023 Chair, Limb Sparing Sub-committee, Pediatric Oncology SIG, APTA
2016-2023 Vice Chair, Pediatric Oncology SIG, Academy of Oncologic Physical Therapy, APTA
2018-present Ad Hoc Reviewer, *Journal of Pediatric Oncology Nursing* (2)
2018-present Volunteer, Disabilities Ministry, Grace Fellowship Church
2019-present Volunteer, American Cancer Society Hope Lodge
2022-present Ad Hoc Reviewer, *Journal of Pediatric Rehabilitation Medicine* (1)

Teaching Service
Ithaca College MSPT/DPT Program
PTMS 618 – Clinical Science: Pediatrics – approximately 70 students

Pediatric Movement Analysis – Lab Instructor (Assistant) – 2009 (2 hrs)
Pediatric Oncology – Guest Lecturer – 2009 (1.5 hrs)

University of Maryland School of Medicine DPT Program

DPTE513: Basic Sciences II – 65 to 70 students
Infant Tests and Observations – Lab Instructor (Assistant) – 2019 (2 hrs)
Child 3+ Years – Lab Instructor (Assistant) – 2019 (2 hrs)
Oncology – Lecturer – 2021-2022 (5 hrs; live online [2021])
Balance – Lab Instructor (Assistant) – 2022 (3 hrs)

DPTE514: Basic Sciences III – 65 to 70 students
Pediatric Balance and Coordination – Lecturer – 2020-2022 (live online)
Lifespan Balance Assessment – Lab Instructor (Co-Lead) – 2020-2022
Pediatric Gait – Lecturer – 2021-2022 (live online [2021])
Pediatric Mobility and Gait – Lab Instructor (Lead) – 2021-2022
Pediatric Test and Measures – Lab Instructor (Lead) – 2021-2022
MMT Hip and Thigh – Lab Instructor (Assistant) – 2021-2022
MMT Leg and Foot – Lab Instructor (Assistant) – 2021-2022
EBP Seminar Facilitator – 2021 (13 students)
Strength Testing in Children – Lecturer – 2022 (live online)
Pediatric Test and Measures – Lecturer – 2022 (live online)

DPTE520: Medical Issues – 65 to 70 students
Oncology – Lecturer – 2020-2022 (live online)

DPTE524: Neuromuscular I – 65 to 70 students
Developmental Disabilities – Lecturer – 2019-2022
Children with Developmental Disabilities – Lab Instructor (Lead) – 2019-2022
EBP Seminar Facilitator – 2019-2020 (13 students)
Autism & Develop. Coordination Disorder – Lab Instructor (Assistant) – 2020

DPTE527: Neuromuscular II – 65 to 70 students
Seminar Facilitator – 2019 (13 students; 2 sessions)
Torticollis and Plagiocephaly – Lab Instructor (Assistant) – 2021-2022
Muscular Dystrophy & Spinal Muscular Atrophy – Lab Instructor (Assistant) – 2021-2022
Orthotics – Lab Instructor (Assistant) – 2022

DPTE528: Professional Issues III – 16 students
Teaching Lab – Lab Instructor (Assistant) – 2021

Concordia University DPT Program

DPT 750: Topics in Pediatric/Adult Geriatric & Neurological PT – 9 to 10 Students
Pediatric Oncology/Sarcoma – Invited Lecturer – 2020-2021

Mentorship

2019 Jacqueline Peters – PTRS Research Summer Intern
2019 Sanjana Rao and Nesreen Alissa – PTRS PhD Students, Big Sibling Mentor
2020 Ruth Akinlosotu and Sandra Deluzio – PTRS PhD Students, Big Sibling Mentor

RESEARCH SUPPORT

Completed Projects

2019-2021 Role: Co-Investigator; PI: V. Marchese
"Exploring muscle characteristics and functional performance in healthy children, adolescents, and young adults"
The Dr. Gladys E. Wadsworth Physical Therapy Research Fund
Total: $52,730

Current Projects

2019-2022 Role: Research Assistant; PI: V. Marchese
"Exploring neuromuscular mechanisms that contribute to physical function deficits and quality of life in children with sickle cell disease"
The Dr. Gladys E. Wadsworth Physical Therapy Research Fund
Total: $32,650

2021-2022 Role: Co-Investigator; PI: V. Marchese
"Muscle properties, neuromuscular activation, and muscle performance and the relationships to gross motor performance and quality of life in survivors of upper-extremity musculoskeletal sarcoma"
University of Maryland School of Medicine, PTRS: PhD Endowment Fund
Total: $1,704

PUBLICATIONS

Journal Articles

1. **O'Mara K**, Miale S. Establishing guidelines for safe and effective treatment of pediatric sarcoma survivors: A mission of the pediatric oncology special interest group. *Rehabil Oncol*. 2016;34(3):117-119. doi:10.1097/01.REO.0000000000000028

2. Miale S, Harrington S, Brown K, Braswell A, Cannoy J, Krisch N, **Rock K**. Academy of Oncologic Physical Therapy EDGE Task Force on Cancer: a systematic review of outcome measures for pain in children. *Rehab Oncol*. 2019;37:47–54. doi: 10.1097/01.REO.0000000000000165

3. Tanner L, Keppner K, Lesmeister D, Lyons K, **Rock K**, Sparrow J. Cancer Rehabilitation in the Pediatric and Adolescent/Young Adult Population. *Semin Oncol Nurs*. 2020;36(1):150984. doi:10.1016/J.SONCN.2019.150984

4. Nelson CM, Marchese V, **Rock K**, Henshaw RM, Addison O. Alterations in Muscle Architecture: A Review of the Relevance to Individuals After Limb Salvage Surgery for Bone Sarcoma. *Front Pediatr.* 2020;8(June):1-10. doi:10.3389/fped.2020.00292

5. **Rock K**, Nelson C, Addison O, Marchese V. Assessing the reliability of handheld dynamometry and ultrasonography to measure quadriceps strength and muscle thickness in children, adolescents and young adults. *Phys Occup Ther Pediatr*. 2021;41(5):540-554. doi:10.1080/01942638.2021.1881200

6. Marchese V, **Rock K,** York T, Creath R, Gray V. Neuromuscular mechanisms that contribute to gross motor performance in survivors of childhood acute lymphoblastic leukemia. *J Pediatr Rehabil Med.* 2021;14(3):415-423. doi:10.3233/PRM-200784

7. Marchese V, **Rock K,** Harpold A, Salazar A, Williams M, Shipper AG. Physical impairment and function in children and adolescents with sickle cell disease: a systematic review. [published online ahead of print, 2021 Sept 27] *Arch Phys Med Rehabil.* 2021;S0003-9993(21)01443-X. doi: 10.1016/j.apmr.2021.08.022

8. Lanza MB, **Rock K,** Marchese V, Addison O, Gray VL. Hip abductor and adductor rate of torque development and muscle activation, but not muscle size, are associated with functional performance. *Front Physiol*. 2021;12:744153. doi: 10.3389/fphys.2021.744153

9. Pravdo A, **Rock K**, Abzug JM, Bowman P, Marchese V. Patellofemoral Pain Syndrome: Characteristics and Outcomes of Physical Therapy Episodes of Care. *Ann Physiother Occup Ther*. 2021;4(4):00211. doi: 10.23880/aphot-16000211

10. Marchese V, **Rock K**, York T, Ruble K, Gray VL. The efficacy of targeted exercise on gross motor and neuromuscular performance in survivors of childhood leukemia: a pilot study. *Front Pediatr*. 2022;11:891650. doi: 10.3389/fped.2022.891650

11. Lanza MB, **Rock K**, Marchese V, Gray VL, Addison O. Ultrasound measures of muscle thickness and subcutaneous tissue from the hip abductors: Inter- and intra-rater reliability. *Musculoskelet Sci Pract*. Published online June 2022:102612. doi:10.1016/j.msksp.2022.102612

12. **Rock K**, Addison O, Gray VL, Nelson CM, Henshaw RM, York T, Ruble K, Marchese V. Quantifying muscle strength, size, and neuromuscular activation in adolescent and young adult survivors of musculoskeletal sarcoma: identifying correlates and responses to functional strengthening. *The Knee*. Accepted.

Book Chapters

1. O'Mara K. A multidisciplinary approach to physical therapy for patients with sarcomas. In Henshaw RM ed. *Sarcoma: A Multidisciplinary Approach to Treatment*. Springer International Publishing Switzerland. June 2017.

2. Marchese VG, **Rock K.** Case Study: Pediatric Leukemia. In Effgen SK & Fiss AL eds. *Meeting the Physical Therapy Needs of Children, 3rd edition*. F.A. Davis Company. December 2020.

3. Marchese V, **Rock K,** Morris GS. Pediatric Oncology. In Palisano RJ, Orlin MN, Schreiber J eds. *Campbell's Physical Therapy for Children, 5th Edition*. Elsevier. November 2022.

PRESENTATIONS

Oral Presentations

1. Packer R, Myseros J, **O'Mara K**, Burton J. Pediatric Brain Tumors – Survivorship: considerations for rehabilitation in pediatric brain tumors. Oral educational session presented at: the American Academy of Physical Medicine and Rehabilitation (AAPMR) Annual Assembly, Washington, DC. October 2013.

2. Coulter C, **O'Mara K**, Tanner L. Orthopedic considerations in pediatric oncology (Pediatric Oncology SIG): bone tumors. Oral educational session presented at: APTA Combined Sections Meeting, Las Vegas, NV. February 2014.

3. **O'Mara K**, Kapoor E, Braswell A. The role of physical therapy in pediatric hematology/oncology: more than just lab values. Oral educational session presented at: APTA Combined Sections Meeting, New Orleans, LA. February 2018.

4. **Rock K**. Updates on limb salvage procedures: the role of physical therapy. Oral presentation at: Musculoskeletal Oncology Conference - Pediatric Grand Rounds, Children's Hospital of the King's Daughters, Norfolk, VA. February 2018

5. **Rock K.** Exploring postural control during walking and running in acute lymphoblastic leukemia childhood cancer survivors. Oral presentation at: University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science - Research Seminar. Baltimore, MD. December 2018.

6. **Rock K**, Lenker H, Thompson A. How not to be afraid of kids (and parents of kids) with cancer. Oral educational session presented at: APTA Combined Sections Meeting, Washington, DC. January 2019.

7. **Rock K**. Examining muscle in child and adolescent bone tumor survivors. Oral presentation at: University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science - Research Seminar. Baltimore, MD. April 2019.

8. Nelson C, **Rock K**, Ruble K, Levin AS, Henshaw RM, Marchese V. Alterations in vastus lateralis architecture in individuals with limb-sparing surgery after osteosarcoma: preliminary results. Presented by Nelson C at: International Society of Biomechanics (ISB) and Annual Meeting of the American Society of Biomechanics (ASB), Calgary, Alberta, Canada. August 2019.

9. **Rock K**. Exploring muscle characteristics and functional performance in healthy children, adolescents, and young adults: preliminary data. Oral presentation at: University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science - Research Seminar. Baltimore, MD. October 2019.

10. **Rock K**. Muscle Assessment in Older Adults with Peripheral Artery Disease (PAD). Oral presentation at: University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science - Research Seminar. Baltimore, MD. February 2020.

11. **Rock K**, Nelson C, Addison O, Marchese V. Relationships between quadriceps muscle strength and thickness in healthy children: implications to muscle performance

testing. Oral presentation at: University of Maryland School of Medicine Graduate Research Conference. March 2020.

12. **Rock K**. Exploring the relationship of neuromuscular activation to gross motor performance in school-aged children. Oral presentation at: University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science - Research Seminar. Baltimore, MD. October 2020.

13. **Rock K.** A Glimpse into Pediatric Oncology Rehabilitation. Virtual seminar provided for oncology clinical staff at Cleveland Clinic Children's Hospital for Rehabilitation, Cleveland, OH. December 2020.

14. **Rock K,** Stevenson D, Marchese V. Unraveled: Using a Diagnostic Framework to Demystify Movement Problems in Pediatric Cancer. Oral education session presented at: APTA Combined Sections Meeting, Orlando, FL (virtual). February 2021.

15. **Rock K**. Physical Impairments and Function in Children with Sickle Cell Disease: Results from a Systematic Review of the Literature. Oral presentation at: University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science - Research Seminar. Baltimore, MD. April 2021.

16. **Rock K**, Tanner L, Sparrow J, Lyons K, Lesmeister D, Keppner K. Taking the Next Steps in Pediatric Oncology: Let's Discuss Where We Are and Where We Are Going. Symposium presented at: American Congress of Rehabilitation Medicine 98th Annual Conference. Virtual. September 2021.

17. Tanner L, Lesmeister D**, Rock K**, Keppner K, Lyons K Sparrow J. Pediatric Cancer Rehabilitation: Screenings and Assessments for Oncology and Rehabilitation Healthcare Providers. Symposium presented at: American Congress of Rehabilitation Medicine 98th Annual Conference. Virtual. September 2021.

18. **Rock K**. Skeletal Muscle Size and Strength and Relationships to Gross Motor Performance in Children with Sickle Cell Disease. Oral presentation at: University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science - Research Seminar. Baltimore, MD. March 2022.

Posters Presentations

1. Buccieri N, Darling J, Kimball K, Myers M, **O'Mara K**, Cecconi C. Interdisciplinary teamwork in Antigua: reflections on culture and education. Poster presented at: James J. Whalen Academic Symposium, Ithaca College, Ithaca, NY. April 2006.

2. Nalette E, Dulkerian J, Galletta C, Lesslie M, **O'Mara K**, Wolf R. The meaning of compassion to individuals with spinal cord injuries: a qualitative study. Poster presented at: Ithaca College Graduate Physical Therapy Research Symposium, Ithaca, NY. April 2008.

3. Burns C, Orlando M, Sulkes S, Mruzek DW, Hebert EB, Yingling JT, **O'Mara K**, Nichols S, Barzotto L, Ryan M, Vogler-Elias D, Roesser J, Gemmell P. Children with special health care needs: evaluating care coordination services for children diagnosed with an autism spectrum disorder. Poster presented at: International Meeting for Autism Research (May 2009) *and* Academy Health Annual Research Meeting (June 2009), Chicago, IL.

4. Mruzek DW, Burns C, Hebert EB, Orlando M, Sulkes S, Yingling JT, **O'Mara K**, Nichols S, Barzotto L, Ryan M, Vogler-Elias D, Roesser J, Gemmell P. Practitioners' disclosure of a child's diagnosis of autism to parents: current practices and identified barriers to effective communication and support. Poster presented at: International Meeting for Autism Research (May 2009) *and* Academy Health Annual Research Meeting (June 2009), Chicago, IL.

5. **Rock K**, Creath R, Marchese V. Exploring postural control during walking and running in acute lymphoblastic leukemia childhood cancer survivors (ALL CCS). Poster presented at: University of Maryland School of Medicine Graduate Research Conference (March 2019) *and* PTRS Research Day (May 2019), Baltimore, MD.

6. **Rock K**, Addison O. Assessing dynamic balance using the Four Square Step Test in adults with peripheral artery disease. Poster presented at: APTA Combined Sections Meeting, Denver, CO (February 2020) *and* APTA Maryland Mini-CSM, Annapolis, MD (February 2020).

7. **Rock K**, Gray V, Lanza MB, Marchese V. Exploring the relationship between neuromuscular activation and a jumping task in healthy children. Poster presented at: University of Maryland School of Medicine PTRS Research Day, Baltimore, MD. May 2020.

8. **Rock K**, Nelson C, Marchese V. Muscle and mobility in adolescent survivors of childhood bone tumors: exploring a functional strengthening intervention. Poster presented at: APTA Combined Sections Meeting, Orlando, FL. February 2021. *Awarded APTA Oncology Outstanding Research Award – Poster Presentation.

9. **Rock K**, Gray V, Lanza MB, Marchese V. Rectus femoris muscle activation and the relationships with gross motor performance in children and young adults. Poster presented at: University of Maryland School of Medicine Graduate Research Conference, Baltimore, MD. March 2021.

10. **Rock K**, Lanza MB, Nelson C, Gray V, Marchese V. Relationships between knee extension strength, muscle thickness, and gross motor performance: application of clinical measures in children and young adults. Poster presented at: University of Maryland School of Medicine PTRS Research Day, Baltimore, MD. May 2021.

11. **Rock K**, Ho S, Marchese V. Muscle performance impairments and gross motor performance limitations in children with sickle cell disease. Poster presented at: APTA Combined Sections Meeting, San Antonia, TX. February 2022 *and* University of Maryland School of Medicine Graduate Research Conference, Baltimore, MD. March 2022.

12. Ho S, **Rock K**, Marchese V. Reliability of assessing diaphragm thickness via B-mode ultrasound in health children and adolescents. Poster presented at: APTA Combined Sections Meeting, San Antonia, TX. February 2022. *Awarded APTA Academy of Cardiovascular and Pulmonary Physical Therapy Best Poster Award.

13. **Rock K**, Marchese V, Ho S, Gray VL. Exploring neuromuscular performance in children and adolescents with sickle cell disease. Poster presented at: University of Maryland School of Medicine PTRS Research Day, Baltimore, MD. May 2022.

ABSTRACT

Dissertation Title: Skeletal muscle properties, gross motor performance, and quality of life in survivors of childhood hematologic and oncologic health conditions

Kelly Rock, PT, DPT, Doctor of Philosophy, 2022

Dissertation Research Directed by: Victoria Marchese, PT, PhD, Jane Kroh Satterfield Professor of Physical Therapy and Rehabilitation Science and Chair, Department of Physical Therapy and Rehabilitation Science University of Maryland School of Medicine

Background: Gross motor skills such as running, hopping, and jumping are important for age-appropriate activities and sports throughout the lifespan. Difficulty with gross motor skills negatively affects one's quality of life (QoL). Gross motor skills require the activation of the large lower-extremity skeletal muscles and the muscle properties of these muscles such as strength, size, and neuromuscular activation contribute to gross motor performance. Children with chronic hematologic and oncologic health conditions, such as sickle cell disease (SCD) and musculoskeletal sarcoma (MSS), are at risk for impairments in skeletal muscle properties, limitations in gross motor performance, and reduced QoL. However, there remains a lack of knowledge of skeletal muscle properties and their relationships to gross motor performance and QoL in children with chronic hematologic and oncologic health conditions.

Methods: Quadriceps skeletal muscle properties (strength, size, and neuromuscular activation), gross motor performance, and quality of life were measured in children with SCD and adolescent, young adult MSS survivors of childhood cancer (CCS), and healthy

controls. The effect of functional strengthening (PT-STRONG) was assessed in a sub-population of MSS CCS.

Results: Children with SCD and adolescent and young adult MSS CCS presented with impairments in muscle properties including decreased knee extension strength and lower quadriceps rate of muscle activation (RoA), poorer gross motor performance, and reduced QoL compared to controls. MSS CCS demonstrated decreased surgical limb knee extension strength, and quadriceps muscle thickness and RoA compared to their non-surgical limb, and decreased bilateral knee extension strength, gross motor performance, and physical QoL compared to normative values. In children with SCD, positive relationships between RoA, strength, gross motor performance, and quality of life were identified. In MSS CCS, positive correlations between muscle thickness and strength, and between strength and gross motor performance were identified. In response to PT-STRONG, MSS CCS participants demonstrated individual improvements in neuromuscular activation, gross motor performance, and physical QoL.

Conclusions: Children with SCD and adolescent and young adult MSS CCS demonstrate changes in muscle properties that are associated with limitations of gross motor performance and reduced quality of life.

Skeletal muscle properties, gross motor performance, and quality of life in survivors of childhood hematologic and oncologic health conditions

by
Kelly E. Rock

Dissertation submitted to the faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements of the degree of
Doctor of Philosophy
2022

DEDICATION

To my husband, Matthew “Matt” Rock, for believing in me and providing me support to persevere through unprecedented challenges and to develop into a stronger, smarter, and healthier human.

ACKNOWLEDGMENTS

To my son, Joey Rock, for being cute and kind. To my parents, Diane and Donald O'Mara, for teaching me the importance to academics, determination, stubbornness, and excellence.

To my advisor Dr. Victoria "Tori" Marchese for your support, mentorship, challenges, and triumphs throughout this academic, professional, and personal journey. I am grateful for your passion for children with hematologic and oncologic health conditions, the profession of physical therapy, the science of research, and the art of caring.

To my committee members, in historical order: Dr. Robert "Bob" Henshaw for taking those initial moments to listen to my questions and for all the subsequent time you have devoted to a collaborative relationship with me and for the rehabilitative needs of your patients; Dr. Odessa Addison for trusting me to be submerged in your "muscle world" and the constant support and nerd sessions that transpired; Dr. Vicki Gray for teaching more than the ABCs of EMG and challenging me to be a better researcher with every passing interaction; Dr. Christopher "Chris" Ward for recognizing the importance of bench-to-bedside muscle research and being patient with my learning of complex muscle physiology concepts well-beyond my 20th century biology roots; and Dr. Mary Rodgers for being a pioneer in the applications of biomechanics to physical therapy research and practice.

To the many important people I have met along this PhD journey, specifically the PTRS faculty, students, and staff; the PhD Program Director Dr. Kelly Westlake; the PhD coordinators Janice Abarro and Joyce Johnson; the PTRS Administrators: Karen Sacks and Melissa Roane; the savvy technical support of Angel Chavez and Cameron Bailey; the financial coordination of Surekha Vishwasrao and Chinwe Ekejiuba; DPT students and research volunteers, interns, and assistants, particularly: Jackie Peters, Dr. William Knight, Dr. Mary Williams, Dr. Abigail Salazar, Dr. Andria Harpold, Kerry Shutt, Kara Bruzdzinski, Beza Ketema, and Afnan Gimie.

To all my fellow PhD students, for making me laugh and holding my hand through the craziness of PhD studies. An extra dose of gratitude to my PhD brother, Dr. Simon Ho.

To my valued mentors Dr. Christa Nelson and Dr. Marcel Bahia Lanza.

I am very grateful for the financial support of the National Institute of Arthritis and Musculoskeletal and Skin Disorders T32 Interdisciplinary Training Program in Muscle Biology and the Department of Physical Therapy and Rehabilitation Science. This work was funded by the Foundation for Physical Therapy Snyder Research Grant, the Gladys E. Wadsworth Physical Therapy Research Fund, and the PhD Endowment Fund from the University of Maryland School of Medicine, Department of Physical Therapy and Rehabilitation Science.

Last, but certainly not least, to all the children with hematologic and oncologic health conditions and their families that have motivated me to further pursue research to address their unique needs, and to all the children and families that participated in these research projects.

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LIST OF ABBREVIATIONS

9RW	9-minute run walk
BF	Biceps femoris
BOT	Bruininks-Oseretsky Test of Motor Proficiency
CCS	Survivor of childhood cancer
CCI	Co-contraction index
cm	Centimeter
CT	Computed tomography
EMG	Electromyography
FMA	Functional Mobility Assessment
HHD	Handheld dynamometer
kg	Kilogram
m	Meter
MRI	Magnetic resonance imaging
MCS	Mental Component Summary
MDC_{95}	Minimal detectable change
MSS	Musculoskeletal sarcoma
MVIC	Maximal voluntary isometric contraction
PedsQL	Pediatric Quality of Life Inventory
PCS	Physical Component Summary
PROMIS	Patient-Reported Outcome Measurement Information System
QoL	Quality of life
RF	Rectus femoris

RSA	Running speed and agility
RoA	Rate of muscle activation
SCD	Sickle cell disease
SF-36v2	Short Form-36, version 2
ST	Semitendinosus
TUDS	Timed up and down stairs
TUG	Timed up and go
US	Ultrasonography
VL	Vastus lateralis

CHAPTER ONE: INTRODUCTION

1. INTRODUCTION TO THE RESEARCH FOCUS

Gross motor skills such as running, hopping, and jumping are important for age-appropriate activities and sports throughout the lifespan. Difficulty with gross motor skills negatively affects one's quality of life (QoL). Gross motor skills require the contraction of the large lower-extremity skeletal muscles and functionally intact muscle properties such as muscle strength, muscle size, and neuromuscular activation. Children with chronic hematologic and oncologic health conditions, specifically sickle cell disease (SCD) and musculoskeletal sarcoma (MSS), are at risk for impairments in skeletal muscle properties, limitations in gross motor performance, and reduced QoL. However, there remains a lack of knowledge of skeletal muscle properties and the relationships to gross motor performance and QoL in children with hematologic and oncologic health conditions. Therefore, exploration of these muscle properties is needed in children with chronic health conditions.

An estimated 2,000 newborns are diagnosed with SCD in the United States per year.[1,2] In children with SCD, the sickled form of hemoglobin (S) results in improper transportation of oxygen and blood flow, known as sickle cell anemia. The adverse changes in the red blood cell can lead to vaso-occlusion in small blood vessels and local ischemia in body tissues, resulting in painful episodes, known as vaso-occlusive crises. Recurrent vaso-occlusive crises and chronic anemia can lead to long-lasting damage to body organs and tissues and create an inflammatory cascade, which can cause further damage to body tissues including skeletal muscle.[2–4] The current medical management for SCD that targets disease modification and symptom management includes pharmacological agents such as

hydroxyurea and L-glutamine, and procedures such as blood transfusion and bone marrow transplant.[5] Approximately 750 children and adolescents per year in the United States are diagnosed with MSS of the bone, such as osteosarcoma and Ewing sarcoma.[6,7] MSS can affect any bone, but most commonly occur in long bones of the lower and upper extremities (i.e., femur, tibia, and humerus) or the pelvis.[8] Although MSS account for 3.4% of childhood cancers, MSS survivors of childhood cancer (CCS) comprise a patient population that has a high likelihood of recovery and survival with a 5-year overall survival rate of 70%.[6,7] Medical treatments typically consist of six or more months of chemotherapy combined with surgical tumor resection. Limb-sparing surgery (LSS), the most common surgical procedure for MSS local control, includes bone and/or soft tissue removal, reconstruction of resected bone segments, and muscular or tendon re-routing.[9] To ensure the entire cancerous tumor is removed, the resection of both cancerous tissues and healthy tissues are often needed.[9] The chemotherapeutic agents and surgical techniques used to treat MSS affect both cancerous and normal cells and cause short- and long-term side effects, including impairments of skeletal muscle such as muscle atrophy, weakness, and impaired contraction physiology.[9–14]

Children with SCD and MSS CCS are at risk for impaired muscle properties (i.e., muscle strength, muscle size, and neuromuscular activation), limited gross motor performance, and lower health-related QoL. Previous studies in children with SCD have identified impaired muscle strength of ankle plantarflexion, handgrip, and the back compared to healthy controls.[15] Children with SCD also presented with activity limitations while performing specific activities required for participation in school, play, and sports activities.[15–17] Similarly, MSS CCS have impaired knee strength[18–20] not only in the

surgical limb but also in the non-surgical limb and poorer gross motor performance compared to controls without health conditions.[21–23] Muscle size and neuromuscular activation have not been explored in children with SCD or MSS CCS. In other complex childhood health conditions such as cerebral palsy and acute lymphoblastic leukemia, relationships have been reported among muscle properties, gross motor performance, and QoL.[23–25]

Comprehensive assessment of muscle strength, muscle size, neuromuscular activation, and gross motor performance are needed in pediatric hematologic and oncologic populations. Due to the pathophysiological effects of SCD and MSS on skeletal muscle, these populations would significantly benefit from further exploration of skeletal muscle. The current body of literature exploring skeletal muscle in survivors of childhood SCD and MSS is just touching the surface. In order to transform rehabilitation referral, screening, and interventions, a comprehensive study of skeletal muscle and the underlying mechanisms that affect muscle strength and gross motor performance is needed. The enhanced knowledge and clinical applications of the quantification of muscle strength, muscle size, neuromuscular activation and identification of the relationships to gross motor performance and QoL are essential to advance rehabilitative care for children with hematological and oncological health conditions.

2. SPECIFIC AIMS

The overall objective of this dissertation is to examine muscle properties, gross motor performance, and QoL children with SCD and adolescent and young adult MSS CCS. The central hypothesis is that children with SCD and MSS CCS will demonstrate impaired muscle properties, limitations in gross motor performance, and poor QoL and that

relationships among these variables exist. Additionally, we hypothesize that a 6-week, two times per week functional strengthening training can change muscle properties, gross motor performance, and QoL in MSS CCS.

Aim 1: Examine muscle properties (strength and size), gross motor performance, and quality of life in children with SCD and MSS CCS.

Hypothesis 1a: Children with SCD and MSS CCS will present with decreased knee extension strength (handheld dynamometry), vastus lateralis (VL) and rectus femoris (RF) muscle thickness (ultrasonography), gross motor performance (standardized functional assessments), and quality of life (questionnaires) compared to a normative sample.

Hypothesis 1b: Compared to the non-surgical limb, MSS CCS will have lower surgical limb knee extension strength and VL and RF muscle thickness.

Hypothesis 1c: VL and RF muscle thickness will have moderate positive correlations with knee extension strength in children with of SCD and MSS CCS.

Hypothesis 1d: Knee extension strength will have moderate positive correlations with gross motor performance and quality of life in children with SCD and MSS CCS.

Hypothesis 1e: Gross motor performance will have a moderate positive correlation with quality of life in children with SCD and MSS CCS.

Aim 2: Examine muscle properties (neuromuscular activation) in children with SCD and MSS CCS.

Hypothesis 2a: Children with SCD will present with decreased VL and RF rate of muscle activation (electromyography) and increased knee muscle co-contraction indices (electromyography) compared to a normative sample.

Hypothesis 2b: Compared to the non-surgical limb, MSS CCS will present with decreased surgical limb VL and RF rate of muscle activation (electromyography) and increased thigh muscle co-contraction (electromyography).

Hypothesis 2c: VL and RF rate of muscle activation will have moderate positive correlations with knee extension strength in children with SCD and MSS CCS.

Hypothesis 2d: VL and RF rate of muscle activation will have moderate positive correlations and co-contraction indices will have moderate negative correlations with gross motor performance in children with SCD and MSS CCS.

Aim 3: Examine whether muscle properties (strength, size, and neuromuscular activation), gross motor performance, and quality of life change after a 6-week functional strengthening intervention (PT-STRONG) in MSS CCS.

Hypothesis 3: After PT-STRONG, MSS CCS will demonstrate improvements in muscle properties (knee extension strength, VL and RF muscle thickness, and neuromuscular activation [rate of muscle activation and co-contraction indices]) and gross motor performance, but not in quality of life measures.

3. ORGANIZATION OF DISSERTATION

This dissertation includes seven chapters. Chapter two presents the prior literature related to the role and measurement of skeletal muscle properties in childhood, the known impairments of skeletal muscle in children with SCD and MSS CCS, and the need for

comprehensive skeletal muscle assessment in survivors of childhood hematologic and oncologic health conditions. Children and adolescents with SCD and adolescents and young adult MSS CCS are at risk for changes in skeletal muscle properties including muscle strength, size, and neuromuscular activation and these changes may affect gross motor performance and QoL. Few studies have explored muscle strength in children with SCD and MSS CCS. However, no previous studies have explored muscle size and neuromuscular activation in these populations. In chapter three, we explored relationships between the properties of muscle size using ultrasonography and muscle strength using handheld dynamometry (HHD) in children, adolescents, and young adults without health conditions. This study identified positive relationships between larger muscle size and higher knee extension strength. In chapter four, we explored relationships between rectus femoris muscle rate of activation (RoA) using electromyography (EMG), knee extension strength using HHD, and gross motor performance in younger children, older children, and young adults without health conditions. In addition, relationships between rate of quadriceps muscle activation and gross motor performance in children, adolescents, and young adults without health conditions were identified. In chapters five and six, we explored muscle properties (strength [HHD], size [US], and neuromuscular activation [EMG]), gross motor performance, and QoL and relationships among these outcomes in survivors of SCD (chapter five) and childhood MSS (chapter six) (Specific Aims 1 and 2). We also explored changes in response to a 6-week PT-STRONG intervention with a sub-sample of MSS CCS (Specific Aim 3). We identified that children with SCD presented with impaired knee extension strength, VL RoA, gross motor performance, and QoL compared to controls. In children with SCD, positive relationships between muscle

strength, gross motor performance, and QoL were identified. Compared to the contralateral non-surgical limb, MSS CCS presented with lower surgical limb knee extension strength, and quadriceps muscle thickness and RoA. MSS CCS also presented with decreased bilateral knee extension strength, gross motor performance, and physical QoL compared to normative values. In MSS CCS, positive relationships between larger quadriceps muscle thickness and greater knee extension strength, and between greater knee extension strength better gross motor performance were identified. In a sub-sample of MSS CCS who underwent a 6-week, two times per week functional strengthening intervention (PT-STRONG) demonstrated individual improvements in VL muscle thickness, VL and RF EMG RoA during a step-up task, gross motor performance, and physical QoL. The final chapter, chapter seven, summarizes the finding of this dissertation project and outlines future directions.

CHAPTER 2: SKELETAL MUSCLE MEASUREMENTS IN PEDIATRIC HEMATOLOGY AND ONCOLOGY: ESSENTIAL COMPONENTS TO A COMPREHENSIVE ASSESSMENT[1]

ABSTRACT

Children with hematologic and oncologic health conditions are at risk of impaired skeletal muscle strength, size, and neuromuscular activation that may limit gross motor performance. A comprehensive assessment of neuromuscular function of these children is essential to identify the trajectory of changes in skeletal muscle and to prescribe therapeutic exercise and monitor its impact. Therefore, this review aims to: a) define fundamental properties of skeletal muscle; b) highlight methods to quantify muscle strength, size, and neuromuscular activation; c) describe mechanisms that contribute to muscle strength and gross motor performance in children; d) recommend clinical assessment measures; and e) illustrate comprehensive muscle assessment in children using examples of sickle cell disease and musculoskeletal sarcoma.

1. INTRODUCTION

The screening and measurement of neuromuscular function in an essential component of the physical examination to identify impairment, provide appropriate referrals, and track changes due to medical and exercise interventions. Neuromuscular strength is the measure of an individual's ability to exert maximal muscle force and produce joint torque statically or dynamically.[26] Strength assessment is routine in physicians', nurses', occupational therapists', and physical therapists' practice. The Guide to Physical Therapy Practice and the Movement Systems Diagnosis Framework identify

[1] Rock K, Addison O, Gray VL, Henshaw RM, Ward C, Marchese V. *Crit Rev Oncol Hematol.* Under Review.

muscle performance and force production deficit as key elements of the physical therapy examination.[27–29] Tests and measures of muscle performance includes muscle force, joint torque, power, and endurance.[29]

Persistent deficits in neuromuscular force production may arise from primary deficits at the muscle, neuromuscular junction, peripheral nerve, or central nervous system. The deficits may affect a focal joint or multiple joints.[27,28] The transient deficit that arises from activity, and recovers with rest, is termed muscle fatigue.[27,28] Ideally, clinical assessments should include outcome measures that aid in identifying the underlying mechanisms that contribute to neuromuscular deficit. Here we focus on children with hematologic and oncologic health conditions in which the disease condition and the medical treatment have negative impacts on neuromuscular function, particularly at the level of the skeletal muscle.[4,10,11,18–20,30,31] Understanding the underlying mechanisms that contribute to muscle strength and those that affect gross motor performance, will allow for the appropriate selection of objective assessment measurements and the development of targeted exercise interventions for children with hematologic and oncologic health conditions.

This review aims to: a) define the fundamentals properties of skeletal muscle; b) highlight research and clinical methodology to quantify skeletal muscle strength, size, and neuromuscular activation; c) describe contributors to skeletal muscle strength in children and adolescents; d) recommend clinical assessment measurements of skeletal muscle; and e) illustrate examples for comprehensive muscle assessment in children with hematological and oncological health conditions using sickle cell disease and musculoskeletal sarcoma diagnoses.

2. SKELETAL MUSCLE FUNDAMENTALS

2.1 Anatomy and Physiology

Skeletal muscle is primarily responsible for voluntary and graded bodily movement.[32] The anatomic structure of skeletal muscle is comprised of muscle fascicles, bundles of long multi-nucleated muscle fibers encased in fibrous connective tissue. Each muscle fiber contains highly organized bundles of myofibrils whose periodic arrangement of thick filament myosin and thin filament actin contractile proteins, termed sarcomeres, defines the 'striated' appearance under the light microscope. Interdigitated with the sarcomeres is the specialized sarco-endoplasmic reticulum (SR) that stores calcium (Ca^{2+}). needed for activation of the thick filament to elicit myosin contraction.

Through a process called excitation-contraction coupling, motor nerve action potentials arriving at the pre-synaptic motor end-plate are transduced into acetylcholine signals released into the neuromuscular junction (NMJ) synapse that generate action potentials in the muscle fiber. It is the rapid propagation of action potentials through invaginations of the muscle cell membrane (t-tubules) that activate membrane L-type Ca^{2+} channels which elicit Ca^{2+} release from ryanodine receptor Ca^{2+} channels in the SR to drive muscle fiber contraction. The relaxation of the muscle fiber is marked by the cessation of action potentials and the sequestration of Ca^{2+} back into the SR via the sarco-endoplasmic ATPase (SERCA).

Within the muscle, groups of muscle fibers are innervated by a motor neuron, together called a motor unit. Motor units vary in the number of fibers, which is inversely proportionate to the level of precision. Smaller motor units that consist of fewer muscle

fibers perform precision actions such as finger and eye movements. On the other hand, larger motor units of many muscle fibers perform more powerful movements, for example the quadricep muscles of the legs. A group of motor units of varying sizes are innervated to provide coordinated contractions within a single muscle to produce the appropriate movement patterns required for gross motor and fine motor tasks.

Specific types of muscle contraction depend on changes in tension or in length of the muscle fibers.[32] The two main types of skeletal muscle contractions are: 1) isometric – increased muscle tension but no change in muscle length; and 2) isotonic – no change in muscle tension but a change in muscle length. Isotonic contractions are further differentiated by concentric contractions in which the muscle length shortens and during eccentric contractions in which the muscle lengthens. Muscle contractions can also be described as isokinetic if the muscle force causes the joint to move at a constant speed. Gross motor tasks such as walking, running, and jumping require a complex interplay between graded muscle activation and orchestrated muscle contraction mechanics, such as isometric contractions that stabilize the torso and a combination of concentric and eccentric contractions that move and then brake the lower extremity joints respectively.

2.2 Muscle Macrostructure

The architecture and anatomic size of skeletal muscle are key determinates of its function (i.e., force, shortening velocity, and the extent of shortening [excursion]). Thus, the quantification of muscle architecture and anatomic size provide important insights into the gain or loss of function, and measurements are used to quantify muscle macrostructure. Muscle architecture is defined as the length of the muscle fibers and their physical arrangement relative to the tendon.[33,34] Given the resolution needed to visualize muscle

fibers, fascicle length is often the surrogate measure for muscle fiber length. Evidence that the number of sarcomeres in series (i.e., muscle fiber length) is positively related to the velocity and excursion, therefore, a change in muscle fiber length can impact shortening velocity, excursion, or muscle power.[33,35] Pennation angle is the measured geometric angle of muscle fibers in relation to the long axis of the muscle/tendon.[33,34] Given that increased pennated muscle have an increased number, yet shorter, muscle fibers per unit volume, these muscles tend to be of greater mass, and produce more force, but have decreased shortening velocity and excursion than non-pennated muscles. [33,34]

Muscle force production is correlated to the number of sarcomeres in parallel which is related to the number of muscle fibers in cross-section.[33,34] Therefore, the cross-sectional area of the muscle measured at its widest point (two dimensional) is often used as a measure of anatomic size. In an attempt to account for muscle fiber pennation, the physiological cross-sectional area (PSCA) is calculated as the cross-sectional area perpendicular to the muscle fibers. While this has been common practice, recent evidence suggests that muscle force measured *in vivo* is not significantly impacted by pennation angle[36]

While the gold standard measure of human skeletal muscle architecture is invasive whole muscle dissection or muscle biopsy, non-invasive measures such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography (US) have been validated to quantify pennation angle, muscle fiber and fascicle length, cross-sectional area, and muscle thickness (Figure 1). MRI, CT, US imaging and bioelectric impedance can also supply important information about muscle volumes. These imaging methods allow for muscle macrostructure to be assessed independently from or in response to muscle contraction and provide insight about muscle performance capacity.

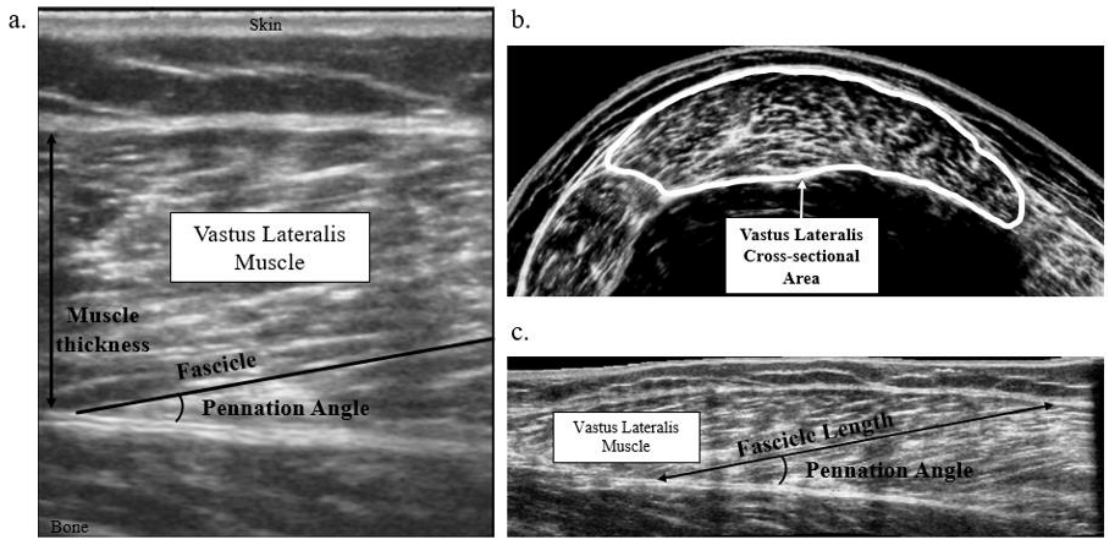

Figure 1. Ultrasonography images of the vastus lateralis muscle. a) static long-axis image identifying muscle thickness, fascicle, and pennation angle; b) extended-field-of-view short axis image identifying muscle anatomical cross-sectional area; c) extended-field-of-view long axis image identifying fascicle length and pennation angle.

2.3 Muscle Performance

Assessments of muscle performance are used to quantify muscle function and to track its change with disease, treatment, or training. Here we focus on *in vivo* assessments in humans where muscle force is an indirect measure of a major muscle contracting across a joint (e.g., quadriceps via knee extension) to generate torque on a lever (i.e., tibia, with force measured at the distal tibia) or a more complex action of multiple muscles (e.g., handgrip). Isokinetic dynamometers can measure the amount of muscle force and joint torque during conditions when the joint does not move (isometric); moves at a constant speed (isokinetic); or moves with a constant tension (isotonic). Handheld dynamometers measure isometric muscle force and joint torque.[37] Maximal muscle force can also be measured using one-repetition max (1RM) testing, the greatest amount of weight that can be moved through an isolated single joint or a functional task such as handgrip or a leg press for one repetition but not for a second repetition.[38] In clinical practice, clinicians often

use manual muscle testing to rate the level of maximal muscle force compared to an external force applied by the assessor.[39] Muscle power, the product of force and contraction velocity, provides information about the ability for explosive or ballistic movements and can be measured through isokinetic and isotonic contractions and timed, rapid functional tasks such as leg presses, sit-to-stands, jumping, or stair climbing.[40–42] Muscle endurance can be measured by examining muscle fatigue as it provides a measure of the muscle's ability to sustain a contraction and force over a longer duration, often greater than 30 seconds. Muscle endurance or fatigue can be quantified after a prolonged or repetitive muscle contraction, typically isometric, with force or torque measurements to indicate the failure of muscle force or torque.[42,43] A summary of assessment techniques to measure muscle performance are outlined in Figure 2.

2.4 Neuromuscular Activation

The contraction of skeletal muscles is under volitional control initiated in the brain, often referred to as central control. Specifically, biochemical processes of voltage changes across cellular membranes (action potential propagation) and chemical synapses, carry signals from the central nervous system through motor neurons to the motor units to regulate skeletal muscle fiber contraction. Each motor unit acts as a group with a unique pattern of activation. Activation of more or fewer motor units causes graded muscle contraction and relaxation, respectively. This neuromuscular activation can be measured using electromyography (EMG), a technique that records motor unit electrical signals (action potentials). EMG, measured in a unit of volts, can quantify the number and intensity of muscle fibers contracting in relationship to a recording electrode, which can be placed on the surface of the skin over (surface EMG) or directly into (needle/fine wire EMG) the

muscle of interest. Motor unit recruitment and firing frequency can be decomposed from multiple electrodes placed on the skin over the muscle (high-density surface EMG) or needle/fine wire EMG. Surface EMG, a non-invasive measurement of muscle fibers directly under the electrode, is commonly used in rehabilitation science as a measure of neuromuscular activation.[44] The amplitude of the EMG signal provides insight into the intensity and velocity of the muscle contraction and regulation of force, and the frequency domain of the EMG signal is a power tool for assessing muscle fatigue where there is a downward shift in frequencies with fatigue. Other neuromuscular activation measures including the ability to quickly (rate of activation) and selectively (co-contraction) activate skeletal muscles are important in understanding the complex muscle activation patterns required for gross motor performance.

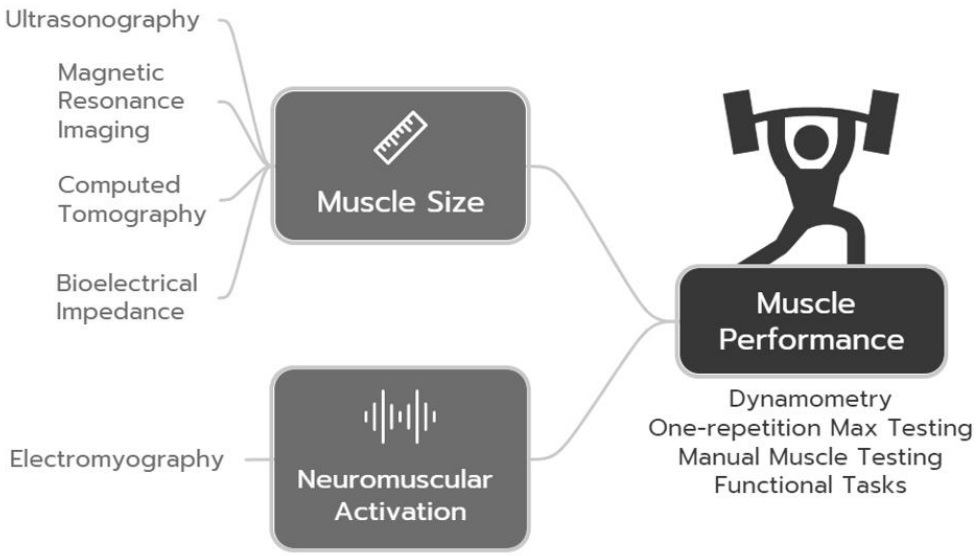

Figure 2. Assessment techniques to measure muscle performance.

3. MUSCLE STRENGTH IN CHILDREN AND ADOLESCENTS

Skeletal muscle strength, a measure of an individual's ability to exert maximum muscle force and produce joint torque statically or dynamically, is an important indicator

of muscle performance.[35] Muscle strength of the lower extremity muscles is associated with the ability to perform gross motor skills.[26] [45,46] Therefore, lower extremity muscle strength is an important element of the rehabilitation assessment to screen for muscle impairment such as muscle strength deficits or to measure changes in response to exercise interventions. Muscle strength impairments, also referred to as muscle weakness or force production deficits, are important to identify in children and adolescents given the relationship between muscle strength and motor performance.[47–56]

3.1 Contributors to Muscle Strength

Muscle strength measurements provide important information about the muscle's ability to produce force or torque, however, these measures provide limited information about the underlying mechanisms that contribute to muscle strength including muscle size, neuromuscular activation, and other biomechanical and developmental considerations. Therefore, to comprehensively measure muscle strength, these additional aspects of skeletal muscle properties and performance need to be assess the underlying mechanism of strength production and muscle performance.

3.1.1 *Muscle Size*

Studies investigating muscle size in healthy children describe moderate to strong correlations between skeletal muscle strength and power with the cross-sectional area, volume, and thickness measurements.[57–61] MRI, CT, and US imaging measuring skeletal muscle volume, cross-sectional area, and muscle thickness have identified decreased muscle size in children with chronic health conditions such as cerebral palsy and hemophilia.[47–56,62,63] The size of the lower extremity muscles is positively correlated with muscle strength.[62,63] Increased lower extremity size is associated with improved gross

motor performance measures such as the Gross Motor Function Measure (GMFM),[50,51,55] the Pediatric Evaluation of Disability Inventory (PEDI),[55] and gait characteristics.[52] Thus, muscle size measured by noninvasive imaging can provide important information about muscle strength and gross motor performance in children with and without health conditions.

3.1.2 *Neuromuscular Activation*

EMG is used to measure neuromuscular activation, such as the rate of muscle activation (RoA) and muscle co-contraction indices. These measures can assess the capacity to rapidly activate and selectively activate the muscles around a joint during isolated and functional movements.[64–66]

3.1.2.1 Rate of muscle activation

The rate of muscle activation (RoA) is a neuromuscular measure dependent on speed and is important for maximum joint torque and the proficiency of motor skills.[46,67] RoA can be measured using surface EMG. Although the maximum torque production is limited by muscle size,[68] maximal joint torque even after normalizing for muscle size increases with age in children.[46,69–71] Therefore, in addition to muscle size, other factors may influence the capacity to generate joint torque, and neuromuscular mechanisms may contribute to these observations in children.

In adults, those with a greater rate of lower extremity muscle activation generate more torque.[72,73] There is evidence that greater early quadriceps activation (i.e. within the first 250 ms) in young adults is related to the performance of gross motor tasks commonly used in sports requiring sprinting faster and jumping higher.[74] This time period occurs before peak torque production and may indicate that the ability to activate the muscles

earlier and faster is necessary for the proficiency of gross motor skills. Neuromuscular activation differs between children and adults, with children demonstrating a lower rate of gastrocnemius muscle activation.[75] Differences in gastrocnemius activation were also demonstrated between younger and older children (age ranges: 5-6 years, 7-8 years, 9-10 years), with the older age group demonstrating a greater rate of muscle activation.[75] This suggests that the rate of muscle activation in children is an important factor that influences the early stages of torque development.[75] Lower rate of activation in younger children compared to older children and adults may also be indicative of neural maturation, which occurs from childhood through adolescence specifically through maturation of the central nervous system.[76] Children also demonstrate decreased capacity to activate type II fast muscle fibers, and may present with slower conduction in peripheral nerve, higher latency at the neuromuscular junction, and lower motor unit firing frequencies.[76] Therefore, the rate of muscle activation may provide important information related to muscle strength in children, especially during tasks that require the ability to rapidly activate the lower extremity muscles such as balance and agility tasks, and warrants further investigation.

3.1.2.2 Co-contraction

Gross motor performance requires the ability to coordinate muscle contraction among multiple joints. Surface EMG can measure co-contraction, the simultaneous activity of agonist and antagonist muscles crossing the same joint but on opposite sides of the joint. Co-contraction indices provide information about the ability to coordinate muscle contraction with low co-contraction indices during isometric joint conditions indicative of selective control.[77] High co-contraction indices may signify difficulty with selective control, underdeveloped reciprocal inhibition, learning a new skill, or pathological or

inefficient movement patterns.[77,78] In adults with Down syndrome,[79] adults with neurological conditions such as stroke,[80] and adults with orthopedic conditions such as chronic neck pain,[81] co-contraction indices have been reported to be elevated. Additionally, compared to adults, children demonstrate higher levels of thigh co-contraction during gross motor tasks such as walking,[82] and younger children presented with higher co-contraction indices compared to older children.[83] Higher levels of co-contraction during gross motor tasks decrease the efficiency of movement and increase the metabolic expenditure.[83] Damiano et al. (2000)[84] identified high thigh co-contraction in children with cerebral palsy and significant relationships between co-contraction indices during isometric strength testing and walking.[84] These studies suggest that the co-contraction index may be an important underlying mechanism that result in deficits of muscle strength and gross motor performance in children with and without health conditions.

3.1.2 Other biomechanical and developmental considerations

Muscle strength is also influenced by muscle fiber types, tendon elasticity, muscle quality, and central activation.[69,85,86] Compared to adults, children may present with fewer type II (fast-twitch) muscle fibers and more type I (slow-twitch) muscle fibers.[85] Since type II fiber motor units have faster contraction speeds, a lower ratio of fast-twitch muscle fibers may adversely contribute to the ability to produce muscle force or joint torque.[87] Inversely, the presence of increased ratios of type I fiber motor units increases endurance capacity in children compared to adults.[43,88] Overall, children have smaller muscle fibers and the size ratio between type I and type II muscle fibers are similar contrary to the expected adult size discrepancy pattern in which type II muscle fibers are larger than type I muscle fibers.[89] Another age-related change throughout childhood into adulthood is that tendon stiffness

increases.[90–92] Given that the mechanical properties affect the transfer of force to joints, decreased tendon stiffness can reduce muscle force, joint torque, and rate of muscle activation measures.[93] Additionally, fat or adipose tissue infiltration into skeletal muscle, known as myosteatosis, is associated with muscle disease processes.[94–97] Using MRI, CT, and US imaging, skeletal muscle adipose tissue quantity and quality can be assessed. Adipose tissue infiltration has been identified in children with gross motor performance limitations with diagnoses such as cerebral palsy and muscular dystrophies.[96,97] Lastly, central activation measures the differences between force elicited during a maximal voluntary muscle contraction compared to the force elicited during a maximal voluntary muscle contraction with simultaneous external electrical stimulation of the muscle or motor nerve.[98,99] Evidence supports that children have lower volitional activation compared to adults, which may contribute to lower muscle force and power production compared to adults.[99,100] Volitional activation may also influence positive changes in force production in response to exercise training without changes in muscle size.[100]

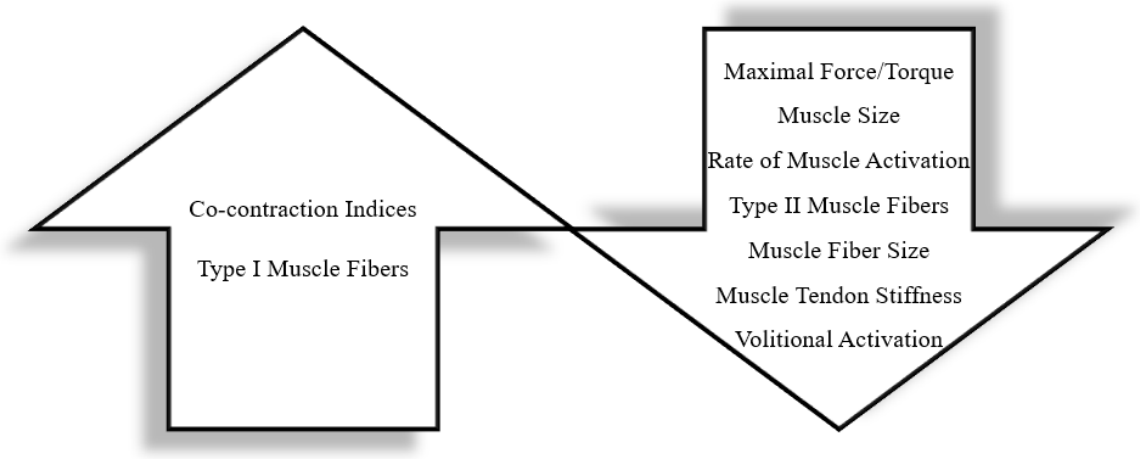

Figure 3. Expected Child-Adult Differences in Skeletal Muscle. The upward arrow includes elements of skeletal muscle that are expected to be increased in children compared to adults. The downward arrow includes elements of skeletal muscle that are expected to be decreased in children compared to adults.

4. CLINICAL ASSESSMENT OF MUSCLE

Current clinical objective assessment of muscle strength often focuses on maximum muscle force or joint torque measurements including manual muscle testing and dynamometry. Handheld dynamometry has moderate-to-good reliability and validity and is a more portable and affordable measurement to quantify muscle strength compared to "gold standard" isokinetic dynamometry (i.e., Biodex and Cybex systems) in children as young as 4 years of age.[101–105] Handheld dynamometry also has favorable psychometric properties compared to manual muscle testing.[106] Thus, the handheld dynamometer is likely the most appropriate and least expensive clinical tool for objective measurement of muscle strength in most clinical settings. Handheld dynamometry has established reliability and validity in children as young as 4 years of age.[103,105] The use of handheld dynamometry also allows for the assessment of muscle strength in a variety of testing positions and across body types, abilities, and medical conditions. Since the level of voluntary activation is unknown, children should be provided with practice trials before formal measurement to familiarize the child with the task.[40]

Noninvasive imaging assessments, such as US, can provide important measurements of muscle size. US can provide accessible, affordable, non-invasive reliable, and valid real-time muscle size measurements, including muscle thickness and anatomical cross-sectional area.[33,49,103,107,108] In healthy adults, quadriceps US muscle thickness has demonstrated concurrent validity with MRI measures of muscle thickness, volume, and cross-sectional area. [109–111] Additionally, changes in muscle thickness have been described as a consequence of post-operative changes, muscle wasting, and aging, demonstrating the clinical utility of this parameter in the examination of normal and impaired skeletal

muscle.[112–114] Therefore, US measurement of muscle thickness may serve as a beneficial non-invasive clinical assessment tool in children and can be performed when medical restrictions prohibit strength testing, or when the child cannot follow instructions to complete a strength testing protocol.

Given that the ability to perform gross motor tasks requires muscle strength, as part of clinical pediatric rehabilitation, muscle strength should be not only assessed during single-joint movements but also during functional tasks, which require multi-joint movements. Many standardized gross motor functional tests exist for children, but tests that specifically address muscle performance include the Bruininks-Oseretsky Test of Motor Proficiency, second edition (BOT-2; ages 4 to 21 years),[115] the EUROFIT Test (ages 6 to 18 years),[116] the Functional Strength Measurement (ages 4 to 10 years),[42] and the Motor Performance Test (ages 4 to 11 years).[117] These tests include gross motor tasks that require skeletal muscle force, power, endurance, rate of muscle activation, and coordination.

5. MUSCLE CONSIDERATIONS IN PEDIATRIC HEMATOLOGY AND ONCOLOGY

The comprehensive assessment of skeletal muscle is essential in children with hematologic and oncologic health conditions, especially given that these diseases and their medical treatments have negative effects on skeletal muscle. Survivors of childhood hematological and oncological health conditions, including sickle cell disease and musculoskeletal sarcoma, are at risk of impaired muscle strength. Therefore, exploration of muscle strength, muscle size, and neuromuscular activation and the relationships to gross motor performance is warranted.

5.1 Sickle Cell Disease

Sickle cell disease (SCD) is a genetically inherited condition that occurs in an estimated 2,000 newborns in the United States per year, predominately of Sub-Saharan African but also Central and South American, Middle Eastern, Asian, and Mediterranean descent.[1,2] The progression of SCD occurs over the first six to 12 months of life in infants with SCD when fetal hemoglobin transitions to abnormal adult hemoglobin (S or C), causing polymerization of abnormal hemoglobin and irregularly shaped red blood cells. In children with SCD, the sickled form of hemoglobin (S) results in improper transportation of oxygen and blood flow, known as sickle cell anemia. The sickle-shaped red blood cells lack the flexibility needed to circulate in blood vessels, are fragile, have a shortened life span, and have increased adhesiveness to vascular endothelium. These adverse changes in the red blood cell can lead to vaso-occlusion in small blood vessels and local ischemia in body tissues, resulting in painful episodes, known as vaso-occlusive crises. Recurrent vaso-occlusive crises and chronic anemia can lead to long-lasting damage to body organs and tissues and create an inflammatory cascade, which can cause further tissue damage to the bones (avascular necrosis and osteomyelitis), muscle (myonecrosis), brain (cerebral infarction), and lungs (acute chest syndrome, pulmonary hypertension, and chronic lung disease).[2–4]

Current medical management for SCD that target disease modification and symptom management include pharmacological agents such as hydroxyurea and L-glutamine, and procedures such as blood transfusion and bone marrow transplant. Hydroxyurea, also known as hydroxycarbamide, increases total and fetal hemoglobin levels, lowers leukocyte levels, and decreases the expression of adhesive molecules on red

blood cells, neutrophils, and vascular endothelium.[5] Hydroxyurea improves blood flow and reduces the number, frequency, and severity of vaso-occlusive crises.[5] L-glutamine is an FDA-approved supplement used to negate the increased demand for glutamine, a necessary amino acid, in states of stress caused by SCD.[5] Blood transfusions are commonly used to resolve acute and/or chronic anemia.[5] The only known cure for SCD is allogenic bone marrow transplantation, in which the recipient's bone marrow is medically suppressed and replaced with a donor's bone marrow.[5] The bone marrow transplantation process carries risks for graft rejection and infection and therefore is indicated only under specific circumstances.[5]

Muscle changes due to vaso-occlusive crises have been shown to lead to muscle atrophy and contractures.[4] Additionally, mice with SCD demonstrate alterations in muscle properties causing impaired muscle performance such as lower electrically induced tetanic contractions, calcium-handling deficiencies, and impaired force relaxation and post-activation potentiation, which influence the effect of previous muscle contractions on subsequent contractions.[4,30,31] Thus, children and adolescents with SCD are at risk for impairments in neuromuscular activation. Impairments in lower extremity muscle strength, muscle size, and neuromuscular activation may affect gross motor performance in survivors of childhood SCD. However, to date, no studies have explored neuromuscular activation nor the relationships between muscle properties and gross motor performance in children with SCD.[15]

Previous studies have identified impaired skeletal muscle strength in survivors of childhood SCD.[15,16,118–121] In studies comparing children with SCD with a control population, children with SCD presented with significantly decreased lower-extremity

strength, maximal handgrip strength, ankle plantarflexion strength, and back strength.[16,118–121] Moheeb et al. (2007)[16] explored leg strength in children aged 9 to 12 years with SCD (n=50), with sickle cell trait (n=50), and healthy controls (n=50). The authors report significantly lower leg muscle strength ($p<0.001$) in children with SCD (23.3±0.7 kg) compared to controls (28.1±1.4 kg).[16] Wali & Moheeb (2011)[121] explored leg strength in 93 children aged 10-14 years and reported decreased leg strength in children with SCD compared to healthy controls ($p<0.05$). In the previous two studies,[16,121] the authors mentioned the use of dynamometry, but methods of muscle testing, including testing position or muscle groups, were not reported.[16,121] Lastly, Doughtery et al. (2020)[120] measured knee extension strength of the left lower extremity using an isokinetic dynamometer at 60°/second. Children with SCD aged 5-20 years (n=21) presented with lower peak knee extension torque (49.6±27.6 Nm) compared to controls (n=23; 51.7±34.0 Nm), however, this comparison did not reach statistical significance.[120]

Gross motor performance has been reported to be limited in children with SCD performing specific tasks required for participation in school, play, and sports activities.[15–17,120,122–127] Children with SCD demonstrate walking below norm-referenced distances on the 6-minute walk test.[122–126] Children with SCD performed poorer on the 20-yard swim, 40-yard swim, 100-yard "potato race", and jump height compared to age- and sex-matched controls.[16,17] The mean Bruininks-Oseretsky Test of Motor Proficiency (BOT) Short Form, a measure of motor performance, in children with SCD was reported as 61.5 to 67.4 and was similar to controls (62.3).[120,127] However, as the BOT Short Form only has one running speed and agility measure (one-legged stationary hop) and two strength measures (push-ups and sit-ups), it is not comprehensive for assessment of the gross motor skills required

for school, play, and sports activities as compared to the complete test of subscales. The relationships between muscle strength and gross motor performance have not been explored in survivors of childhood SCD. Thus, further studies objectively measuring skeletal muscle strength, muscle size, and neuromuscular activation and relationships between these variables and gross motor performance are needed in children with SCD. The identification of underlying skeletal muscle mechanisms such as myosteatosis are warranted.

5.2 Musculoskeletal Sarcoma

Musculoskeletal sarcomas (MSS), such as osteosarcoma and Ewing sarcoma, generally arise in the second decade of life from transformed mesenchymal connective tissue cells. MSS can affect any bone, but most commonly occur in long bones of the lower and upper extremities (i.e. femur, tibia, and humerus) or the pelvis.[8] Although MSS accounts for 3.4% of childhood cancer and affects approximately 750 children and adolescents per year in the United States, these children and adolescents comprise a patient population that has a high likelihood of recovery and survival.[6,7] Improvements in chemotherapeutic, radiation, and surgical management in child and adolescent survivors of MSS have increased long-term survivorship over the past few decades, with a 5-year overall survival rate reaching 70%.[6,7]

Treatment for MSS has evolved with the primary goal of not only improving survival, but also preserving the individual's long-term physical function and social participation. Medical treatments vary but typically consist of more than six months of intensive chemotherapy with surgical tumor resection performed approximately three months into treatment. Radiation therapy may be used in tumors that are responsive to

radiation (such as Ewing sarcoma) or that may not be resectable. The most common antineoplastic chemotherapy agents for bone sarcoma are methotrexate, doxorubicin, cisplatin, vincristine, and cyclophosphamide.[128,129] Additionally, etoposide and ifosfamide are used in combination with the other chemotherapy agents or as a second-line treatment for recurrent or refractory disease.[128,129] These components of the medical intervention affect both cancerous and normal cells and cause short- and long-term side effects. Short-term side effects include nausea, vomiting, hair loss, and myelosuppression. Long-term effects include changes in the musculoskeletal (muscle weakness, decreased bone mineral density, asymmetry), neuromuscular (peripheral neuropathy), cardiopulmonary (increased risk for cardiovascular disease), and endocrine systems (short stature, diabetes mellitus, obesity).[12–14] Additionally, specific cytotoxic chemotherapy agents, such as doxorubicin, have been associated with muscle atrophy, weakness, and impaired excitation-contraction coupling via downstream effects of elevated reactive oxygen species, alpha-tumor necrosis factor, and mitochondrial dysfunction.[10,11]

In addition to chemotherapy, surgical management consists of limb amputation or resection of the tumor with extensive reconstruction, known as limb-sparing surgery (LSS). LSS is the most common surgical procedure for local control of MSS and requires bone and/or soft tissue removal, reconstruction of resected bone segments, and muscular or tendon re-routing.[9] This is necessary to ensure the cancerous tissue is adequately resected and functional potential is maintained in the limb. The resected bone segments are reconstructed by endoprosthesis, hardware, autograft, and/or allograft placement. In addition to complex surgical techniques, considerations of growth are necessary in the management of children with immature musculoskeletal systems to prevent further

secondary complications such as leg length discrepancies and biomechanical imbalances in muscle length and tension due to muscle re-routing.[9] Therefore, survivors of childhood MSS may present with impaired muscle strength and muscle properties, including smaller muscle size and lower neuromuscular activation of surgical and non-surgical limbs.

In survivors of childhood MSS of the lower extremities, muscle strength deficits are common. Tsauo et al. (2006)[18] reported ratios of muscle strength between the surgical and non-surgical limbs ranging from 37.4 to 47.5% for knee extension and 54.5 to 71.7% for knee flexion in 20 patients aged 13 to 40 years old who were treated for osteosarcoma proximal or distal to the knee joint, underwent limb-sparing total knee reconstruction, and completed chemotherapy. Muscle strength deficits are not only identified in the limb of the primary tumor but also have been identified in the non-surgical limb.[19,20] A case series by Beebe et al. (2009)[19] examined four skeletally immature children aged 9 to 11 years treated for MSS around the knee, underwent limb-sparing total knee reconstruction greater than one year prior, and received endoprosthesis lengthening. These same children demonstrated decreased non-operative knee and hip muscle force production compared to normative values for knee flexion (74%), knee extension (63%), hip flexion (35%), and hip extension (13%).[19] Corr et al. (2017)[20] also found ankle dorsiflexion, hip flexion, and knee extension strength deficits in the non-operative limb in 13 children treated for MSS with an average age of 13.5 years. These strength deficits declined from baseline to post-surgery and did not recover by 20 to 22 weeks post-surgery.[20] Compared to a control group, Fernandez-Pineda et al. (2017) found significant impairment in MSS in maximal isokinetic knee extension and ankle plantarflexion and dorsiflexion joint torque when assessing the averaged peak value of the surgical and non-surgical limb.[130] In addition to skeletal muscle

strength impairments, survivors of childhood MSS experience gross motor performance limitations such as spatiotemporal gait dysfunction, participation restrictions, and adverse general health affecting the quality of life.[18,19,21,60,130–146] One-third of survivors of MSS report high levels of physical limitations, a quarter reported moderate to severe limitations in daily tasks (25%), and survivors of MSS are more likely to report a decreased ability to perform personal care and routine activities.[138,141,143,144,146–148]

There is evidence that survivors of childhood MSS have impairments in strength that contribute to gross motor performance deficits, such as gait dysfunction, after surgical management. Carty et al. (2009)[137] examined gait characteristics in 20 individuals with osteosarcoma after limb-sparing surgery greater than 1-year after their procedure and found that the amount of soft tissue removal during surgery, knee extension strength, and knee flexion range of motion predicted changes in gait patterns that reduced surgical limb knee and hip biomechanical demands. However, further exploration of contributing factors to muscle strength such as muscle size and neuromuscular activation and their relationships to gross motor performance is needed in survivors of childhood MSS.

6. SUMMARY

The assessment of lower extremity muscle strength and its underlying mechanisms of muscle size and neuromuscular activation can provide valuable information about skeletal muscle performance in children, adolescents, and young adults with and without chronic health conditions. Clinicians and researchers should establish and implement measurements of skeletal muscle strength, size, and gross motor performance to assess changes in skeletal muscle related to health conditions and changes due to exercise interventions.

Comprehensive assessment of muscle performance, muscle size, neuromuscular activation, and gross motor performance are needed in clinical pediatric hematologic and oncologic populations. Survivors of childhood SCD and MSS undergo prolonged periods of medical and symptom management that increase inflammation and increase sedentary behaviors.[10,149,150] Due to the pathophysiological effects of SCD and MSS on skeletal muscle, these populations would significantly benefit from further exploration of skeletal muscle (Figure 4). The current body of literature exploring skeletal muscle in survivors of childhood SCD and MSS is just touching the surface. In order to transform rehabilitation referral, screening, and interventions, a comprehensive study of skeletal muscle and the underlying mechanisms that affect muscle performance and gross motor performance is needed. The enhanced knowledge and clinical applications of the measurements of muscle performance, muscle size, neuromuscular activation and identification of their relationships to gross motor performance are essential to advance rehabilitative care for children with hematological and oncological health conditions.

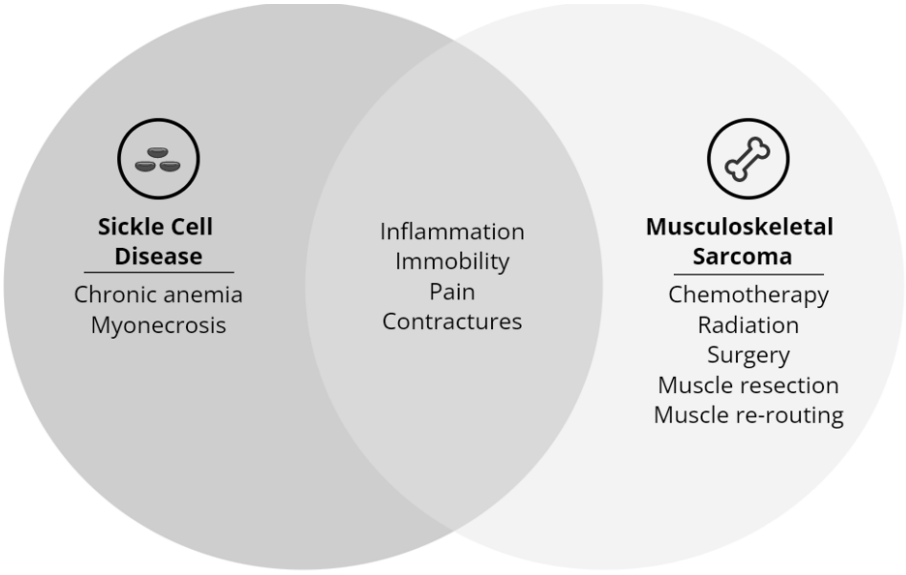

Figure 4. Underlying causes of skeletal muscle impairment in children with sickle cell disease (left), musculoskeletal sarcoma (right), and common causes across both diseases (center).

7. ACKNOWLEDGEMENTS

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CHAPTER THREE: RELATIONSHIPS BETWEEN QUADRICEPS MUSCLE THICKNESS AND STRENGTH IN HEALTHY CHILDREN, ADOLESCENTS, AND YOUNG ADULTS USING ULTRASONOGRAPHY AND HANDHELD DYNAMOMETRY

ABSTRACT

Background*:* Muscle strength is important for daily physical function, and muscle thickness is a clinically-relevant parameter that has been correlated with muscle strength. Examination of quadriceps muscle thickness and knee extension strength using ultrasonography and handheld dynamometry, which are valid, reliable, and clinically practical. However, these outcome measures and their relationships have yet to be explored together in healthy children, adolescents, or young adults.

Methods*:* In n=30 participants (6-26 years), muscle thickness of rectus femoris and vastus lateralis were measured from ultrasonography, and knee extension joint torque was measured in seated and supine positions with knee flexion at 90° and 35° by handheld dynamometry. Pearson product-moment coefficients were used to assess relationships between muscle thickness and joint torque. One-way repeated measures ANOVA tests were conducted to compare the effect of strength testing positions on joint torque, and of age group on muscle thickness and on joint torque.

Findings*:* Significant differences were identified in knee extension joint torque between knee positions 90° and 35° in seated and in supine (P<0.001). Significant positive correlations between rectus femoris and vastus lateralis muscle thickness and joint torque were observed (rectus femoris: r=0.63 to 0.75, P<0.001; vastus lateralis: r=0.50 to 0.63, P<0.005).

Interpretation*:* The results of this study suggest rectus femoris and vastus lateralis muscle thickness measurements correlate with knee extension strength, therefore, may be useful in the clinical examination of children, adolescents, and young adults and should be considered when examining contributing factors to poor muscle strength performance.

1. INTRODUCTION

Muscle strength testing is a core aspect of the clinical examination and evaluation of an individual's diagnosis, prognosis, and treatment.[44,151,152] Measurements of muscle strength and muscle size (i.e. muscle thickness), provide valuable information about how a muscle performs and help to quantify outcomes throughout the rehabilitation process.[33,151] In order to assess muscle strength in individuals with disease and/or after injury or surgery, the non-pathological relationships between muscle thickness and strength in children, adolescents, and young adults need to be identified.

Ultrasonography (US) is a reliable and valid device that can be used as an accessible, affordable, non-invasive measure of muscle size.[33,107,108] Muscle size measurements, including muscle volume, cross-sectional area, and muscle thickness are predictors of muscle force generation capacity.[33,35] Quadriceps muscle thickness has been identified as a valid estimator of muscle volume and CSA when compared with magnetic resonance imaging (MRI).[109–111] Additionally, decreases in muscle thickness have been associated with muscle post-operative changes, muscle wasting, and sarcopenia, therefore demonstrating the clinical utility of this parameter in the examination of normal and impaired skeletal muscle.[112–114] Given that muscle strength is influenced by many factors including muscle size, neuromuscular activation, muscle fiber types, tendon elasticity, muscle quality, and central activation,[69,85,86] providing objective measurements of muscle

thickness can provide important information about the potential causes of muscle strength impairments.

Lower extremity muscle strength is associated with the ability to perform gross motor skills.[45,46] Muscular strength is a measure of an individual's ability to exert maximal muscle force and produce joint torque statically or dynamically.[26] Compared with the "gold standard" isokinetic dynamometer (i.e. Biodex and Cybex systems), handheld dynamometry provides a moderate-to-good reliable, portable, and affordable measurement to quantify muscle strength in clinical settings.[101,102] The use of handheld dynamometry also allows for the examination of muscle strength in a variety of testing positions, and across different body types, abilities, and medical conditions.

Studies investigating measurements of muscle size in healthy children and adolescents describe moderate to strong correlations between muscle CSA, muscle thickness, and muscle strength.[57–61] However, these studies used lab-based measures such as non-portable ultrasound machines and large isokinetic dynamometers, making translation to the clinic difficult. US muscle thickness measurements require minimal time to perform, can provide real-time muscle architecture data, and have been used in clinical populations.[107] Children and adolescents with cerebral palsy and hemophilia have decreased muscle thickness and strength and there are relationships between these impairments and functional measures such as the Gross Motor Function Measure (GMFM) and gait characteristics.[47–56] Therefore, US measurement of muscle thickness may serve as a beneficial clinical examination tool in children, adolescents, and young adults, particularly when the examination is limited due to pain, medical restrictions that prohibit

strength testing, or there is an inability to follow instructions to complete the testing protocol.

To date, the relationships between muscle thickness and strength as measured by portable ultrasonography and handheld dynamometry within the same individuals have not been used to assess muscle performance across children, adolescents, and young adults. The primary purpose of this study was to examine the relationship between muscle thickness of rectus femoris (RF) and vastus lateralis (VL) muscles at rest as measured by ultrasonography and knee extension joint torque as measured by handheld dynamometry in children, adolescents, and young adults. The secondary purpose was to compare if there were significant differences between joint torque and muscle thickness measurements between age groups of children, adolescents, and young adults. We also compare knee extension joint torque at differing the hip and knee angles.

2. METHODS

2.1 Study Participants

We conducted a cross-sectional observational study from July 2019 to August 2019. This study was approved by the University of Maryland Baltimore Institutional Review Board. All participants provided informed consent and minors provided assent. Participants were included if they were between the ages of 6 to 26 years and were able to communicate proficiently in English. A wide age range was selected to allow for the comparison of strength and muscle thickness between age groups of children (6 to 11 years), adolescents (12 to 17 years), and young adults (18 to 26 years). The lower age limit was chosen based on evidence that children as young as six years of age can complete muscle strength testing using a handheld dynamometer with good to excellent intra-rater

and inter-rater reliability.[153,154] The ranges for specific age groups were established based on data from Hägg et al. (1982) who identified that peak growth spurt rates begin around 12 years of age and decrease after 17 years of age.[155] The upper age limit was selected to include the young adult age group (18 to 26 years), individuals in which skeletal growth has likely ceased.[156,157] Participants were excluded if they had a history of neurological or muscular disorder such as cerebral palsy, Down syndrome, muscular dystrophy, or myopathy; a history of lower extremity surgery or serious injury, such as lower extremity fracture, tendon or ligament repair, or surgical correction of leg length discrepancy; or were currently pregnant.

2.2 Procedures

To ensure consistency in instruction and data collection, a single pediatric physical therapist (KR), trained in ultrasonography for quadriceps muscle thickness measures, completed the testing across all of the participants. All measurements were obtained in a single visit. Only the dominant limb was examined based on previous evidence supporting no significant between-limb differences in lower extremity muscle force production in healthy populations.[158,159] Lower extremity dominance was determined by the hand with which the participant writes.[160]

2.3 Muscle Thickness

Two-dimensional B-mode ultrasonography (Whale Sigma P5, Whale Imaging Inc., Waltham, MA, USA) with a 5-12 MHz frequency, 38-mm linear array probe was used to image the dominant limb rectus femoris (RF) and vastus lateralis (VL) muscles at rest as verified by real-time surface electromyography on the quadriceps muscle belly (iWorx, Dover, NH, USA). The participant was positioned in supine with the knee at 0° (neutral),

and the hip positioned in 0° of hip joint abduction and rotation. The probe was placed parallel to the long axis of the muscle and perpendicular to the skin surface at 40% of the distance from the anterior superior iliac spine (ASIS) to tibial tuberosity for rectus femoris and 50% of the distance from the inferior margin of the greater trochanter to the tibial tuberosity for vastus lateralis. This method was chosen to provide a consistent site of muscle thickness imaging scaled to each participant. Three images of each muscle were collected for off-line analysis of muscle thickness. A custom Matlab code was used to convert exported US DICOM images to jpeg format. Images were manually digitized using Image J v1.52s (National Institutes of Health, Bethesda, MD, USA). Muscle thickness was measured as the distance between the superficial and deep aponeuroses (Figure 5). Four measurements were taken at the left (distal) and right (proximal) border of each image and muscle thickness is reported as the mean of these values. These methods for RF and VL muscle thickness using US have excellent intra-rater and inter-rater reliability.[103]

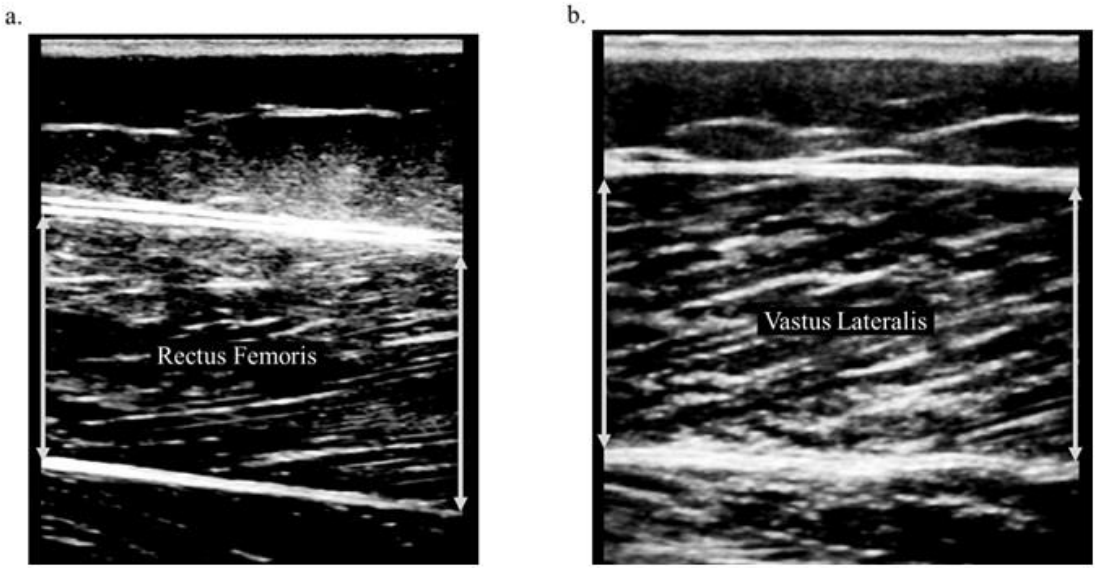

Figure 5. Ultrasonography images of (a) rectus femoris (RF), and (b) vastus lateralis (VL). Arrows indicate muscle thickness measurements for distal (left) and proximal (right) of each image.

2.4 Muscle Strength

Handheld dynamometer force during active knee extension was measured on the dominant lower extremity. Knee extension force (Newtons) at the distal tibia was measured using a Lafayette Manual Muscle Testing System model 01165 (Lafayette Instrument, Lafayette, IN, USA). Knee extension force was measured at four different participant testing positions: seated on the edge of the mat and in supine, with knees supported at either 90° or 35° of flexion for both positions. These testing positions were selected based on previous evidence of favorable intra-rater and inter-rater knee extension force reliability seated with the knee at 90° and supine with the knee at 35°.[45,161,162] The testing position of supine with the knee at 35° was selected as this position more closely represents mean joint angles during gait.[54] Additionally, seated knee extension at 35° and supine knee extension at 90° were also measured to assess the influence of hip and knee positions on the length-force relationships of the biarticular RF and uniarticular VL muscle. The dynamometer was placed immediately proximal to the malleolar line and the participant was instructed to take a normal inhalation and slow expiration during maximum voluntary isometric contractions (MVIC) with the instructions, "hold the position you are placed in and kick as hard as you can into the testing device." Participants completed MVICs for three trials of five seconds each, with a 30-second to 2-minute rest break in between trials. The average of the two highest values of the three trials was used for analysis. To compare strength across participants, knee extension joint torque was calculated as the MVIC force in Newtons multiplied by the length of the tibial shaft, measured as the distance from tibial tuberosity to medial malleolus in meters. Muscle strength measurement of knee extension using HHD has excellent intra-rater and inter-rater reliability.[103,163]

2.5 Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Inc., Chicago, IL, USA). The normality of the data was tested by a one-sample Kolmogorov-Smirnov test. Descriptive data with normal distribution were reported as mean (standard deviation [SD]) and data with non-normal distribution were reported as median (range). Pearson product-moment coefficients were used to assess relationships between knee extension joint torque and RF and VL muscle thickness. Post-hoc one-way repeated measures ANOVA tests were conducted to compare the effect of 1) strength testing positions on joint torque and 2) age group on joint torque and on muscle thickness. All comparisons were made at the $\alpha < 0.050$ level of significance.

3. RESULTS

A total of 30 children, adolescents, and young adults aged 6 to 26 years participated in this study with a median age of 13.58 (range: 6.17 to 26.33) years; 14 males and 16 females. The mean height was 1.46 (SD 0.18) meters (m), mean tibial shaft length was 0.26 (SD 0.05) m, mean weight was 44.58 (15.96) kilograms (kg), and average BMI was 19.41 (SD 3.30) kg/m^2. Characteristics of individual participants for all n=30 individuals are listed in Table 1.

Across all individuals, knee extension mean joint torque was greatest at 59.70 (SD 23.60) newton-meters (Nm) in seated 90° flexion, followed by 57.30 (SD 28.28) Nm in supine 90° flexion, 32.36 (SD 14.06) Nm in seated 35° flexion, and 32.02 (SD 16.38) Nm in supine 35° flexion (Figure 6a). There was a significant main effect of strength testing position on knee extension joint torque ($P<0.001$). Pairwise comparison identified

Table 1. Participant Demographic and Anthropometric Characteristics

Participant	Age (years)	Sex	Height (m)	Weight (kg)	BMI (m/kg^2)
1	6.17	F	1.14	21.36	16.35
2	6.17	F	1.22	20.45	13.76
3	6.17	F	1.22	22.27	14.98
4	7.92	F	1.27	29.09	18.04
5	7.92	M	1.22	24.55	16.51
6	8.75	M	1.27	23.64	14.65
7	9.42	F	1.46	51.36	24.08
8	9.67	F	1.35	31.82	17.56
9	9.83	F	1.52	45.45	19.57
10	9.92	M	1.36	48.18	26.09
11	9.92	M	1.37	34.55	18.36
12	9.92	M	1.55	40.45	16.85
13	9.92	F	1.42	36.36	17.97
14	10.25	F	1.46	37.73	17.69
15	10.92	M	1.50	35.87	15.97
16	11.83	F	1.55	39.09	16.28
17	12.08	F	1.55	43.64	18.18
18	12.75	M	1.47	34.50	15.90
19	13.00	M	1.57	46.36	18.70
20	13.67	M	1.47	43.64	20.11
21	15.33	F	1.60	58.64	22.90
22	16.33	M	1.78	72.73	23.01
23	17.42	F	1.52	51.82	22.31
24	19.42	F	1.65	63.64	23.35
25	21.50	F	1.63	54.09	20.47
26	22.25	M	1.78	72.19	22.83
27	22.92	M	1.80	76.36	23.48
28	23.92	F	1.57	54.55	21.99
29	25.75	M	1.70	67.65	23.36
30	26.33	M	1.63	55.45	20.99

significant differences in knee extension joint torque between knee positions 90° and 35° in sitting and in supine (P<0.001), but not between seated and supine testing positions when the knee was positioned in the same amount of flexion (35°: P=0.810; 90°: P=0.280) (Figure 6a). The mean muscle thickness of RF was 2.02 (SD 0.40) centimeters (cm) and VL was 1.89 (SD 0.44) cm (Figure 6b).

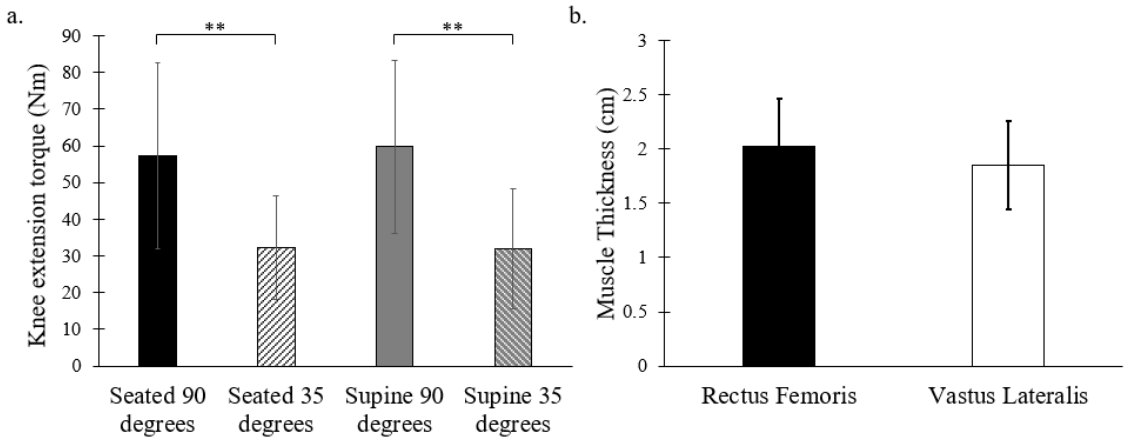

Figure 6. (a**)** Knee extension torque (Nm) in the four testing positions, and **(b)** Average muscle thickness (in centimeters). Error bars represent standard deviation (SD). ** indicates P < 0.001

Moderate to good correlations existed between joint torque and muscle thickness measures. RF muscle thickness demonstrated good correlations with knee extension joint torque at supine 35° (r=0.75, P<0.001), and moderate correlations at supine 90° (r=0.69, P<0.001), seated 35° (r=0.66, P<0.001), and seated 90° (r=0.63, P<0.001) (Figure 7a-d). Moderate correlations existed between VL muscle thickness and knee extension joint torque at supine 35° (r=0.63, P<0.001), seated 35° (r=0.57, P=0.001), seated 90° (r=0.54, P=0.002), and supine 90° (r=0.50, P=0.005) (Figure 8a-d).

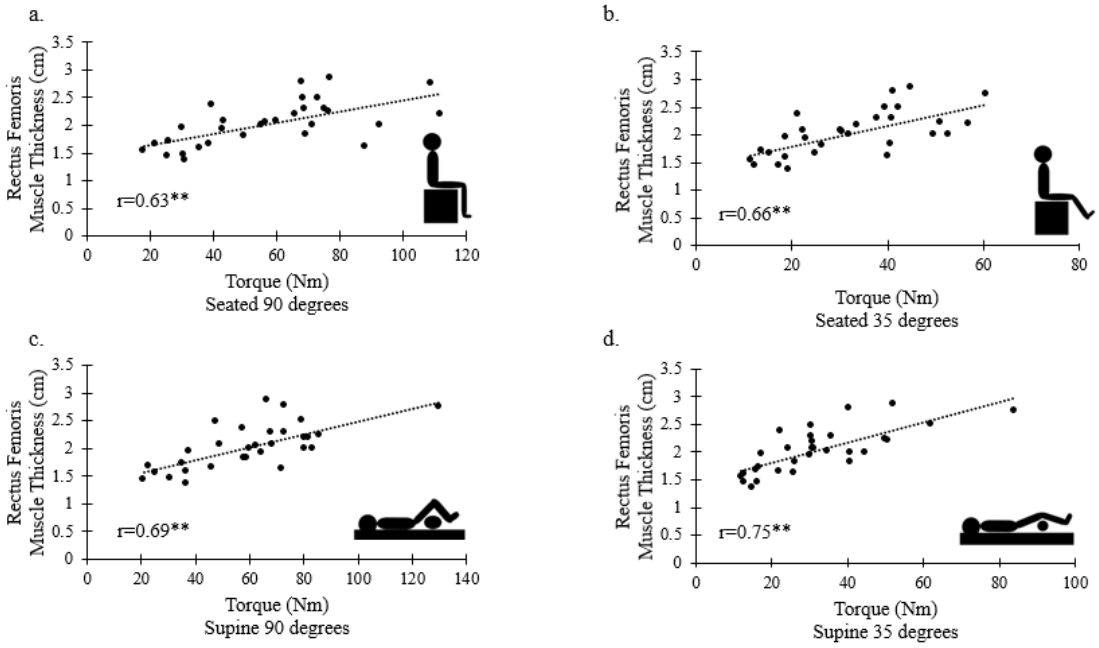

Figure 7. Relationships between mean rectus femoris muscle thickness (in centimeters) and knee extension joint torque (in Newton-meters) at **(a)** seated 90 degrees of knee flexion, **(b)** seated 35 degrees of knee flexion, **(c)** supine 90 degrees of knee flexion and **(d)** supine 90 degrees of knee flexion. ** indicates $P < 0.001$

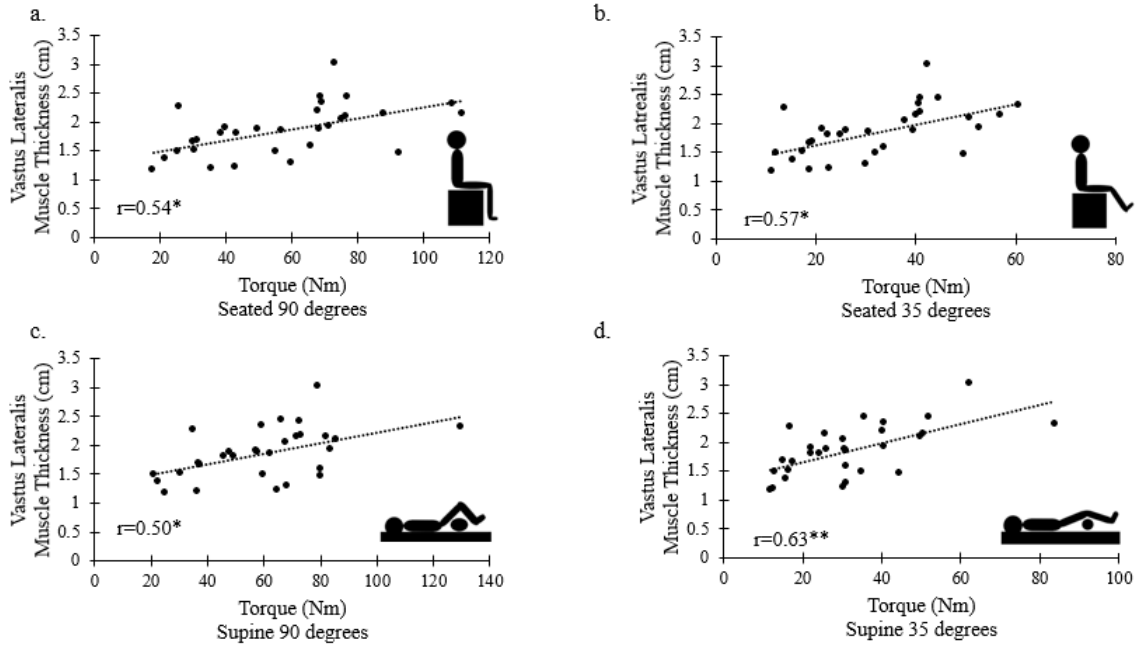

Figure 8. Relationships between mean vastus lateralis muscle thickness and knee extension joint torque at **(a)** seated 90 degrees of knee flexion, **(b)** supine 90 degrees of knee flexion, **(c)** seated 35 degrees of knee flexion, and **(d)** seated 90 degrees of knee flexion. * indicates $P < 0.050$; ** indicates $P < 0.001$

Subgroup analysis, by age group, identified different trends in children versus adolescents and young adults. There was a significant main effect of age group on knee extension joint torque (Seated 90°: P=0.001; Seated 35°: P<0.001; Supine 90°: P=0.005; Supine 35°: P=0.005). Significant differences in knee extension joint torque were detected between children and adolescents (Seated 90° and 35°: P<0.001; Supine 90 and 35°: P=0.001) and children and young adults (Seated 90°: P=0.001; Seated 35°: P<0.001; Supine 90°: P=0.002; Supine 35°: P=0.001). However, only significant between-group differences in adolescents and young adults were noted for the supine 90° of knee flexion position (Seated 90°: P=0.400; Seated 35°: P=0.104; Supine 90°: P=0.012; Supine 35°: P=0.068). A significant main effect of age group on RF and VL muscle thickness existed (RF: P=0.005; VL: P=0.008). Pairwise comparison identified significant differences in RF and VL muscle thickness between children and adolescents (RF: P=0.016; VL: P=0.018;) and children and young adults (RF: P=0.001; VL: P=0.001). However, only significant between-group differences in adolescents and young adults were detected for VL muscle thickness (RF: P=0.454; VL: P=0.005).

4. DISCUSSION

This study identified relationships between larger RF and VL muscle thickness measured with ultrasonography and higher knee extension strength measured by joint torque within a sample of children, adolescents, and young adults. To our knowledge, this is the first study to examine this relationship among children, adolescents, and young adults using clinically-available testing equipment, at multiple strength testing positions, and across a wide age range. These data suggest that measurements of quadriceps muscle thickness may provide useful insight into knee extension strength. Therefore, these findings

are important to the examination and evaluation of muscle performance in children, adolescents, and young adults, especially in situations when voluntary maximal strength measurements cannot be obtained. These methods would also be useful to aid in differentiating a potential cause for the decreased muscle strength by providing an objective measure of muscle size.

Relationships between RF and VL muscle thickness and knee extension joint torque were observed, with the greatest of these in supine at 35° of knee flexion. Moreau et al. (2010) identified that VL muscle thickness, measured at a resting position of 10° knee flexion, is a strong predictor of isometric knee extension joint torque, measured isometrically in sitting with 60° of knee flexion with an isokinetic dynamometer in 12 children, adolescents, and young adults (age range 7-20) with typical development; however, these were different testing positions from our study.[164] The supine position with 35° of knee flexion more closely mimics mean joint angles during gait, therefore may be a useful strength testing position to consider when examining lower extremity muscle performance in ambulatory children, adolescents, and young adults.[54] The relationships between muscle thickness and knee extension joint torque in supine with the knee flexed 35° may be related to 1) this strength testing position is more representative of the resting position at which muscle thickness was measured, and/or 2) this strength testing position is more representative of muscle performance during functional use of the quadriceps muscles.[54]

In this study, mean seated knee extension joint torque measurements at 90° of knee flexion in children (17.9 to 65.9 Nm) were consistent with published values (Hébert (2015): 16.4 to 78.1 Nm; Eek (2006): 26.0 to 63.3 Nm).[154,165] However, in adolescents, there were

lower in seated knee extension joint torque measurements at 90° of knee flexion (55.3 to 88.0 Nm) compared to published values (91.6 to 202.5 Nm).[154,165] These differences among adolescents are likely due to the small sample size (n=7). While we had a small sample size within the subgroups, an advantage of this study is that strength testing was performed in multiple positions. Torque values at the other strength testing positions are not commonly reported in the literature using handheld dynamometry. During muscle performance examination, the position of strength testing is important to consider with respect to the hip and knee joint angles. Worrell et al. (1989) describe a similar relationship of decreased knee extension joint torque, related to the hip position, in the supine position (<90°) compared to the seated position (90°) during isokinetic testing.[166] In our study, the significant difference in knee extension joint torque was related to the knee flexion position, with knee flexion at 90° significantly greater than at 35°, which is consistent with the optimal ranges of the force-tension relationship of the quadriceps muscles previously reported.[167,168]

The mechanisms underlying muscle growth and strength development throughout the lifespan continue to be explored, however, they consist of changes in muscle fiber size, the proportion of muscle fiber type, motor unit recruitment, and metabolic changes.[69,85,86] Therefore, cross-sectional trends may not be representative in these populations, and longitudinal exploration is warranted when determining changes within a child, adolescent, or young adult related to injury, disease, or recovery.

4.1 Limitations

To calculate torque in this sample, we used tibial shaft length to represent the moment arm distance, therefore this length is an approximate measure of the true moment

arm. We used age to categorize children, adolescents, and young adults, as opposed to using puberty-related biomarkers or milestones, therefore this categorization is an estimate and may not fully reflect the maturity status of each participant. In addition, muscle thickness measurements were not obtained in the same position as the strength tests, therefore the changes in muscle thickness measurements that may result due to changes in the knee and hip angles were not captured during this study. Muscle thickness is not the only contributing factor to muscle strength, therefore, other measures of muscle properties, such as fascicle length and neuromuscular activation, are needed to elucidate the differences observed in muscle performance between children, adolescents, and young adults. Additionally, exploration of the influence of muscle thickness measurements in varying positions, such as congruence with strength testing positions should be explored.

4.2 Implications for Clinical Practice

In order to develop effective physical therapy examination and evaluation of muscle properties in patient populations with injury, disease, or post-surgically, we must consider muscle properties that relate to muscle strength, such as muscle thickness and the position of the extremity. Muscle strength testing may not always be feasible due to pain, medical restrictions that prohibit strength testing, or the inability to follow instructions to complete testing protocol. Ultrasonography measurements of muscle thickness at rest provide important insight into strength potential. This study demonstrates trends in muscle thickness adaptations as they may relate to strength development and maturation.

5. CONCLUSIONS

Knee extension strength measurements and muscle thickness of RF and VL demonstrate relationships across children, adolescents, and young adults. Strength testing

positions with varying hip and knee flexion influence knee extension joint torque values. The results of this study suggest quadriceps muscle thickness measurements at rest may be useful in the examination of muscle performance in healthy children, adolescents, and young adults.

6. ACKNOWLEDGEMENTS

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CHAPTER FOUR: EXPLORING KNEE EXTENSION TORQUE, RECTUS FEMORIS MUSCLE ACTIVATION, AND GROSS MOTOR PERFORMANCE IN CHILDREN AND YOUNG ADULTS

ABSTRACT

Purpose: To examine maximal quadriceps torque and rectus femoris neuromuscular activation (mean frequency [MNF] and rate of activation [RoA]) during knee extension contractions in healthy children compared to adults, and to examine relationships between torque and neuromuscular activation with gross motor performance.

Methods: Participants, grouped by age (younger children [6 to 8 years; n=6], older children [OC; 9 to 11 years; n=10], adults [19 to 26 years; n=6]), performed isometric knee extension contractions to measure maximal torque, RoA across 50-ms-epochs ($RoA_{50\text{-}200}$), and MNF. Gross motor performance was measured through a 15-second two-legged hopping task. This study was approved by the institutional review board. Participants/guardians provided assent and consent.

Results: Normalized maximal torque (by muscle thickness) was lower in younger children compared to older children and adults ($p< 0.05$). Normalized RoA_{150} and RoA_{200} (by peak signal amplitude) were lower among younger children and older children compared to adults ($p< 0.05$). There were significant positive correlations between RoA_{150} and RoA_{200} with gross motor performance ($p< 0.05$).

Conclusions: Early and rapid muscle activation differs between children and adults and may be important for gross motor performance, which require quick and coordinated movements. Exercise testing and prescription should consider the neuromuscular challenges of tasks that require rapid muscle activation.

1. INTRODUCTION

Gross motor skills such as running, hopping, and jumping are important for age-appropriate activities and sports across the lifespan.[169] Development is essential for acquiring skills needed to participate in school and leisure activities[170] and establishing lifelong patterns of development into adulthood.[171] Gross motor skills require quick and coordinated movements with sufficient torque and neuromuscular activation. Throughout childhood, gross motor skills that require quick movements, such as forward and side-to-side jumping, increase in proficiency between 5 years of age to 15 years of age.[172] Therefore, exploring the mechanisms that are associated with gross motor performance in children, both younger and older, compared to adults, will aid in the assessment and development of interventional strategies for those children with poor gross motor performance.

Scientists have studied underlying mechanisms, such as muscle strength and balance control, that influence the ability to perform gross motor skills in healthy children. Strengthening the lower-extremity muscles and improving balance control in children has been demonstrated to improve performance in specific sports activities like soccer, basketball, and volleyball.[173–175] In children, particularly those with neuromuscular impairments secondary to chronic health conditions, impaired knee extension strength and balance deficits lead to poor gross motor performance.[176,177] Therefore, further exploration of the underlying neuromuscular mechanisms that contribute to the performance of gross motor skills is needed.

Greater neuromuscular activation, an electromyographic measure of the collaboration of the brain and muscles during a muscle contraction, is important for greater

joint torque production[99] and potentially important for the increased proficiency of gross motor skills.[178,179] Neuromuscular activation can be quantified using surface electromyography (EMG), with measures such as mean frequency (MNF) and rate of activation (RoA). EMG frequency provides insight into the number and threshold levels of motor unit recruitment and can quantify muscle fatiguability. Studies exploring EMG frequency (e.g. MNF) found that the recruitment at higher frequencies is associated with greater torque values in adults.[180,181] We do not know if similar findings are found in children, as frequency studies focused on the effects of muscle fatiguing protocols.[182,183] Therefore, the MNF values in children during non-fatiguing conditions and the relationship of EMG frequencies to gross motor performance is unclear. RoA measurements can provide insight into the capacity to activate the muscle rapidly, and have been studied broadly in adults.[64,65] In adults, those with a greater quadriceps and soleus RoA generate more knee extension and plantarflexion torque than those with lower RoA during maximal isometric voluntary contractions.[72,73] There is evidence to suggest in adults that greater and early quadriceps activation (i.e., first 250 ms) during isometric squatting results in faster sprinting and greater jump height.[184] The early activation period precedes maximal torque and indicates that the ability to activate the muscles earlier and faster may be necessary for the proficiency of gross motor skills. Few studies have examined the relationship between quadriceps and gastrocnemius rate of neuromuscular activation and gross motor performance in healthy prepubertal children and adolescents.[76,185]

Some studies show that children demonstrate lower MNF and RoA of the gastrocnemius[75] and biceps brachii[186] muscles compared to adults. Younger children also present with decreased gastrocnemius, rectus femoris, and semitendinosus muscle RoA and

MNF compared to older children.[76,187] Waugh et al.[76] reported a smaller gastrocnemius RoA in prepubertal children (aged 5 to 12 years) compared to adults. Furthermore, they reported children, aged 7-8 had a smaller RoA than children 9-10 years.[76] The authors also suggested that for prepubertal children, RoA may be an important factor influencing the early stages of torque development.[76] However, these studies did not assess the contribution of EMG measures of neuromuscular activation to gross motor performance.

To effectively examine and develop intervention programs to improve gross motor performance in children, researchers need to explore the underlying neuromuscular mechanisms that contribute to gross motor performance. The quadriceps muscles, especially the rectus femoris, are important for gross motor performance, especially in tasks that require directional changes.[188] To our knowledge, it is unknown if neuromuscular activation of the rectus femoris muscle differs in children versus adults and furthermore if rectus femoris muscle torque and neuromuscular activation is associated with gross motor performance across childhood into adulthood. Therefore, this study aimed to explore quadriceps femoris maximal torque and the rectus femoris neuromuscular activation (MNF and RoA) in younger (6-8 years old) and older (9-11 years old) children compared to adults. The secondary aim was to identify a relationship between neuromuscular activation with gross motor performance using a two-legged side hop task. We hypothesized that compared to adults, younger and older children would produce lower quadriceps maximal torque, RoA, and MNF and that RoA and MNF would be positively associated with the number of two-legged side hops performed.

2. METHODS

2.1 Participants

This is a cross-sectional observational study. Twenty-two participants were included in this study between the ages of 6 to 18 years (younger children; n=6), 9 to 11 years (older children; n=10), or 19 to 26 years (adults; n=6) who could communicate in English. Participants were excluded if they had a history of neurological or muscular disorder such as cerebral palsy, Down syndrome, muscular dystrophy, or myopathy; a history of lower extremity surgery or a serious injury, such as lower extremity fracture, tendon or ligament repair, or surgical correction of leg length discrepancy; or were currently pregnant. This study was approved by the University of Maryland Baltimore Institutional Review Board. All participants provided informed consent and minors provided assent.

2.2 Experimental Procedures

To ensure consistency in the instructions and data collection, a single pediatric physical therapist completed the testing across all of the participants. After a familiarization trial, all measurements were obtained in a single visit on the dominant lower extremity. Dominance was determined by the hand with which the participant writes due to limitations in lower-extremity performance tasks in identifying laterality in school-aged children.[160]

2.2.1 Quadriceps Muscle Measurements

Knee extension maximal torque was measured using a handheld dynamometer, Lafayette Manual Muscle Testing System model 01165 (Lafayette Instrument, Lafayette, IN, USA), with the participant positioned in supine and knees supported by a bolster in 90° of knee flexion. The dynamometer was placed two centimeters proximal to the

intermalleolar line on the distal tibia. The participants were instructed to take a normal inhalation and slow expiration during maximal voluntary isometric contractions with the instructions, "hold the position you are placed in and kick as hard as you can into the testing device." After two familiarization trials at submaximal effort, the participants completed three maximal voluntary isometric contractions for five seconds each, with a rest break for at least 30 seconds to prevent fatigue, but no more than 2 minutes in between trials. The two highest torque values, force multiplied by the moment arm, were used for analysis. These methods have demonstrated reliability in younger children (CV%: 5.22%), older children (CV%: 4.06%), and adults (CV%: 6.56%).[37] The maximal torque values were normalized by dividing by the sum of the vastus lateralis and rectus femoris muscle thickness (Nm/cm).[189]

Resting vastus lateralis and rectus femoris muscle thickness was measured by two-dimensional B-mode ultrasonography (Whale Sigma P5, Whale Imaging Inc., Waltham, MA, USA) of the rectus femoris (40% of the distance from the anterior superior iliac spine to tibial tuberosity) and vastus lateralis muscle (50% of the distance from the inferior margin of the greater trochanter to the tibial tuberosity). Images were acquired using a 5-12 MHz frequency, 38-mm linear array probe placed parallel to the long axis of the muscle and perpendicular to the skin surface with the participant in supine with the hip and knee in neutral (0°) position. Three images of each muscle were collected. The muscle was verified to be at rest using real-time surface EMG (iWorx, Dover, NH, USA). Off-line analysis of muscle thickness was performed using a custom MATLAB code and ImageJ v1.52s (National Institutes of Health, Bethesda, MD, USA). Muscle thickness was measured using the average of four repeated measurements of the distance between the

deep and superficial aponeuroses taken at the distal and proximal border of the rectus femoris and vastus lateralis muscle ultrasound images.

2.2.2 Neuromuscular Activation

EMG data were collected using iWorx IX-BIO4 system (iWorx, Dover, NH, USA) during the maximal knee extension contractions. Surface electrodes were placed on the rectus femoris during MVIC. The electrodes were bipolar, disposable, pre-gelled, 1-cm-diameter, Ag/AgCl self-adhesive, circular snap electrodes with 20 mm interelectrode spacing (Noraxon, Scottsdale, AZ, USA). Before electrode placement, the skin was cleaned with alcohol. The electrodes were placed on the muscle belly of the rectus femoris at 50% of the distance between the anterior superior iliac spine and tibial tuberosity, and a reference electrode was placed on the anterior tibia bone.

2.2.3 Gross Motor Performance

Participants performed a two-legged side hop task as measured in the Bruininks-Oseretsky Test of Motor Proficiency, 2nd Ed. (Pearson Assessments, London, United Kingdom). The participants stood next to a line with their feet no more than 2 inches apart and placed their hands on their hips. The participants were instructed to “hop back and forth over the line until I tell you to stop”. The test was scored by the number of hops over the line completed in 15 seconds. Hops were counted if the participant’s feet remained less than 2 inches apart, hands were maintained on the hips, and the lateral distance of the hop exceeded at least four inches (Figure 9).

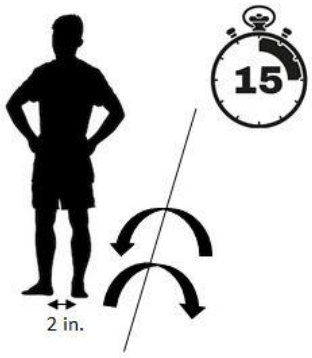

Figure 9. Timed Two-legged Side Hop Task

2.3 Data Analysis

EMG data were analyzed using Visual 3D (C-Motion Research Biomechanics, Germantown, MD, USA) and Spike2 software (Cambridge Electronic Design Ltd., Cambridge, UK). The EMG data were sampled at 1000Hz and filtered using a fourth-order Butterworth digital bandpass filter (10-500Hz). The EMG amplitude was calculated as the root mean square (RMS) of the EMG signal. The baseline mean and standard deviation (SD) amplitude were calculated over 500 ms before the EMG activity for each contraction. The EMG onset was identified as 2 SD over the baseline mean amplitude and verified visually. The RoA was calculated during early rectus femoris activation across epochs of 0-50 ms (RoA_{50}), 0-100 ms (RoA_{100}), 0-150 ms (RoA_{150}), 0-200 ms (RoA_{200}) from EMG onset, and was normalized to 150 ms around the maximal EMG amplitude, the highest RMS value within the active signal. For the analysis of the frequency domain, MNF was calculated from the power spectrum curve computed by taking the Fast Fourier Transform of 512 points, with 50% overlapping segments across the whole contraction[190] and normalizing to the maximal MNF value from the contraction. This method of normalization potentially controls for intrinsic factors such as conduction velocity, skin and adipose thickness, muscle length, intramuscular heterogeneity, position of motor endplate, fiber

alignment, and active motor unit discharge rate, in addition to the degree of synchronization that can influence individual maximal mean frequencies.[191–193]

2.4 Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Inc., Chicago, IL, USA). The normality of the data was evaluated by the Shapiro-Wilk test. One-way ANOVA followed by a Tukey posthoc test was conducted to assess group differences between younger children aged 6 to 8 years, older children aged 9 to 11 years, and adults aged 18 to 26 years. Effect size (ηp^2) calculations are reported to reflect the magnitude of the differences between age groups (small= 0.01, medium= 0.06, and large= 0.14).[194] Pearson product-moment coefficients and 95% confidence intervals (95% CI) were used to assess the relationships between maximal torque, EMG measures (RoA, MNF), and the number of two-legged side hops. All comparisons were made at the $p \leq 0.05$ level of significance, and data were reported as mean ± SD.

3. RESULTS

Data from 16 school-aged children, 6 younger (2 males/4 females) and 10 older (4 males/6 females), and 6 adults (3 males/3 females) were included in this study and were normally distributed. A summary of participant characteristics is listed in Table 2.

Normalized torque showed a main effect of age group on knee extension maximal torque ($F_{(2, 19)}= 7.90$, $p= 0.003$, $\eta p^2= 0.45$) with significantly lower torque for younger children compared to older children ($p= 0.018$) and adults ($p= 0.003$), but no differences between older children and adults ($p= 0.447$; Table 3).

Table 2. Participant Characteristics

	Younger Children (n=6)	Older Children (n=10)	Adults (n=6)
Age, years	7.18 ± 1.15*†	10.16 ± 0.71*‡	22.72 ± 2.33†‡
Height, m	1.22 ± 0.05*†	1.45 ± 0.08*‡	1.68 ± 0.09†‡
Weight, kg	23.56 ± 3.09*†	40.09 ± 6.32*‡	62.60 ± 9.70†‡
BMI, kg/m^2	15.68 ± 1.54†	17.71 ± 3.28‡	22.14 ± 1.25†‡
Gross Motor Performance			
Two-legged side hop, count	29.33 ± 9.03†	37.80 ± 8.30	42.67 ± 6.89†

Mean values ± standard deviations. Symbols indicate: significant difference between * younger and older children, † younger children and adults, ‡ older children and adults; $p \leq 0.05$

Table 3. Quadriceps muscle measurements and neuromuscular activation

	Younger Children (n=6)	Older Children (n=10)	Adults (n=6)
Quadriceps Muscle Measurements			
Maximal Torque, Nm	28.21 ± 7.60*†	55.28 ± 13.99*‡	81.66 ± 23.75†‡
RF+VL Muscle Thickness, cm	3.00 ± 0.32*†	3.65 ± 0.39*‡	4.59 ± 0.37†‡
Normalized Torque, Nm/cm	9.40 ± 2.35*†	15.27 ± 4.13*	17.67 ± 4.13†
Neuromuscular Activation			
RoA_{50}, s^{-1}	0.76 ± 0.57	0.74 ± 0.59	1.13 ± 0.32
RoA_{100}, s^{-1}	0.60 ± 0.36†	0.73 ± 0.56	1.37 ± 0.60†
RoA_{150}, s^{-1}	0.53 ± 0.30†	0.70 ± 0.51‡	1.35 ± 0.57†‡
RoA_{200}, s^{-1}	0.51 ± 0.27†	0.67 ± 0.44‡	1.21 ± 0.43†‡
Mean EMG Frequency, %	84.68 ± 6.52	87.27 ± 2.46	85.29 ± 3.95

Mean values ± standard deviations. Abbreviations: RF= rectus femoris; VL= vastus lateralis; RoA= rate of activation for epochs 50, 100, 150, and 200 ms; and EMG = electromyography. Symbols indicate: significant difference between * younger and older children, † younger children and adults, ‡ older children and adults; $p \leq 0.05$

There was a significant main effect of age group on rectus femoris RoA_{100} ($F_{(2, 19)}$= 3.93, p= 0.037, ηp^2= 0.29), RoA_{150} ($F_{(2, 19)}$= 5.10, p= 0.017, ηp^2= 0.35), and RoA_{200} ($F_{(2, 19)}$ = 5.29, p= 0.015, ηp^2= 0.36), but not for RoA_{50} ($F_{(2, 19)}$= 1.13, p= 0.343, ηp^2= 0.11). Rectus femoris RoA was significantly lower among younger children and older children compared to adults for RoA_{150} (younger children: p= 0.020; older children: p= 0.042) and RoA_{200} (younger children: p= 0.017; older children: p= 0.042), and only different between younger children and adults for RoA_{100} (p= 0.050; Figure 10). No group differences existed for MNF (p= 0.502; Figure 11) There was a significant main effect of age group on timed two-legged side hop count $F_{(2, 19)}$= 4.14, p= 0.032, ηp^2= 0.304, with younger children performing significantly fewer hops compared to adults (p= 0.003), but no differences between younger children and older children (p= 0.137) or older children and adults (p= 0.493; Table 2)

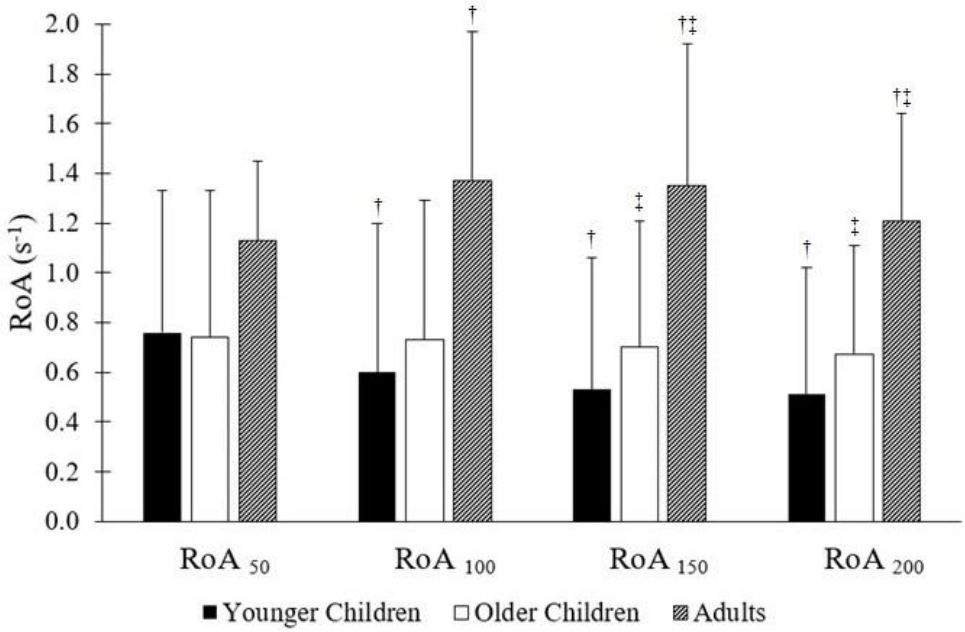

Figure 10. Rectus femoris rate of activation (RoA), normalized to maximal RMS, for younger children (black bars), older children (white bars), and adults (striped bars) expressed as mean and standard deviation. Symbols indicate: significant difference between * younger and older children, † younger children and adults, ‡ older children and adults; p≤ 0.05

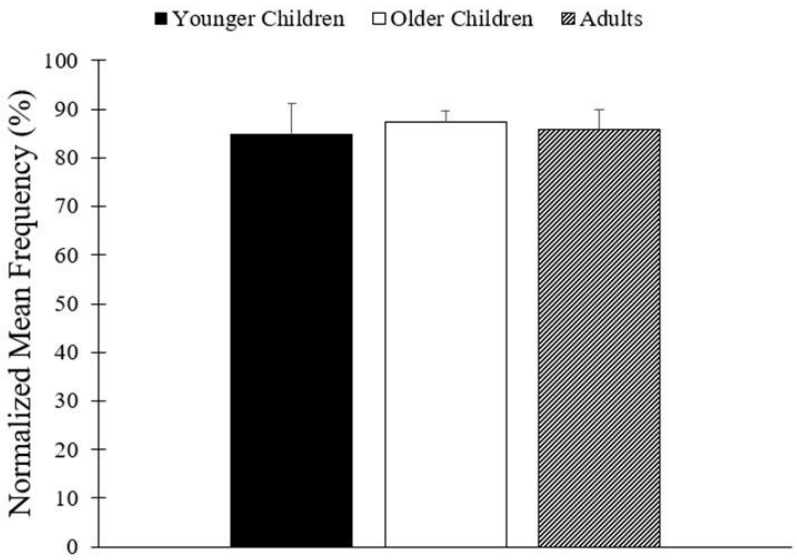

Figure 11. Rectus femoris normalized mean frequency (MNF) for younger children (black bar), older children (white bar), and adults (striped bar) expressed as mean and standard deviation.

There were significant correlations between rectus femoris RoA and timed two-legged side hop count (Figure 12C-D) for RoA_{150} ($r= 0.46$; $p= 0.031$; 95% CI [0.05, 0.87]) and RoA_{200} ($r= 0.43$; $p= 0.046$; 95% CI [0.01, 0.85]), but not RoA_{50} ($p= 0.383$; Figure 12A) or RoA_{100} ($p= 0.059$; Figure 12B). Additionally, there were no significant relationships between the timed two-legged side hop count with normalized maximal torque ($p= 0.153$) or MNF ($p= 0.916$).

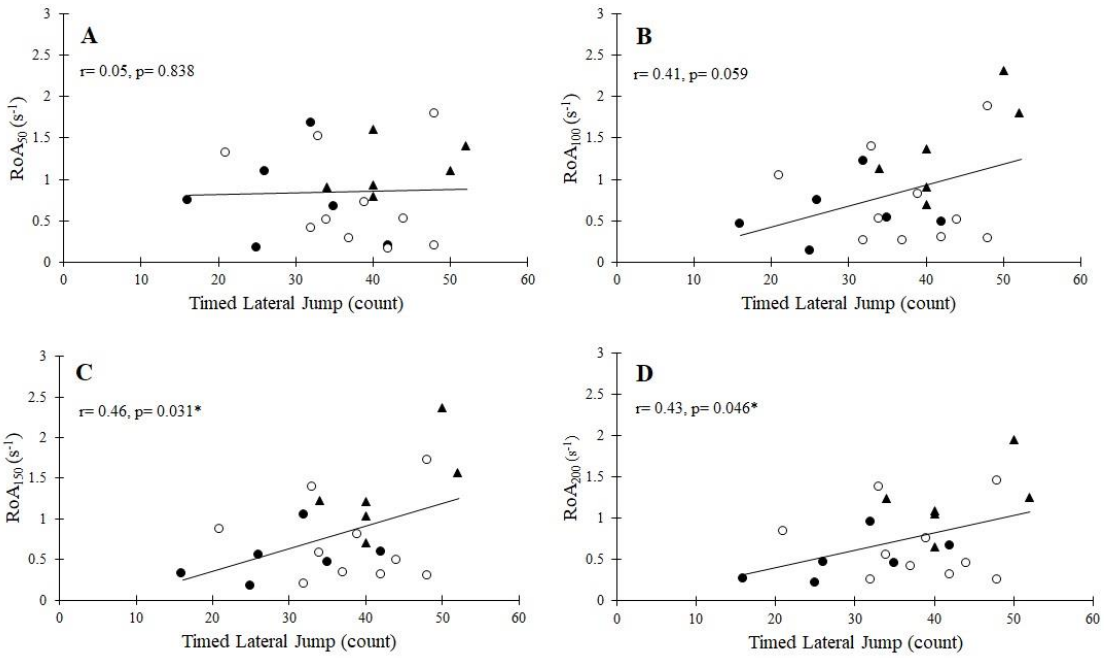

Figure 12. Relationships between timed lateral jump count and rectus femoris rate of activation (RoA) epochs (A) 50 ms, (B) 100 ms, (C) 150 ms, and (D) 200 ms among younger children (closed circle), older children (open circle), and adults (closed triangle). * indicates $p \leq 0.05$

4. DISCUSSION

This study explored maximal quadriceps torque and rectus femoris neuromuscular activation during isometric knee extension contractions in healthy younger and older children as compared to adults. Additionally, we explored relationships between maximal torque, neuromuscular activation, and the number of two-legged side hops. Although the neuromuscular activation, the rate of torque development, and maximal torque production can be limited by muscle size,[68] maximal torque even after normalizing for muscle size increases with age throughout childhood.[46,69,70] After adjusting the maximal torque for the differences in muscle size across the groups, younger children produced less torque than the older children and adults. This may indicate that other factors besides muscle size influence the participant's capacity to generate torque. Neuromuscular mechanisms, such as rate of muscle activation, may contribute to these observed changes in children. In contrast, the maximal torque of older children did not differ from adults. Children (younger

children and older children) had significantly lower rectus femoris muscle $RoA_{150\text{-}200}$ but not RoA_{50} for all children and RoA_{100} for older children compared to adults.. However, there were no differences in the MNF among the three groups. Lastly, those with a higher RoA_{150} and RoA_{200} performed better on the two-legged side hop test (i.e., a greater number of hops).

In accordance with other studies, maximal knee extension torque increases throughout childhood, and significant differences can be found between younger children and adults [46,69,70]. Changes in muscle size during development potentially contribute to torque differences. Although, we normalized to the size of the muscle, younger children presented with lower torque compared to older children and adults,[58,59,186,195] however, we did not identify differences between older children and adults. These data suggest that muscle size alone cannot explain the differences in torque between younger children and adults. Therefore, other factors need to be considered to explain the differences observed between age groups, including neuromuscular activation (e.g. EMG frequency and RoA) and elastic properties of the muscle and tendon. Previous studies have suggested that neuromuscular activation capacity increases throughout childhood while muscle and tendon stiffness also increases.[90–92] Given that we did not assess muscle and tendon stiffness properties, further research is needed to determine the influence of these properties.

EMG frequency did not differ among the groups, which differs from earlier studies. Lauer et al.[187] found that an older group of children (mean age 11.2 years) demonstrated a higher EMG frequency of rectus femoris muscle during gait compared to children with a mean age of 3.4 years.[187] Armatas et al.[182] also identified higher EMG frequency in boys (mean age 10.0 years) compared to adults (mean age 26.18 years) of the vastus lateralis

and vastus medialis muscles during an isometric knee extension fatiguing protocol.[182] The higher frequency in boys compared to adults observed by Armatas et al.[182] may be due to a decrease in EMG frequency with fatigue, thus suggesting the children in this study present with higher percentage of slow twitch fibers compared to fast twitch fibers.[182,196] The additional discrepancy between this study and previous studies of EMG frequency could suggest that changes may occur in a different developmental phase than represented by the children in our study. These differences may be due to different age-groups, data collection procedures such as the task during which EMG signals were collected (explosive vs. fatiguing contractions vs. functional gait), and normalization procedures. Our study did not aim to explain the mechanisms behind MNF. Due to confounding factors contributing to frequency domain analysis, we chose to normalize MNF to maximal frequency during the isometric contraction to allow for between-subject comparison. Therefore, MNF may not be the best measure of neuromuscular activation when assessing the performance of producing quick maximal torque for between-participant comparison with different age groups.

In this study, we explored the RoA of the rectus femoris muscle during the early phase of muscle contraction, a phase prior to maximal torque. Children (younger and older children), compared to adults, had a lower rectus femoris $RoA_{150\text{-}200}$ and adults demonstrated almost double the RoA values compared to younger and older children for RoA_{100} and RoA_{200}. These findings suggest that adults have a higher capacity to increase motor unit recruitment and potentially more fast twitch fibers compared to younger and older children.[76] Although $RoA_{100\text{-}200}$ was lower in the younger children compared to older children and older children compared to adults for $RoA_{50\text{-}100}$, these changes were not

statistically significant. In contrast, others have found that the RoA of the gastrocnemius muscle was less in children than adults from 0 to 75 and 150 ms, but not at 25 ms.[76] However, we did not find differences in ROA_{50}. The lack of difference in the first 50 ms of the contraction between younger and older children might be due to the inherent large variance of RoA, consistent with previous reports in adults,[64,73] or this very early phase of activation (0 to 50 ms) may not be as important for maximal torque development or gross motor performance.

The lower RoA in children compared to adults might be explained by different factors. For instance, it was previously suggested that children have a larger delay between muscle activation and force production compared to adults,[76,197,198] which would greatly influence RoA favoring higher values in adults than in children. Falk et al.[70] suggest a larger delay could result from a lesser ability to recruit or fully use their higher-threshold motor units. Furthermore, the development of the motor cortex and corticospinal pathway contributes to the ability to perform movements, and total maturation may still be occurring up until adolescence.[199,200] Although not directly measured in this study, the adults may have greater inter- and intra-muscular coordination, which could contribute to a greater RoA than in children due to increased selective contraction of the knee extensors. Nevertheless, increased EMG amplitude is consistently attributed to increases in motor unit recruitment and other motor unit characteristics such as motor unit recruitment thresholds, firing frequency, and/or synchronization of motor units.[201,202] The results of this study suggest the smaller early $ROA_{100\text{-}200}$ observed in younger and older children may reflect the inability to recruit available motor units and/or higher-threshold motor units to the extent of adults.[75]

The ability to generate muscle activity rapidly ($RoA_{150\text{-}200}$), but not maximal torque, was observed to correlate with gross motor performance, specifically a task that required a change in direction quickly while maintaining balance, strength, speed, and control of the body. Thus, these results are consistent with studies in adults that support a greater capacity to rapidly activate the rectus femoris muscle being associated with the ability to produce quick and coordinated movements such as jumping and running.[184,203] In older adults, the rate of neuromuscular activation distinguishes individuals who were fallers from those that are non-fallers.[204] Thus, early neuromuscular activation is critical to producing quick and coordinated movements as required to learn gross motor skills across the lifespan and prevent falls later in life.

This study explored assessments and relationships between children (younger and older children) and adults using testing procedures that were quick and well-tolerated. However, limitations to this study exist. We categorized the participants by chronological age, which estimates pre-pubertal status, instead of using puberty-related biomarkers or milestones. This age-based categorization is typical for gross motor assessments.[115] The handheld dynamometer measured maximal torque but did not record continuous torque signals, therefore we could not explore the relationship between rate of torque development and gross motor performance. Nevertheless, the benefits of the handheld dynamometer used in this study include affordability, clinical availability, and ease of use. Additionally, the maximal torque values may not represent full volitional muscle activation, which is typically assessed with an interpolated twitch. Although, due to associated discomfort, this technique carries ethical considerations in the assessment of children. This study explored maximal isometric quadriceps torque in one position and neuromuscular activation of one

knee extensor muscle. The rectus femoris is a primary knee extensor and hip flexor, which are important for gross motor performance. However, assessment of neuromuscular activation of additional quadriceps and lower extremity muscles and during dynamic movements may be beneficial as these other muscles might also present activation characteristics associated with gross motor performance.[185,203] Furthermore, cross-sectional trends within a small sample size may not be fully representative in these populations, and longitudinal exploration is warranted when determining changes related to injury, disease, or recovery.

5. CONCLUSIONS

The results of this study suggest differences in maximal quadriceps torque and early rectus femoris RoA between younger children, older children, and adults. Gross motor performance was correlated with the rectus femoris RoA and not the maximal joint torque of the quadriceps, suggesting that the ability to rapidly activate the muscles may be more important than joint torque for gross motor performance. Therefore, exercise testing and prescription for children and adults should consider the neuromuscular challenges of tasks that require rapid activation and submaximal torque production, such as agility training.

6. ACKNOWLEDGEMENTS

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CHAPTER FIVE: EXPLORING MUSCLE PROPERTIES, GROSS MOTOR PERFORMANCE, AND QUALITY OF LIFE IN CHILDREN WITH SICKLE CELL DISEASE[2]

ABSTRACT

Purpose: To explore muscle properties gross motor performance, and quality of life (QoL) in children with sickle cell disease compared to controls and to assess relationships among these outcomes.

Methods: A cross-sectional study of 24 children (SCD=14; control=10; aged 6-17 years) assessed muscle properties including: knee extension strength by dynamometry; vastus lateralis (VL) and rectus femoris (RF) muscle thickness by ultrasonography; and VL and RF neuromuscular activation (rate of muscle activation [RoA]) by electromyography. Gross motor performance and QoL were assessed by standardized tests and questionnaires.

Results: Children with SCD presented with impaired knee extension strength, VL RoA, gross motor performance, and QoL compared to children without SCD. Relationships among muscle properties, gross motor performance, and quality of life were identified.

Conclusions: These findings indicate that comprehensive muscle properties, gross motor performance, and QoL assessments should be considered to support and develop individualized physical therapy plans for children with SCD.

1. INTRODUCTION AND PURPOSE

Sickle cell disease (SCD) is a genetically inherited condition with a rate of one in every 350 African American newborns in the United States and occurs in an estimated 2,000 children per year.[15] SCD develops over the first 6 to 12 months of life in infants with

[2] Rock K, Ho S, Gray VL, Addison O, York T, Keegan Wells D, DeLuca H, Marchese V. *Pediatr Phys Ther*. Under Review

SCD when fetal hemoglobin transitions to abnormal adult hemoglobin and forms irregularly shaped red blood cells. The sickled form of hemoglobin results in improper transportation of oxygen and blood flow, known as sickle cell anemia. The sickle-shaped red blood cells are inflexible, fragile, adhesive to vascular endothelium, and have a shortened life span. These adverse changes in the red blood cells lead to vaso-occlusive crises, presenting as local ischemia in body tissues and pain. Vaso-occlusive crises and persistent anemia can lead to chronic inflammation and damage to body organs and tissues, including skeletal muscle.[4]

Children with SCD are at risk for impaired skeletal muscle properties including muscle strength, size, and neuromuscular activation that may contribute to gross motor performance limitations and restricted health-related quality of life (QoL). In context of the International Classification of Functioning, Disabilities and Health (ICF) framework, children with body structure and function impairments present with activity limitations in gross motor performance as well restricted QoL.[23–25] Previous studies in children with SCD have identified impaired muscle strength of ankle plantarflexion, handgrip, and the back compared to healthy controls.[15] Children with SCD also presented with activity limitations while performing specific activities required for participation in school, play, and sports activities.[15–17]

The assessment of skeletal muscle properties, gross motor performance, and QoL outcomes or the relationships among these measures have not been comprehensively reported in children with SCD. The quadriceps muscles, specifically the vastus lateralis (VL) and rectus femoris (RF) muscles, are responsible for knee extension contractions needed for gross motor tasks such as walking, running, and jumping. The VL is the primary

extender of the knee during gross motor activities. The RF is a biarticular muscle that performs hip flexion and knee extension, which are movements required to kick a ball or climb stairs. Therefore, muscle properties of the VL and RF may relate to gross motor performance in children with SCD. Skeletal muscle strength assessed using handheld dynamometry (HHD) provides objective, affordable, and practical measurements of knee extension force/torque.[103,205] Skeletal muscle size assessed using ultrasonography (US) provides valid measurements of quadriceps muscle size via muscle thickness measurements.[24,103] Neuromuscular activation using electromyography (EMG) provides a measure of the ability to rapidly activate (rate of muscle activation [RoA]) a muscle during contraction.[75] QoL questionnaires measure a child's perception of their health, social, emotional, and physical function. In children with other comorbid conditions such as cerebral palsy and cancer, relationships have been reported among body structure and function impairments, activity limitations, and participation restrictions.[23–25]

Thus, this study aimed to comprehensively explore quadriceps skeletal muscle strength, muscle size, neuromuscular activation, gross motor performance, and QOL in children with SCD compared to controls and to assess the relationships among outcome measures. The authors hypothesized that children with SCD would present with decreased muscle strength, muscle size, neuromuscular activation, gross motor performance, and QoL compared to controls without SCD and that relationships among these variables would be identified.

2. METHODS AND PROCEDURES

2.1 Study Participants

A total of 24 children were recruited for this cross-sectional observational study between May 2021 and July 2022. Fourteen children with SCD were recruited from the University of Maryland Medical Center Pediatric Hematology Clinic for participation in this study at the University of Maryland School of Medicine, Department of Physical Therapy & Rehabilitation Science (UMSOM PTRS). Ten control participants were recruited through a sample of convenience by the UMSOM PTRS faculty and staff. Participants were included if they were children between 6 and 17 years old. Participants with SCD were included if they had a diagnosis of HbSS, HbSC, HbSβ^+, or HbSβ^-. Participants were excluded if they: 1) had a neurological or muscle disorder, not related to SCD; 2) had a history of a serious lower-extremity injury or surgery; or 3) were currently pregnant based on participant report. This study was approved by the University's institutional review board. All participants provided informed assent and caregivers provided informed consent.

2.2 Procedures

A single pediatric physical therapist completed the testing across all of the participants. All measurements were obtained on the dominant extremity, determined by the limbs the participant reported they used to write and kick a ball. Participants were asked to rate their pain on a scale from 0 to 10 using the Wong-Baker Faces Scale.[206]

2.3 Knee Extension Strength

Knee extension joint force at the distal tibia was measured using a Lafayette Manual Muscle Testing System model 01165 (Lafayette Instrument, Lafayette, IN, USA) HHD in

the supine position with both knees supported at 35° of flexion, measured by a standard goniometer. This testing position was selected based on previous evidence of favorable reliability.[103,207] The HHD was placed on the anterior tibia 2 cm proximal to the intermalleolar line. The participants were instructed to take a normal inhalation and slow exhalation during maximal voluntary isometric contractions (MVIC) with the instructions, "hold the position you are placed in and kick as fast and as hard as you can into the testing device." Participants performed two familiarization trials of sub-maximal effort followed by three MVIC trials of five seconds each with at least a 30-second but no more than a 2-minute rest break between trials. To calculate knee extension joint torque (Nm), the HHD force (N) was multiplied by the moment arm (m), which was the distance between the knee joint axis of rotation and the placement location of the HHD. Knee extension joint torque was recorded as the average of the highest two torque values.[103] The assessor has previously established good to excellent intra-rater reliability using HHD to measure knee extension joint torque,[103] and excellent inter-rater reliability for knee extension torque on 10 control participants with an intraclass correlation coefficient of 0.91.

2.4 Muscle Size

Resting quadriceps muscle thickness of the VL and RF was measured by two-dimensional B-mode US (Whale Sigma P5, Whale Imaging Inc., Waltham, MA, USA) of the VL (50% of the distance from the inferior margin of the greater trochanter to the tibial tuberosity and the RF (40% of the distance from the anterior superior iliac spine to tibial tuberosity).[103] Three images of each muscle were collected with the participant positioned in supine with the hips and knees in neutral positions using a 5-12 MHz frequency, 38-mm linear array probe placed parallel to the long axis of the muscle and perpendicular to the

skin surface. The muscles were verified to be at rest using real-time surface EMG (IX-BIO04, iWorx, Dover, NH, USA). Off-line analysis of muscle thickness was performed using a custom MATLAB code and ImageJ v1.52s (National Institutes of Health, Bethesda, MD, USA).[103] The muscle thickness was measured using the average of four measurements of the distance between the deep and superficial aponeuroses taken at the left (distal) and the right (proximal) borders of the US images.[103] The authors of this study have previously reported these methods for muscle thickness using US to have excellent intra-rater and inter-rater reliability.[103]

2.5 Neuromuscular Activation

VL and RF muscle activity was measured during dominant limb knee extension MVIC using EMG. The surface electrodes were bipolar, disposable, pre-gelled, 1-cm-diameter, Ag/AgCl self-adhesive, circular snap electrodes with 20 mm interelectrode spacing (Noraxon, Scottsdale, AZ, USA). Before electrode placement, the skin was cleaned with alcohol. The electrodes were placed at 60% of the distance between ASIS and tibial tuberosity (VL), 50% of the distance between the anterior superior iliac spine and tibial tuberosity (RF), the anterior tibial bone of the ipsilateral limb (reference).

EMG data were analyzed using Visual 3D (C-Motion Research Biomechanics, Germantown, MD, USA) and band-pass filtered 10-500 Hz. EMG data from the two trials corresponding with the two highest torque values were averaged and used for analysis. The EMG amplitude was calculated as the root mean square of the EMG signal. The baseline amplitude means and standard deviations (SD) were calculated over 500 ms before EMG activity for each contraction.[208] The EMG onset was identified as 2 SD over the baseline mean amplitude and verified visually. The RoA was calculated across epochs of 0-50 ms

(RoA_{50}), 0-100 ms (RoA_{100}), 0-150 ms (RoA_{150}), and 0-200 ms (RoA_{200}).[208] The data were normalized to 150 ms around the maximal EMG amplitude, the highest value within the active signal.

2.6 Gross Motor Performance

2.6.1 Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition (BOT-2)

The BOT-2 subtests were used to assess bilateral coordination, balance, running speed and agility (RSA), and strength.[115] Two composite scores were calculated: 1) the body coordination composite score (bilateral coordination and balance), and 2) the strength and agility composite score (strength and RSA). Items were administered and scored according to BOT-2 standardized procedures.[115] The BOT-2 has established excellent inter-rater and test-retest reliability for children.[115]

2.6.2 Timed Tests

The 6-minute Walk Test (6MWT) was performed using standard procedures over a 30-meter walkway and the distance the participant walked (m) in 6 minutes was recorded.[209] Participants performed the Timed Up and Down Stairs (TUDS) by walking up and down a flight of stairs.[210] Participants performed the Timed Up and Go (TUG) by standing up from sitting in a chair, walking three meters, turning around, returning to the chair, and sitting down.[211] A stopwatch was used to record the seconds to complete the TUDS and TUG. These timed tests have established excellent intra-rater, inter-rater, and test-rest reliability.[209–211]

2.7 Quality of Life Questionnaires

The participants with SCD completed the self-report paper versions of the Pediatric Quality of Life Inventory, 4.0 Generic Core Scale and SCD Module (PedsQL and PedsQL-

SCD) and the Patient-Reported Outcome Measurement Information System (PROMIS) Strength Impact questionnaires. If the child requested assistance, the study staff aided the child in completing the questionnaire. The PedsQL and the PedsQL-SCD are valid and reliable self-report measures of health-related QoL in children with and without SCD.[212] A higher score on these questionnaires represents higher QoL. Cut-off scores to indicate impaired QoL have been established for the PedsQL (≤69.71) and to indicate poor QoL for the PedsQL-SCD (≤60).[212] The PROMIS Strength Impact is a self-report questionnaire that measures the perceived effect of strength on activities of daily living in which a lower score indicates more negative effects of strength.[213] The PROMIS Strength Impact is reliable and valid in children with and without SCD with a score ≤40 indicating fair/poor QoL.[213]

2.8 Statistical Analysis

Differences between SCD and control participants in muscle strength, size, neuromuscular activation, and gross motor performance (6MWT) were assessed using Mann-Whitney U tests and data are presented as median (interquartile range [IQR]). Differences between established normative values, the BOT-2 scaled and standard score,[115] TUDS time,[210] and QoL (PedsQL[214] and PROMIS Strength Impact[213]) were assessed using a one sample t-test compared to a standardized population and data are presented as mean (SD). Relationships were assessed using the Spearman rank correlation coefficient (r_s). The level of significance was set at $P \leq 0.05$. The effect size was calculated as Cohen's d (d) in which the effect size is considered large if $d \geq 0.5$, medium if $d \geq 0.3$, and small if $d \geq 0.1$.[194] The sample size was determined by a priori and interim post hoc power analyses that detecting a sample of n=9 in each group would have sufficient power to detect a moderate-to-large difference for knee extension strength (G*Power v.3.1.9.4, Germany).

3. RESULTS

3.1 Participants

Of the 24 total participants, 21 participants completed all outcome measures. In group of children with SCD, one participant elected not to complete the majority of the gross motor performance tasks (BOT-2, TUDS, TUG, 6MWT) and could not maintain the testing position for strength testing; one did not complete the BOT-2 due to a time constraint; and one's 6MWT distance was not recorded.

In the group of children with SCD, 13 had HbSS, and one had HbSC. Related to the SCD diagnosis, 86% of the participants with SCD had at least one medical complication of cerebrovascular accident (n=4), acute chest syndrome (n=10), and/or osteonecrosis (n=3). The most common medical management for SCD was hydroxyurea in 79%. The three children with SCD who were not taking hydroxyurea were receiving chronic blood transfusions. The median number of yearly hospitalizations for SCD complications was one time per year (range: 0 to 12 yearly hospitalizations). At the time of the assessment, no participants reported experiencing pain. The demographics for all the participants are reported in Table 1 with no significant differences between groups.

Table 4. Participant Characteristics

	SCD (n=14)	**Control (n=10)**
Age, years	11.6 (10.3-13.9)	11.4 (9.8-12.3)
Sex, # male	7	5
Limb Dominance, # right	14	9
Weight, kg	34.0 (29.0-47.6)	42.0 (28.3-50.8)
Height, m	1.5 (1.4-1.5)	1.5 (1.7-1.6)
Leg Length, m	0.8 (0.7-0.9)	0.8 (0.7-0.9)

Median (interquartile range [IQR])

3.2 Muscle Properties

Compared to control participants, children with SCD presented with lower knee extension joint torque (P=0.01; d=0.27; small) and lower VL RoA_{150} (P=0.03; d=0.20; small) (Table 5).

Table 5. Muscle Properties

	SCD	**Control**	***P***
Knee Extension Strength			
Joint Torque, Nm	24.8 (20.0-29.4)	32.6 (30.5-42.4)	0.01*
Muscle Thickness			
Vastus Lateralis, cm	1.5 (1.1-1.9)	1.5 (1.5-1.9)	0.63
Rectus Femoris, cm	1.9 (1.7-2.2)	1.9 (1.8-1.9)	0.67
Rate of Muscle Activation (RoA)			
Vastus Lateralis			
RoA_{50}, s^{-1}	0.7 (0.5-1.1)	0.7 (0.4-1.1)	1.00
RoA_{100}, s^{-1}	0.8 (0.4-1.7)	1.0 (0.7-1.4)	0.63
RoA_{150}, s^{-1}	0.8 (0.6-1.0)	1.4 (1.2-1.6)	0.03*
RoA_{200}, s^{-1}	1.2 (0.7-1.7)	1.4 (1.2-1.7)	0.51
Rectus Femoris			
RoA_{50}, s^{-1}	0.5 (0.2-0.8)	0.6 (0.4-1.2)	0.75
RoA_{100}, s^{-1}	0.6 (0.2-1.8)	0.9 (0.6-1.5)	0.59
RoA_{150}, s^{-1}	0.7 (0.3-1.7)	1.4 (0.7-1.6)	0.17
RoA_{200}, s^{-1}	1.1 (0.5-1.8)	1.4 (0.8-1.6)	0.51

Median (interquartile range [IQR])

3.3 Gross Motor Performance

Compared to normative values, children with SCD demonstrated poorer gross motor performance on the BOT-2 balance subtest (P<0.01; d=2.3; large), RSA subtest (P<0.01; d=2.7; large), body coordination composite score (P=0.01; d=1.3; large), and strength and agility composite scores (P=0.001; d=1.2; large). However, no significant differences in performance were detected in the bilateral coordination and strength subtests (Figure 13).

Children with SCD walked shorter distances on the 6MWT (mean 457.1 m, SD 74.1) compared to control participants (mean 575.0, SD 69.6; P<0.01; d=0.4; medium). Compared with normative values, children with SCD took longer in seconds to complete

the TUDS (mean 10.0, SD 1.7; *P*<0.01; *d*=2.6; large) and TUG (mean 7.2, SD 1.8; *P*<0.01; *d*=1.0; large) tests.

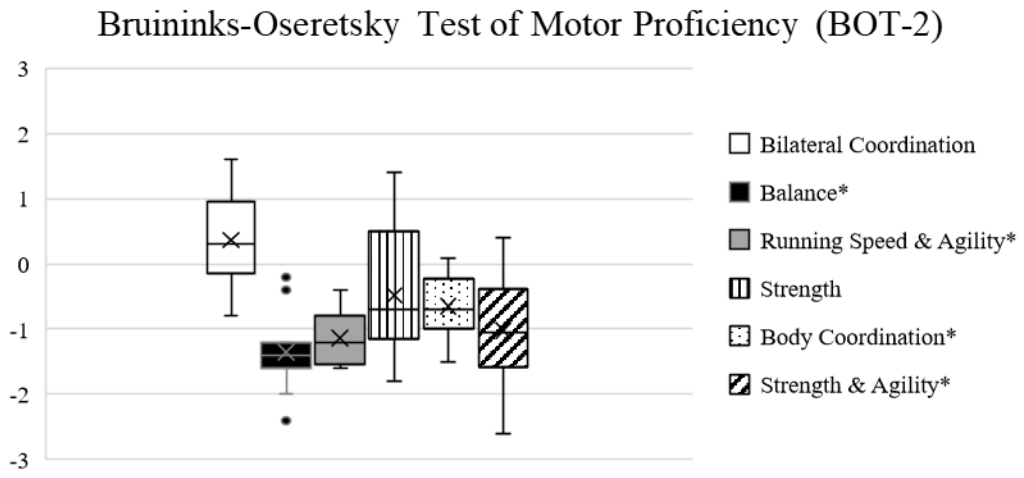

Figure 13. Boxplot of the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) subtest and composite z-scores for children with SCD. A score of 0 is indicative of the normative mean. *Indicates p<0.05 using a single-sample t-test comparing children with SCD with normative data.

3.4 Quality of Life

Compared to a normative sample, children with SCD reported poorer QoL on the PedsQL (mean 66.9, SD 0.2; *P*=0.02; *d*=0.7; medium) and the PROMIS Strength Impact Scale (mean 39.0, SD 7.4; *P*<0.01; *d*=1.5; large). On average, the children with SCD reported a score of 68.9 (SD 1.3) on the PedsQL-SCD.

3.5 Relationships in Children with SCD

3.5.1 Muscle Strength

Significant relationships were identified between knee extension strength and VL $RoA_{100\text{-}200}$ (r_s=0.6-0.6; *P*=0.02-0.03).

3.5.2 Gross Motor Performance

Increased proficiency on the BOT-2 balance subtest was positively related to knee extension strength (r_s=0.7; *P*=0.02) and VL $RoA_{100\text{-}200}$ (r_s=0.7-0.9; *P*<0.01). BOT-2 RSA

performance was positively associated with knee extension strength (r_s=0.6; *P*=0.04) and VL RoA_{200} (r_s=0.6; *P*=0.03).

3.5.3 Quality of Life

QoL measures were positively correlated with the distance walked on the 6MWT (PedsQL: r_s=0.7, *P*<0.01; PedsQL-SCD: r_s=0.7, *P*<0.01).

4. DISCUSSION

This is the first study to comprehensively explore the mechanisms that contribute to skeletal muscle strength, including muscle size and neuromuscular activation, and the relationships among gross motor performance and QoL in children with SCD. The results of this study identified impaired knee extension strength, lower VL RoA_{150}, decreased gross motor performance, and poorer QoL in children with SCD compared to controls. Relationships were detected between knee extension strength, VL RoA, and BOT-2 balance and RSA gross motor performance. Higher QoL scores were associated with greater 6MWT distance.

The participants with SCD in our study presented with decreased knee extension strength. In studies by Dougherty et al.[120] and Brownell et al.,[127] they assessed isokinetic (60°/second) knee extension strength in children with SCD (Dougherty: 5-20 years; Brownell: 9-19 years). Dougherty et al.[120] reported children with SCD presented with lower peak knee extension strength (mean 49.6 Nm, SD 27.6) compared to controls (mean 51.7, SD 34.0), however, the difference did not reach statistical significance (*P*≥0.05). Brownell et al.[127] reported relatively higher knee extension strength values in participants with SCD (74.8 Nm), however these scores were not compared to controls.[127] The differences in testing procedures, and testing positions likely contributed to the discrepancies in findings.

Children with SCD in our study presented with decreased gross motor performance compared to controls on the BOT-2, 6MWT, TUDS, and TUG. Children with SCD on average demonstrated a 5-year lag in BOT-2 balance and RSA gross motor skills compared to children with typical development. These findings indicate that children with SCD may be at high risk for having difficulty keeping up with peers in play and sports-related activities. Previous studies have reported that children with SCD performed poorer on gross motor activities including the 6MWT, 20-yard swim, 40-yard swim, 100-yard "potato race", and jump height compared to controls.[16,17] In contrast, studies by Dougherty et al.[120] and Brownell et al.,[127] did not identity gross motor performance deficiencies as measured by BOT Short Form in children with SCD (61.5-67.4) compared to controls (62.3).[120,127] The performance of children with SCD on the TUDS or TUG has not been previously reported.[15] The children with SCD in this study took longer to complete the TUDS and TUG tests compared to normative values. These measures did not correlate with muscle strength, size, neuromuscular activation, or QoL measures. Although the BOT Short Form, TUDS, and TUG include motor tasks required for activities of daily living, they may require a lower level of physical demand compared to the 6MWT and BOT-2 subtests. Thus, these measures may be less sensitive to detecting gross motor limitations in children with SCD.

In children without health conditions and children with cerebral palsy a positive relationship between quadriceps muscle thickness and knee extension strength is expected.[24] However, our findings of no difference in quadriceps muscle thickness but decreased knee extension strength between children with SCD and controls is more consistent with diseases that affect muscle quality, for example, pseudohypertrophy

experienced by children with Duchenne muscular dystrophy.[215] In our study, knee extension strength correlated with balance and RSA BOT-2 subtest scores. These data suggest that muscle size alone cannot explain the differences in strength and gross motor performance between children with and without SCD. Therefore, other factors need to be considered to explain the differences observed between groups, such as neuromuscular activation (i.e. RoA).

Overall, children with SCD presented with lower VL $RoA_{100\text{-}200}$ with a significant difference between SCD and controls at RoA_{150}. VL RoA correlated with knee extension strength ($RoA_{100\text{-}200}$), and BOT-2 balance ($RoA_{100\text{-}200}$), and RSA subtests (RoA_{200}). These findings are consistent with reports that adults with greater quadriceps and soleus RoA can generate more knee extension and ankle plantarflexion strength than those with lower RoA during MVIC.[72,73] The relationships between VL RoA and gross motor performance is also supported by Tillin et al.[184] who reported that greater and early quadriceps activation (i.e., first 250 ms) during isometric squatting resulted in faster sprinting and greater jump height.[184] This early activation period precedes maximal strength values and indicates that the ability to activate the muscles earlier and faster may be necessary for the proficiency of gross motor skills.[208] Through these finding, we show that agility and balance training programs that target neuromuscular activation through quick and explosive functional muscle contractions should be considered for children with SCD.

According to the children with SCD in this study, 64% reported impaired QoL on the PedsQL, 50% reported poor QoL on the PedsQL-SCD, and 79% reported fair/poor QoL on the PROMIS Strength Impact questionnaires. The children with SCD in our study reported similar levels of QoL as previously reported in children with SCD.[213,216,217]

Furthermore, relationships between QoL measures and gross motor performance on the 6MWT were identified. These relationships are supported by previous studies of children with cerebral palsy and survivors of childhood lower-extremity sarcoma that found greater gross motor performance ability to be associated with higher reported QoL.[23,25]

Children with SCD present with decreased strength, neuromuscular activation, gross motor performance, and QoL, therefore, it is important that a comprehensive physical therapy assessment is performed as part of the multidisciplinary care for children with SCD. We recommend including knee extension strength, the BOT-2 gross motor subtests including balance and RSA, the 6MWT, and QoL questionnaires (PedsQL, PedsQL-SCD, and PROMIS Strength Impact) in the physical therapy assessment. The information obtained from these assessments will aid in the development of targeted individualized physical therapy interventions and clinical research trials aimed to improve skeletal muscle properties, gross motor performance, and QoL in children with SCD.

4.1 Limitations

This study's procedures included clinically feasible assessment methods, however, as with many outcome measures, there are limitations. First, due to the nature of HHD, the lack of total stabilization may contribute to increased variability in measurements compared to isokinetic dynamometry; however, the methods used in this study demonstrated excellent interrater and interrater reliability. Secondly, the EMG and US measurements of muscle characteristics were collected using standardized procedures, however, the muscle thickness and RoA data were collected from a single area of the muscle and therefore is a representative sample of these muscle characteristics for the whole muscle. Thirdly, to improve the external validity, a study with a larger sample size

from a variety of institutions is warranted. Lastly, although there has been an increase in the use of US as a clinical assessment tool, the use of EMG remains very limited in clinical settings. Therefore, further development of clinically available assessment tools to identify muscle size and neuromuscular activation in children is needed.

5. CONCLUSIONS

Children with SCD present with decreased strength, neuromuscular activation, gross motor performance, and QoL, therefore, they could benefit from a physical therapy for a comprehensive assessment and the development of a targeted intervention plan addressing skeletal muscle properties, gross motor performance, and QoL.

CHAPTER SIX: QUANTIFYING MUSCLE STRENGTH, SIZE, AND NEUROMUSCULAR ACTIVATION IN ADOLESCENT AND YOUNG ADULT SURVIVORS OF MUSCULOSKELETAL SARCOMA: IDENTIFYING CORRELATES AND RESPONSES TO FUNCTIONAL STRENGTHENING[3]

ABSTRACT

Purpose: To explore muscle properties, gross motor performance, and quality of life (QoL) and the changes in response to a 6-week functional strengthening intervention (PT-STRONG) in adolescent and young adult survivors of musculoskeletal sarcoma (MSS).

Methods: Eight lower extremity MSS survivors of childhood cancer (CCS) (13-23 years old) performed baseline testing and three completed PT-STRONG. Participants completed measurements of muscle properties including knee extension strength using handheld dynamometry, vastus lateralis (VL) and rectus femoris (RF) muscle thickness using ultrasonography at rest, and neuromuscular activation using electromyography during strength testing and a step-up task. Participants also completed gross motor and QoL assessments.

Results: Compared to the non-surgical limb, MSS CCS had lower surgical limb knee extension strength, VL muscle thickness, and RF step-up muscle rate of activation (RoA). Compared to normative values, MSS CCS had decreased bilateral knee extension strength, gross motor performance, and physical QoL. Positive correlations among muscle strength, muscle thickness, and gross motor performance were identified. After PT-STRONG, MSS CCS had improvements in VL muscle thickness, VL and RF RoA during a step-up, gross motor performance, and physical QoL.

[3] Rock K, Addison O, Gray VL, Nelson CM, Henshaw RM, York T, Ruble K, Marchese V. *The Knee*. Accepted.

Conclusions: Positive association between larger muscle thickness with greater knee extension strength, and higher knee extension strength with better gross motor performance indicate that comprehensive physical therapy assessment and interventions that identify and target impairments in muscle properties should be considered for MSS CCS into survivorship.

Implications for Cancer Survivors: MSS CCS would benefit from comprehensive rehabilitation assessment to guide clinical decision-making to promote physical performance participation in daily activities.

1. INTRODUCTION

Musculoskeletal sarcomas (MSS) of the bone, such as osteosarcoma and Ewing sarcoma, generally arise from transformed mesenchymal connective tissue cells. MSS most commonly occurs by 25 years of age in the long bones of the lower and upper extremities (i.e., femur, tibia, and humerus) or the pelvis.[8] Although MSS account for a small percentage (3.4%) of childhood cancer and affect approximately 750 children and adolescents per year in the United States, these MSS survivors of childhood cancer (CCS) have a high likelihood of recovery and survival.[6,7] Improvements in chemotherapeutic, radiation, and surgical management in MSS CCS have increased long-term survivorship, with a 5-year overall survival rate reaching 70%.[6,7] Due to the complex medical and surgical management, MSS CCS are at risk for impaired muscle properties (muscle strength, muscle size, and neuromuscular activation) of the surgical and non-surgical limbs,[18–20,130,132] limited gross motor performance,[18,19,21,130–132,135,137–139,142,143,145,146] and lower health-related quality of life (QoL).[138,141,143,144,146–148]

The evolving medical and surgical treatments for MSS have the goal of not only improving survival but also preserving the individual's long-term physical function and participation in school, work, and recreation. Medical treatments typically consist of six or more months of chemotherapy combined with surgical tumor resection. The chemotherapeutic agents used for MSS affect both cancerous and normal cells and cause short- and long-term side effects in multiple body systems.[12–14] In addition to chemotherapy, MSS CCS undergo a wide surgical resection of the tumor, which may consist of limb amputation, rotationplasty, or limb-sparing surgery (LSS). LSS is the most common surgical procedure for local control for 90% of patients with MSS.[9,218] LSS includes oncologic resection of the bone and/or soft tissue tumor, reconstruction of resected bone segments, and muscular or tendon re-routing.[9] To ensure the entire tumor is removed, the resection of both cancerous tissues and healthy tissues is required.[9] During an LSS surgery, the resected bone segments are reconstructed using an endoprosthesis, hardware, autograft, and/or allograft, and tendons and muscles are re-routed to optimize the functional potential of the limb.[9] For example, the common LSS procedure for a proximal tibial MSS involves resection of the tumor, bone, and surrounding soft tissue, endoprosthetic replacement of the resected tibia and knee joint, reconstruction of the patellar tendon attachment to the endoprosthesis, and a medial gastrocnemius muscle flap.[9]

Due to the multimodal medical and surgical treatment, MSS CCS are at risk for impairments in quadriceps muscle strength due to multiple underlying mechanisms beyond surgical loss of muscle such as impairments in muscle size and neuromuscular activation. Specific chemotherapy agents (i.e. doxorubicin), cancer cachexia, pain, immobilization, and disuse have been associated with changes in skeletal muscle properties such as muscle

atrophy, weakness, and impaired neuromuscular activation.[10,11,132,219,220] MSS CCS are also at risk for alterations in neuromuscular activation due to changes in the knee joint kinematic patterns (i.e., stiff knee gait) that may affect the quadriceps muscles rate of activation (RoA) and knee muscle co-contraction index (CCI).[11,132,219–222] Given that MSS of the lower extremities are most commonly located in the distal femur or proximal tibia, the function of the quadriceps muscles is at high risk for impairment. The vastus lateralis (VL) and rectus femoris (RF) muscles are typically conserved after LSS and are critical to gross motor tasks such as walking, running, and jumping. The VL is the primary extender of the knee, and the biarticular RF performs hip flexion and knee extension, the movements required to kick a ball or climb stairs.[223,224] Therefore, VL and RF muscle properties including muscle strength as measured by handheld dynamometry (HHD),[103,205] muscle thickness measured by ultrasonography (US),[24,103,225] and neuromuscular activation measured by electromyography (EMG) may relate to gross motor performance in MSS CCS and have yet to be comprehensively explored. In other complex childhood health conditions such as cerebral palsy and acute lymphoblastic leukemia, relationships have been reported among quadriceps muscle thickness, gross motor performance, and quality of life.[23–25]

Previous MSS CCS exercise intervention studies have focused on pre-surgical rehabilitation and increasing physical activity levels during medical treatment.[20,226] Despite the benefits of pre-surgical interventions, significant impairments in muscle strength and gross motor performance persist well beyond medical and surgical treatment.[18–21,23,131,132,137,139,142,143] Therefore, current efforts are focused on developing exercise interventions to effectively mitigate these declines into survivorship. Functional strength

training targets lower extremity muscles that are required to produce functional movements such as walking, rising from a chair, and climbing stairs. Previous studies in healthy children and acute lymphoblastic leukemia CCS using functional strengthening interventions have demonstrated a two times per week six-week program effectively increased strength and improved gross motor performance.[220,227] Building on this evidence, we sought to determine if a functional strengthening intervention would be effective in MSS CCS.

Therefore, this study aimed to explore the muscle properties (muscle strength, muscle size, and neuromuscular activation) of the lower extremity that underwent surgery (surgical limb) and the contralateral lower extremity (non-surgical limb) and the relationships among muscle properties, gross motor performance, and QoL in adolescent and young adult MSS CCS. We hypothesized that MSS CCS would present with decreased knee extension strength, smaller muscle thickness, lower VL and RF muscle rate of activation (RoA), and increased knee muscle co-contraction index (CCI) in the surgical limb compared to the non-surgical limb, and poorer gross motor performance and QoL compared to a normative population. We also hypothesize that muscle size and neuromuscular activation would be correlated with muscle strength and gross motor performance. Also, a 6-week functional strengthening intervention would increase knee extension strength, increase VL and RF muscle thickness and RoA, decrease knee CCI, and improve gross motor performance.

2. METHODS

2.1 Study Participants

Eight adolescent and young adult MSS CCS participants were recruited from Pediatric Hematology/Oncology Clinics at the University of Maryland Medical Center, Children's National Hospital, and Johns Hopkins Hospital between July 2018 and June 2022 for participation in this study at the University of Maryland, School of Medicine, Department of Physical Therapy & Rehabilitation Science (UMSOM PTRS). Participants were eligible if they were adolescents or young adults between 13 and 26 years old, had a previous diagnosis of osteosarcoma or Ewing sarcoma of the femur or tibia, underwent lower extremity surgery greater than one year before enrolling in this study, and completed chemotherapy prior to enrollment in this study. Participant exclusion criteria included a diagnosis of a neurological or muscle disorder not related to a diagnosis of MSS, a history of a serious lower-extremity injury or surgery six months before the enrollment in the study, or currently pregnant based on participant report. This study was approved by the University's institutional review board. All participants <18 years of age provided informed assent and caregivers provided informed consent. All participants ≥ 18 years of age provided informed consent.

2.2 Study Procedures

The initial baseline assessment, performed in a single session, included measurements of knee extension strength, quadriceps muscle thickness, gross motor performance, and quality of life. Participants were given the option to participate in the intervention component of this study. The intervention group participants (n=3) were asked to attend treatment sessions 2x per week for 6 weeks (12 sessions total). The non-

intervention group participants were instructed to continue with their usual activity. Post-intervention assessments (post-test) consisted of identical measures performed at baseline. To maintain consistency and reduce bias in data collection, the same assessor performed baseline and post-test outcome measures for all participants and a different study team member performed all of the intervention sessions.

2.3 Outcome Measures

2.3.1 Muscle Properties

2.3.1.1 Knee extension strength

Knee extension joint force at the distal tibia was measured using an HHD (Lafayette Manual Muscle Testing System model 01165, Lafayette Instrument, Lafayette, IN, USA) in the seated position with both knees flexed to 90° (seated 90°) and in the supine position with both knees supported at 35° of flexion (supine 35°) as measured by a standard goniometer.[207,219,228] The HHD was placed on the anterior tibia 2 cm proximal to the intermalleolar line. The participants were instructed to take a normal inspiration and slow expiration during maximum voluntary isometric contractions (MVIC) with the instructions, “hold the position you are placed in and kick as fast and as hard as you can into the testing device.” Participants performed two familiarization trials of sub-maximal effort followed by three MVIC trials of five seconds each with at least a 30-second but no more than a 2-minute rest break between trials. Knee extension force was recorded as the average of the highest two force values in kilograms (kg).[103] To account for the difference in lever arms for the participant with a transtibial amputation, the surgical limb force was scaled by multiplying the ratio of the length of the non-surgical lower leg divided by the

length of the surgical lower leg. Muscle strength measurement of knee extension using HHD has excellent intra-rater and inter-rater reliability.[103,163]

2.3.1.2 Muscle Size

Resting quadriceps muscle thickness was measured by two-dimensional B-mode US (GE Logiq v9, GE Healthcare, Milwaukee, WI, USA; Whale Sigma P5, Whale Imaging Inc., Waltham, MA, USA) of the VL at 50% of the distance from the inferior margin of the greater trochanter to the tibial tuberosity and the RF at 40% of the distance from the anterior superior iliac spine to the tibial tuberosity.[103] Images were acquired using a 5-12 MHz frequency, 38-mm linear array probe placed parallel to the long axis of the muscle and perpendicular to the skin surface. Three images of each muscle were collected with the participant positioned supine with the hips and knees in neutral positions. The muscles were verified to be at rest using real-time surface EMG (iWorx, Dover, NH, USA). Off-line analysis of muscle thickness was performed using a custom MATLAB code and ImageJ v1.52s (National Institutes of Health, Bethesda, MD, USA).[103] The muscle thickness was measured using the average of four measurements of the distance between the deep and superficial aponeuroses taken at the left (distal) and the right (proximal) borders of the US images.[103] These methods for VL and RF muscle thickness using US have excellent intra-rater and inter-rater reliability.[103]

2.3.1.3 Neuromuscular Activation

Muscle activity was measured during knee extension in supine 35° MVIC and during a step-up task using the iWorx IX-BIO4 EMG system (iWorx, Dover, NH, USA). This position of knee flexion for MVIC testing was selected based on previous evidence for VL and RF EMG activity to be at their greatest.[229] The participants performed the step-

up task by standing in front of a 15.8 cm rise standard stair and stepping onto the stair with one limb followed by the other limb. Surface electrodes were placed on the VL, RF, biceps femoris (BF), and semitendinosus (ST) muscles of the limb that was performing the MVIC or step-up task. The electrodes were bipolar, disposable, pre-gelled, 1-cm-diameter, Ag/AgCl self-adhesive, circular snap electrodes with 20 mm interelectrode spacing (Noraxon, Scottsdale, AZ, USA). Before electrode placement, the skin was cleaned with alcohol. For VL, the electrodes were placed at 60% of the distance between ASIS and tibial tuberosity. The electrodes were placed on the muscle belly of RF at 50% of the distance between the anterior superior iliac spine and tibial tuberosity. The electrodes were placed for the BF and ST at 50% of the distance between the ischial tuberosity and the lateral and medial epicondyle, respectively. A reference electrode was positioned on the anterior tibial bone of the ipsilateral limb.

2.3.1.3.1 Rate of Muscle Activation (RoA)

EMG data were analyzed using Visual 3D (C-Motion Research Biomechanics, Germantown, MD, USA) and band-pass filtered 10-500 Hz. EMG data from the two trials corresponding with the two highest torque values for the MVIC and the two trials of the step-up task were averaged and used for analysis. The EMG amplitude was calculated as the root mean square of the EMG signal. The baseline EMG means and standard deviations (SD) were calculated over 500 ms before EMG activity for each contraction.[208] The EMG onset was identified as the time at which the signal increased by at least 2 SD over the baseline mean and verified visually. The RoA was calculated across epochs of 0-50 ms (RoA_{50}), 0-100 ms (RoA_{100}), 0-150 ms (RoA_{150}), and 0-200 ms (RoA_{200}).[208] The data were

normalized to 150 ms around the maximal EMG amplitude, the highest value within the active signal.

2.3.1.3.2 Knee co-contraction index (CCI)

Knee co-contraction index (CCI) was calculated for both the MVIC supine 35° and the step-up tasks. A 500-ms window around the maximal VL EMG amplitude was used to calculate the co-contraction index and normalized to the peak amplitude during this MVIC knee extension task for VL and RF, and during an MVIC knee flexion task in sitting with the knee flexed to 90° for BF and ST.[66] These testing positions selected for normalization were based on knee flexion angles associated with the highest VL, RF, BF, and ST EMG activity.[229,230] Co-contraction index between agonist and antagonist muscles was calculated by applying the co-contraction index (CCI) equation: $CCI = \left(\frac{2 \times I_{ant}}{I_{tot}}\right) \times 100$. In this equation, I_{ant} is the sum of the EMG activity from antagonist muscles and I_{tot} is the sum of the EMG activity from the agonist and antagonist muscles.[231] A CCI value of 0% represents pure agonist activation and 100% represents total co-contraction.[231,232]

2.3.2 Gross Motor Performance

Gross motor performance was assessed using the Functional Mobility Assessment (FMA), which includes the timed up and down stairs (TUDS), the timed up and go (TUG), and the 9-minute run-walk (9RW) tests. The FMA is valid and has excellent intrarater and interrater reliability in MSS CCS.[22] Participants performed the TUDS by walking up and down a flight of stairs.[233] Participants performed the TUG by rising from a chair, walking three meters, turning around, returning to the chair, and sitting down.[233,234] A stopwatch was used to record the time for the TUDS and TUG in seconds.[233,234] The 9RW test was performed using standard procedures over a 65-feet walkway and the distance (m) the

participant completed in 9-minutes was recorded.[22,235] These timed tests have established excellent intra-rater, inter-rater, and test-rest reliability.[211,236] At rest and after each timed test, heart rate (HR) was measured using a finger pulse oximeter (Zacurate, Stafford, TX, USA) and rate of perceived exertion was reported using the Borg Scale (6 to 20) in which 7 is labeled is "very, very light" and 19 as "very, very hard".[237] The physiological cost index (PCI) was calculated using the data from the 9RW test and the formula: $PCI = \frac{(working\ HR - resting\ HR)}{speed}$. A total FMA score was calculated using the standard procedure.[233]

2.3.3 Quality of Life Questionnaire

The Short Form-36, version 2 (SF-36v2) is an established, reliable, and validated measure of health-related quality of life.[238] The questionnaire consists of 36 items with eight subscales (physical functioning, role limitations due to physical problems, general health perceptions, vitality, social functioning, role limitations due to emotional problems, general mental health, health transitions) and two composite domains (physical health [PCS] and mental health [MCS]). A higher score on these scales indicates a higher perceived QoL. A score of 50 on the PCS and MCS is representative of the United States (U.S.) general population norm.[238]

2.4 PT-STRONG Physical Therapy Intervention

Adolescent and young adult MSS CCS participants assigned to the intervention group were asked to perform in-person exercise sessions with a physical therapist two times per week for six weeks. Each therapy session included: 1) ***Discussion***: Session goals of repetitions and sets; 2) ***Warm-up***: The participant walked overground for 5 minutes (at least 11 of 20 "light" on the Borg scale); 3) ***Stretching***: The participant performed gentle trunk (flexors/extensors, lateral flexors), hip (flexors/extensors, internal/external rotators),

knee (flexors/extensors), and ankle (dorsiflexors/plantarflexors) stretching exercises for 3 repetitions of 10 seconds each; 4) ***Strengthening Exercises***: the participant performed rapid functional strengthening exercises, which included body squats, step-ups, and step-downs. During these exercises, the physical therapist ensured the participant used proper body mechanics. Exercises were progressed by the number of repetitions (6 to 15), followed by the number of sets (1 to 3), and then by the range (squat depth and step height); 5) ***Cool-Down***: the participant walked overground for 5 minutes (11 on the Borg scale). During exercises, the physical therapist provided verbal cues and feedback for proper body position, but only provided hands-on contact to maintain safety, not to physically assist with performing the movement. In each session, the physical therapist advanced the program based on the participant's progress with a goal of 3 sets of 15 repetitions for squatting and stepping. The physical therapist kept a weekly log to document the number of sets and repetitions of each exercise performed.

2.5 Statistical Analysis

Descriptive data are presented as mean ± SD. The normality of the data was assessed using the Shapiro-Wilk Test. Differences between limbs at baseline in muscle strength, size, and neuromuscular activation during MVIC and the step-up task were assessed using paired t-tests. Differences between established normative values for knee extension force in seated 90°, the 9RW distance, TUG time, TUDS time, total FMA score, and SF-36v2 PCS and MCS were assessed using a one-sample t-test compared to a standardized population.[233,238,239] Relationships between baseline data were assessed using the Spearman rank correlation coefficient (r_s). The level of significance was set at $P \leq 0.05$. The sample size was determined by a priori power analysis and an interim post hoc power

analysis that detecting a sample of n=5 participants would have sufficient power to detect a moderate-to-large difference between groups for knee extension strength (G*Power v.3.1.9.4, Germany). Differences between baseline and post-test surgical limb outcomes for the intervention group are reported as a percentage change. The minimal detectable change (MDC_{95}) was calculated using the baseline data for surgical limb knee extension force, VL and RF muscle thickness, RoA, knee CCI, TUDS, TUG, and 9RW tests using the formula $MDC_{95} = 1.95 \times \sqrt{2} \times SEM$, in which SEM is the standard error of the mean.[240]

3. RESULTS

3.1 Participants

Eight MSS CCS participants with a mean age of 17.34±3.33 years (5 males and 3 females) completed baseline assessments. All participants were survivors of a primary bone sarcoma of the femur (n=4) or tibia (n=4), with 6 having a diagnosis of conventional high-grade osteosarcoma and two participants (participants 4 and 8) having a positive BCOR gene rearrangement, a small round cell sarcoma with similarities to Ewing sarcoma.[241] For medical management, all the participants received a combination of chemotherapy including doxorubicin plus methotrexate, cisplatin, vincristine, and/or Cytoxan. At the time of enrollment in our study, the average time since completion of chemotherapy was 3.55±2.30 years, and since surgery was 4.09±2.00 years. For local control, seven of the eight (87.5%) participants underwent an LSS, and one participant underwent a transtibial amputation. Table 6 summarizes the medical and surgical history of the MSS CCS participants.

Table 6. Medical and Surgical History of Study Participants

	Tumor location	Surgery	Time since surgery	Time since completion of chemotherapy	Known Complications	PT-Strong Intervention
1	Left proximal femur	Limb salvage fibular allograft	Over 6 years	6.09 years	None	No
2	Right distal femur	Limb salvage expandable endoprosthesis	5.78 years	5.44 years	Significantly limited knee flexion range of motion	Yes
3	Right proximal tibia	Limb salvage endoprosthesis with medial gastrocnemius muscle flap	1.66 years	1.10 years	Right toes amputation due to necrosis	Yes
4	Left proximal tibial	Limb salvage endoprosthesis with medial gastrocnemius muscle flap	1.74 years	0.37 years	None	No
5	Right distal femur	Limb salvage endoprosthesis	5.94 years	5.51 years	None	No
6	Left distal femur	Limb salvage endoprosthesis	1.98 years	1.48 years	Poor wound healing requiring rotational gastrocnemius muscle flap and skin graft	Yes
7	Right distal femur	Limb salvage endoprosthesis	5.53 years	5.16 years	Post-surgical foot drop; uses an ankle-foot orthosis	No
8	Right distal tibia	Transtibial amputation	4.04 years	3.26 years	Wound debridement; uses a prosthetic limb	No

All MSS CCS participants completed the baseline data testing for knee extension strength in seated 90°, VL muscle thickness, gross motor performance, and QoL measures. However, only four of the participants performed strength testing in supine 35°, RF muscle thickness, quadriceps neuromuscular activation measurements as these exploratory outcomes were added to the original study design after further examination of previous findings. The participant with a transtibial amputation did not complete neuromuscular

activation measures during the step-up task due to restrictions from the prosthetic sock and socket fitting comfortably over the electrodes. Four of the participants were assigned to the intervention group. Three of the four participants completed >80% of the intervention sessions and these data were analyzed for baseline to post-test changes.

3.2 Muscle Properties

Compared to the non-surgical limb, knee extension force (seated 90°; $P<0.001$), muscle thickness (vastus lateralis; $P<0.001$), and rectus femoris $RoA_{150\text{-}200}$ during the step-up task ($P=0.016\text{-}0.038$) were significantly lower in the surgical limb (Table 7). Compared to normative values, MSS CCS demonstrated decreased knee extension force for both the surgical and non-surgical limbs (seated 90°; $P<0.001$).

Table 7. Measured Muscle Properties

	Surgical Limb	Non-Surgical Limb	n	*P*
Knee Extension Force				
Seated 90°, kg	10.70 (5.59)	21.34 (6.02)	8	<0.001**
Supine 35°, kg	10.39 (5.36)	14.05 (5.64)	4	0.076
Muscle Thickness				
Vastus Lateralis, cm	1.52 (0.45)	2.19 (0.54)	8	<0.001**
Rectus Femoris, cm	1.70 (0.67)	2.56 (0.48)	4	0.126
Neuromuscular Activation				
MVIC - Vastus Lateralis				
RoA_{50}, s^{-1}	1.00 (0.84)	1.41 (0.90)	4	0.630
RoA_{100}, s^{-1}	0.89 (0.84)	1.18 (0.76)	4	0.716
RoA_{150}, s^{-1}	0.91 (0.78)	1.11 (0.69)	4	0.779
RoA_{200}, s^{-1}	0.79 (0.71)	0.99 (0.51)	4	0.709
MVIC - Rectus Femoris				
RoA_{50}, s^{-1}	0.93 (0.72)	0.93 (0.49)	4	0.998
RoA_{100}, s^{-1}	0.95 (0.69)	0.94 (0.48)	4	0.994
RoA_{150}, s^{-1}	0.98 (0.69)	0.96 (0.49)	4	0.963
RoA_{200}, s^{-1}	0.99 (0.60)	0.94 (0.58)	4	0.925
MVIC – Knee CCI	0.51 (0.28)	0.61 (0.09)	4	0.391
Step-Up – Vastus Lateralis				
RoA_{50}, s^{-1}	5.44 (5.09)	9.35 (2.71)	3	0.312
RoA_{100}, s^{-1}	3.68 (2.34)	6.81 (1.23)	3	0.187
RoA_{150}, s^{-1}	3.25 (1.07)	5.29 (0.96)	3	0.192
RoA_{200}, s^{-1}	2.85 (0.36)	4.13 (0.75)	3	0.159
Step-Up – Rectus Femoris				
RoA_{50}, s^{-1}	8.85 (6.66)	14.41 (1.75)	3	0.276
RoA_{100}, s^{-1}	5.25 (1.90)	8.19 (1.08)	3	0.152
RoA_{150}, s^{-1}	3.52 (0.42)	5.60 (0.51)	3	0.038*
RoA_{200}, s^{-1}	2.64 (0.10)	4.16 (0.25)	3	0.016*
Step-up – Knee CCI	0.79 (0.46)	0.41 (0.14)	3	0.369

Mean (standard deviation [SD]); MVIC = maximal voluntary isometric contraction measured in supine with knees flexed to 35°; RoA = rate of muscle activation; CCI = co-contraction index

3.3 Gross Motor Performance

Compared to normative values, MSS CCS presented with limitations in gross motor performance (Table 8).

Table 8. Functional Mobility Assessment (FMA)

	MSS CCS	Normative[233]	*P*
Timed up and Down Stairs, s	17.31 (11.41)	6.18 (0.8)	0.030*
Timed up and Go, s	7.63 (2.45)	3.78 (0.6)	0.003*
9-minute Walk Run, m	706.53 (215.3)	1268.28 (272.19)	<0.001**
FMA Total Score	49.75 (2.43)	59.00 (3.00)	<0.001**

3.4 Quality of Life

On average, MSS CCS reported scores of 44.52 (4.06) and 57.87 (16.58) on the SF36v2 PCS and MCS scores, respectively. These reported scores are lower than normative values for PCS (p=0.007) and similar to normative values for MCS.

3.5 Relationships

Significant relationships were identified between knee extension strength and muscle thickness (r_s=0.76-0.95; *P*<0.001 to 0.03; Figure 14a-d), surgical limb knee extension strength and the TUDS (r_s=-0.71; *P*=0.05; Figure 15), and non-surgical limb knee extension strength and the TUG (r_s=-0.71; *P*=0.05) and 9RW (r_s=0.76; *P*=0.03) tests (Figure 16). No significant relationships between gross motor performance and quality of life were detected.

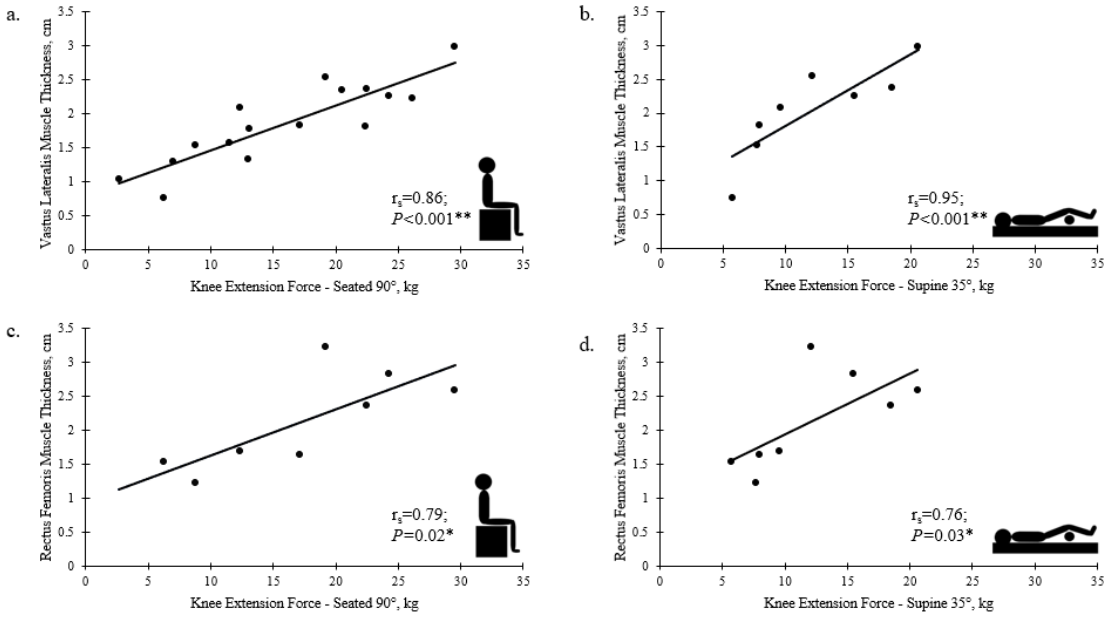

Figure 14. Relationships between knee extension strength and muscle thickness.

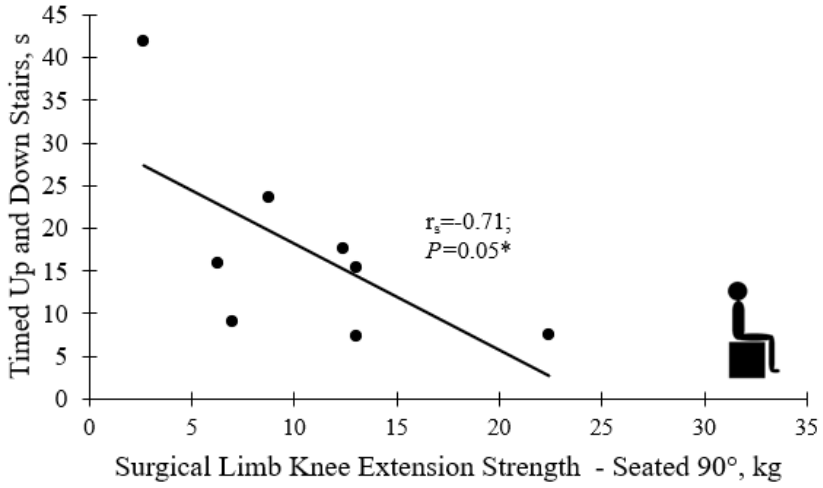

Figure 15. Relationships between surgical limb knee extension strength and the Timed Up and Down Stairs test.

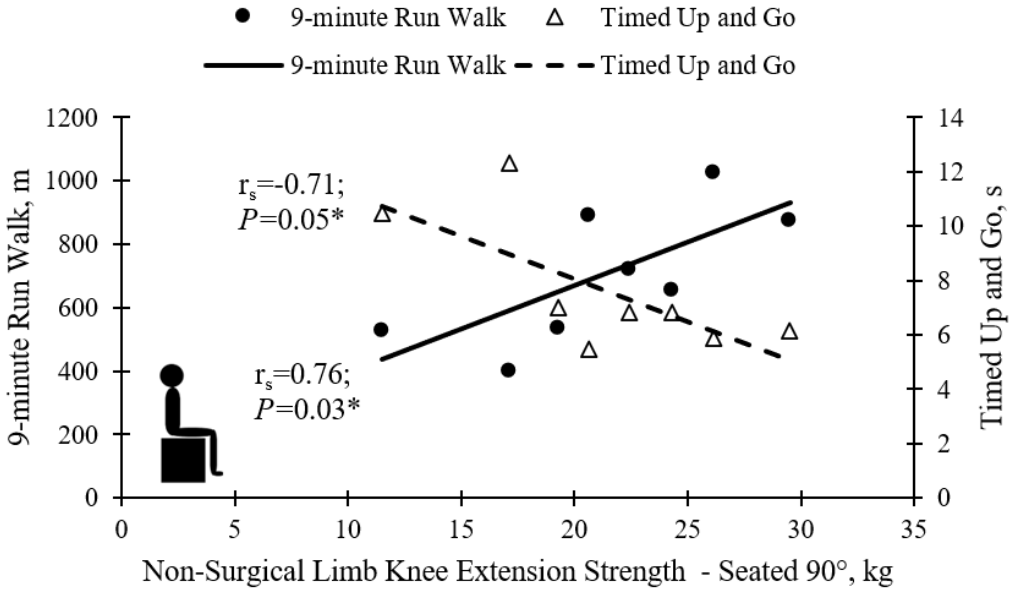

Figure 16. Relationships between non-surgical limb knee extension strength and the Timed up and Go (open triangles; dotted line) and 9-minute Run Walk (filled circles; solid line) tests.

3.6 PT-STRONG Intervention

Three MSS CCS participants completed 100% of the 12 PT-STRONG intervention sessions. Two of the three participants demonstrated improvements between baseline and post-test in surgical limb knee extension strength at seated 90° and VL

muscle thickness (Table 9). The VL muscle thickness increase for Participant #6 exceeded the MDC_{95}. On average, the participants that completed PT-STRONG improved in gross motor performance measures by decreasing the time to complete the TUDS by 1.80 seconds and TUG by 1.86 seconds and increasing the distance walked on the 9RW by 41.86 meters (Table 9). The improved performance on the TUG for Participants #3 and #6 exceeded the MDC_{95} (Table 9). On average, the participants that completed PT-STRONG improved SF-36v2 PCS scored by 10.74 points and decreased MCS scores by 14.67 points.

Of the three participants that completed the intervention, only Participant #6 completed knee extension strength at supine 35° and neuromuscular activation testing. Compared to baseline, this participant demonstrated increased surgical limb knee extension strength in supine 35°, decrease in RF muscle thickness, and increased VL and RF RoA, and decreased knee CCI during MVIC and step-up tasks (Table 3). The increases in VL $RoA_{50\text{-}200}$ and RF $RoA_{100\text{-}200}$ during the step-up task exceeded the MDC_{95} (Table 9).

4. DISCUSSION

This study quantified the muscle properties (muscle strength, muscle size, and neuromuscular activation) of the surgical and non-surgical limbs and assessed relationships among muscle properties, gross motor performance, and QoL in adolescent and young adult MSS CCS. Participants in this study presented with decreased muscle strength, muscle thickness, and RoA in the surgical limb compared to their non-surgical limb and poorer gross motor performance and physical QoL compared to a normative population. At baseline, a positive correlation between muscle strength, muscle size, and gross motor

performance was identified. We showed that our 6-week PT-STRONG functional strengthening intervention produced individual improvements in MSS CCS for VL muscle thickness, VL and RF RoA during a step-up task, gross motor performance on the TUG, and physical QoL.

MSS CCS presented with decreased bilateral knee extension strength with significantly less strength in the surgical limb compared to the non-surgical limb, consistent with previously reported data.[18–20] This current study identified a 26.1 to 49.9% between-limb deficit in knee extension strength. Tsauo et al.[18] reported ratios of muscle strength between MSS CCS surgical and non-surgical limbs ranging from 37.4 to 47.5% for knee extension. Muscle strength deficits have not only been identified in the surgical limb but also have been identified in the non-surgical limb.[19,20] The results of our study identified a 72.7% decrease in surgical limb and a 45.6% decrease in non-surgical limb knee extension compared to a normative population.[239] A case series by Beebe et al.[19] examined four children (aged 9 to 11 years) and reported a decrease in non-surgical knee force production by 63% compared to normative values.[19] Corr et al.[20] also found knee extension strength deficits in the non-operative limb and these strength deficits declined from baseline to post-surgery and did not recover by 20 to 22 weeks post-surgery.[20] These findings, along with the results of this study, support that MSS CCS have strength deficits that persist well beyond the initial post-operative period.

The relationships between the properties of skeletal muscle have not been previously defined in MSS CCS. The participants in this study had lower surgical limb VL and RF thickness compared to the non-surgical limb. Both the VL and RF muscle thickness measurements were found to correlate with knee extension strength. These findings are

Table 9. PT-Strong Intervention Outcome Measures

		Participant 2			Participant 3			Participant 6		
Outcome Measure	MDC_{95}	Baseline	Post-test	Difference	Baseline	Post-test	Difference	Baseline	Post-test	Difference
Knee Extension Force										
Seated 90°, kg	1.98	13.02[a]	10.75[a]	-17.42%	2.68	2.72	**+1.69%**	6.26	6.80	**+8.67%**
Supine 35°, kg	7.39	–	–	–	–	–	–	5.75	6.88	**+19.79%**
Muscle Thickness										
Vastus Lateralis, cm	0.16	1.34	1.16	-12.90%	1.04	1.09	**+4.80%**	0.75	0.92	**+22.38%***
MVIC - Vastus Lateralis										
RoA_{50}, s^{-1}	1.16	–	–	–	–	–	–	0.71	0.91	**+26.85%**
RoA_{100}, s^{-1}	1.16	–	–	–	–	–	–	0.46	0.63	**+37.46%**
RoA_{150}, s^{-1}	1.08	–	–	–	–	–	–	0.33	0.82	**+146.50%**
RoA_{200}, s^{-1}	0.98	–	–	–	–	–	–	0.25	0.85	**+240.04%**
MVIC - Rectus Femoris										
RoA_{50}, s^{-1}	0.99	–	–	–	–	–	–	0.44	0.73	**+63.05%**
RoA_{100}, s^{-1}	0.95	–	–	–	–	–	–	0.38	0.71	**+85.61%**
RoA_{150}, s^{-1}	0.95	–	–	–	–	–	–	0.49	0.63	**+28.80%**
RoA_{200}, s^{-1}	0.83	–	–	–	–	–	–	0.51	0.57	**+12.52%**
MVIC – Knee CCI	0.39	–	–	–	–	–	–	0.42	0.19	**-55.14%**
Step-Up – Vastus Lateralis										
RoA_{50}, s^{-1}	8.10	–	–	–	–	–	–	6.40	15.74	**+145.99%**
RoA_{100}, s^{-1}	3.73	–	–	–	–	–	–	3.82	9.35	**+145.06%***
RoA_{150}, s^{-1}	1.70	–	–	–	–	–	–	2.89	6.48	**+124.43%***
RoA_{200}, s^{-1}	0.57	–	–	–	–	–	–	2.63	4.68	**+77.97%***
Step-Up – Rectus Femoris										
RoA_{50}, s^{-1}	10.60	–	–	–	–	–	–	9.74	16.24	**+66.71%**
RoA_{100}, s^{-1}	3.03	–	–	–	–	–	–	5.40	10.18	**+88.48%***
RoA_{150}, s^{-1}	0.67	–	–	–	–	–	–	3.51	6.62	**+88.82%***
RoA_{200}, s^{-1}	0.16	–	–	–	–	–	–	2.90	4.30	**+48.47%***
Step-up – Knee CCI	0.73	–	–	–	–	–	–	0.66	0.52	**-20.91%**
Timed up and Down Stairs, s	4.03	15.43	12.38	**-19.77%**	41.92	41.94	+0.05%	15.90	13.55	**-14.78%**
Timed up and Go, s	0.87	6.82	6.00	**-12.02%**	10.52	9.15	**-13.02%***	12.33	8.93	**-27.58%***
9-minute Walk Run, m	76.13	722.99	789.74	**+9.23%**	531.57	534.92	**+0.63%**	401.12	456.59	**+13.83%**

Abbreviations: MDC_{95}= minimal detectable change; RoA= rate of activation for epochs 50, 100, 150, and 200 ms; CCI= co-contraction index. *indicates difference between baseline and post-test >MDC_{95}.

consistent with previous reports in children and adolescents with cerebral palsy and adults with osteoarthritis and after total knee arthroplasty, which are populations with known knee joint kinematic changes and decreased activity levels.[24,242–244]

Compared to those without health conditions, children and adolescents with cerebral palsy have lower VL and RF muscle thickness, and positive relationships between muscle thickness and knee extension strength have been reported.[24,242] In adults, after total knee arthroplasty RF muscle thickness is lower on the surgical limb compared to the non-surgical limb and control participants, and relationships between higher muscle thickness with greater knee extension muscle strength have been identified.[243] Quadriceps muscle thickness is negatively correlated with pain levels and positively related to patient-reported physical function and gross motor performance, including the TUG test, in adults with osteoarthritis and post-total knee arthroplasty.[243,244] Therefore, utilizing US muscle thickness measurements may be a beneficial alternative for MSS CCS, especially if pain or medical restrictions prevent formal muscle strength testing.[225]

The MSS CCS in our study presented with limited gross motor performance and lower physical QoL compared to normative values on the FMA, TUDS, TUG, 9RW, and SF-36v2 PCS. These findings are consistent with previously reported performance on these measures in a larger cohort of MSS CCS.[21–23] Marchese et al.[23] identified relationships between hip and knee joint range of motion and performance on the TUDS, TUG, 9RW, and SF-36v2 PCS. Relationships between increased knee extension strength and better gross motor performance were present for the MSS CCS. Surgical limb knee extension strength was correlated with better performance on the TUDS. Non-surgical limb knee extension strength was related to a shorter time to complete the TUG and a farther distance

on the 9RW test. These findings are reflective of the lower extremity demands required for walking and climbing stairs. During walking, adaptive gait deviations (i.e. hip Trendelenburg, vaulting) can compensate for a lack of surgical limb function.[19] Okita et al.[245] reported that MSS CCS who underwent LSS increased bilateral hip, bilateral ankle, and non-surgical limb knee power to increase walking speed. However, the participants in this study performed stair climbing with a reciprocal pattern, which requires the isolated surgical limb to extend to ascend the stairs. Given that these participants also demonstrated decreased bilateral knee extension strength, performing a variety of functional tasks that require muscular challenges to both single and double limbs should be considered. The findings from these assessments could help support the development of physical therapy interventions and goals for MSS CCS.

In response to a 6-week PT-STRONG intervention, individual improvements in VL muscle thickness, VL and RF RoA during a step-up task, gross motor performance on the TUG, and physical QoL but not mental QoL were identified in MSS CCS. These findings add to the evidence that exercise can elicit improvements in these patients. The decreased time to perform the TUG for two of the participants dropped below 10 seconds, which is the cut-off score sensitive to detect near-falling risk in older adults with hip osteoarthritis.[246] These participants also decreased their TUG time by greater than 0.87 seconds, which is the MDC_{95} calculated from the baseline data. Previous intervention studies in CCS demonstrated positive improvements in knee extension strength,[247,248] lower extremity RoA,[220] and gross motor performance in response to an exercise intervention.[220,248] In MSS CCS, Winter et al.[226] demonstrated that an individualized exercise intervention could improve post-surgical physical activity levels. Participant #2

demonstrated decreased knee extension strength and decreased VL muscle thickness post-intervention. Although the reason for the decline in this participant is unknown, it may be due to the participant's baseline limitations in knee flexion range of motion, which improved from baseline to post-test. The decreased knee extension force and decreased VL muscle thickness may represent reduced muscle stiffness due to the static and dynamic stretching effects of the intervention, which were not specifically measured in this study.[249] Nonetheless, muscle property and gross motor performance deficits in MSS CCS may be amendable to physical therapy interventions. Specifically, our PT-STRONG intervention included body-weight resisted functional strengthening and rapid squat and step-up tasks that targeted muscle size through hypertrophy and neuromuscular activation through challenging RoA respectively.

Despite the clinically-relevant and sensitive outcome measures used in this study, the small sample size arising from the rarity of MSS diagnosis is a limiting factor in generalizing these findings to the broader population. To this end, while this study identifies that MSS CCS are at risk for impairments in muscle properties and gross motor performance that may be responsive to exercise intervention, an expansion of this study is warranted before generalizing these results. The control condition for the exploratory outcomes in this study was the participant's non-surgical limb, which also demonstrated deficits, therefore greater impairments may be identified if these participants were compared to healthy controls. For the SF-36v2, the participants in this study were compared to the U.S. general population (>18 years old). In a study by Mones et al.[250] they reported a mean PCS score of 90.57 and MCS score of 89.33 in a cohort of healthy adolescent controls (n=174; age=12-18 years). Therefore, the normative sample used for

comparison in this study may be conservative and underrepresent the degree of QoL differences among adolescent MSS CCS and peers. Additional studies with larger samples of MSS CCS and healthy age- and sex-matched controls should be performed to further explore the dosage of training and the effects of an intervention on muscle properties and gross motor performance.

5. CONCLUSIONS

Adolescent and young adult MSS CCS present with decreased quadriceps muscle strength, muscle size, neuromuscular activation, gross motor performance, and physical QoL, which may be amendable to physical therapy interventions. Due to the interplay between skeletal muscle properties and gross motor performance, comprehensive rehabilitation assessments that identify impairments in muscle properties, such as muscle thickness and neuromuscular activation, and interventions that target these impairments may enhance the rehabilitation of MSS CCS well into survivorship. The results of these assessments should be used to guide clinical decision-making to promote physical performance and participation in daily activities.

CHAPTER SEVEN: SUMMARY OF FINDINGS AND FUTURE DIRECTIONS

1. MAJOR FINDINGS & DISCUSSION

The purpose of this dissertation was to explore skeletal muscle properties, gross motor performance, and quality of life and relationships among these outcomes in children, adolescents, and young adults with chronic hematologic and oncologic health conditions, specifically sickle cell disease (SCD) and musculoskeletal sarcoma (MSS) as these patients are at risk for skeletal muscle dysfunction. Specific Aim 1 examined the muscle properties of knee extension strength as measured by handheld dynamometry (HHD) and quadriceps muscle size as measured by ultrasonography (US), gross motor performance as measured by standardized tests, and quality of life (QoL) as measured by self-report questionnaires in children with SCD and MSS survivors of childhood cancer (CCS). Specific Aim 2 examined the muscle properties of neuromuscular activation as measured by electromyography (EMG) including quadriceps muscles rate of muscle activation (RoA) and knee muscle co-contraction indices (CCI) during strength testing and a step-up task in children with SCD and MSS CCS. Specific Aim 3 examined whether a 6-week functional strengthening program could change muscle properties, gross motor performance, and quality of life in adolescent and young adult MSS CCS. The central hypothesis was that children with SCD and MSS CCS would present with decreased knee extension strength, smaller vastus lateralis (VL) and rectus femoris (RF) muscle thickness, lower VL and RF RoA, and higher knee co-contraction indices (CCI) compared to controls for children with SCD and the contralateral non-surgical limb for MSS CCS. We hypothesized that children with SCD and MSS CCS would have poorer gross motor performance and quality of life compared to a normative sample and that positive relationships between muscle properties,

gross motor performance, and quality of life would be identified. We also hypothesized that a 6-week two times per week functional strengthening program would have positive effects on muscle properties (strength, muscle thickness, neuromuscular activation) and gross motor performance in a sub-sample of MSS CCS.

Given that minimal studies have explored skeletal muscle properties in children, adolescents, and young adults, we first explored these measures in 30 children, adolescents, and young adults without health conditions using HHD, US, and EMG. In chapter 3, we identified positive relationships between larger VL and RF muscle thickness and higher knee extension strength in children, adolescents, and young adults without health conditions. In chapter 4, we describe the relationships between the rate of RF muscle activation and a gross motor performance hopping task in children and young adults without health conditions. We then explored skeletal muscle properties, gross motor performance, and quality of life in children with SCD and adolescent and young adult MSS CCS. In chapter 5, we identified that children with SCD presented with impaired knee extension strength, lower VL RoA, poorer gross motor performance, and lower QoL compared to controls. In children with SCD, positive relationships between muscle strength, gross motor performance, and QoL were identified. In chapter 6, compared to the contralateral non-surgical limb, MSS CCS presented with lower surgical limb knee extension strength, and quadriceps muscle thickness and RoA. MSS CCS also demonstrated decreased bilateral knee extension strength compared to normative values. In MSS CCS, positive relationships between larger quadriceps muscle thickness, higher knee extension strength, and better gross motor performance were identified. In a sub-sample of MSS CCS who underwent a 6-week, 2 times per week functional strengthening

intervention (PT-STRONG) demonstrated individual improvements in muscle strength, muscle thickness, neuromuscular activation (RoA and knee co-contraction), gross motor performance, and physical QoL.

The common findings among children with SCD and adolescent and young adult MSS CCS support that these diseases and the medical and surgical management affect skeletal muscle properties, gross motor performance, and quality of life. These studies identified impaired knee extension strength and quadriceps neuromuscular activation in both patient samples. These common findings could be a result of many factors, but a could be potential adverse effects due to oxidative stress. Specifically, SCD and anthracycline chemotherapies used to treat MSS including doxorubicin are known to cause elevated levels of reactive oxygen species (ROS) that can impair skeletal muscle contraction and force production.[251] Given that we did not assess relationships between medical management or other biomarkers, further exploration of this theory is necessary. One major divergent finding between children with SCD and adolescent and young adult MSS CCS is that children with SCD did not present with decreased muscle size compared to controls yet impaired strength and limitations in gross motor performance. This finding warrants further exploration of the underlying skeletal muscle pathophysiology which may be related to inflammation, necrosis, or adipose infiltration (myosteatosis).

2. FUTURE DIRECTIONS

Children with SCD did not present with decreased VL or RF muscle thickness compared to controls yet had significantly decreased knee extension strength. This finding is not consistent with the expected pathophysiological change of decreased strength and size. The methods used in this dissertation are not sufficient to quantify myosteatosis or

microvascular blood flow, which are associated with muscle disease processes.[94–97,252,253] Therefore, assessment of these muscle characteristics would be beneficial to determine the mechanisms that underlie impairments in muscle RoA, strength, and gross motor in children with SCD using magnetic resonance imaging (MRI), computed tomography (CT), or further development of US methodology to quantify these muscle characteristics.

The methods used in this dissertation could be used as biomarkers to identify changes due to medical interventions and the effects of clinical trials of pharmacological interventions that aim to reduce the adverse effects of SCD and cytotoxic chemotherapy in CCS, such as hydroxyurea and dexrazoxane. Hydroxyurea is an antimetabolite ribonucleotide reductase inhibitor, which has the capacity to increase fetal hemoglobin production thus decreasing the likelihood of red blood cell sickling.[254] Mice with anemia that received hydroxyurea demonstrated higher specific force, a measure of force normalized by muscle size, compared to mice that did not receive the medication.[255] Chronic hydroxyurea therapy has also been associated with higher levels of skeletal muscle microvascular blood flow in patients with SCD.[256] Dexrazoxane is a bisketopiperazine that acts as a chelating agent to reduce the number of metal ions that can compound with anthracyclines (i.e. doxorubicin) thus interfering with the generation of iron-mediated free radicals and decreasing tissue damage.[257] Dexrazoxane has demonstrated protection against doxorubicin cardiomyopathy in patients undergoing treatment for MSS.[258] These medications demonstrate promise in mitigating physical symptoms and serious medical complications due to SCD[254] and doxorubicin,[258] and have common pharmacodynamic pathways to protect skeletal muscle dysfunction. However, the degree of this protection to human skeletal muscle is unclear. Using non-invasive techniques such as strength testing,

US, and EMG can provide insight into the early and late effects of hydroxyurea and dexrazoxane and compare outcomes to individuals who did not receive these medications.

Future studies that explore the efficacy and effectiveness of exercise interventions on skeletal muscle properties in children with SCD and MSS CCS are needed as well as in a wide range of childhood chronic health conditions. To date, most of the pediatric physical therapy and rehabilitation science research exploring skeletal muscle is centered around children with cerebral palsy, however, there are many health conditions that could benefit from physical therapy referral and interventions but lack sufficient research support. The methods used in this dissertation can be reproduced in both laboratory-based and clinically-based research settings to provide objective measurements of skeletal muscle properties in children with health conditions. Exercise intervention studies should also consider the types and dosage of exercise to target specific skeletal muscle properties.[259] For example, to target impaired muscle strength, typically resisted exercise is prescribed. However, if the primary underlying mechanism contributing to the strength deficit or gross motor performance limitation is reduced RoA, then exercises that require quick, coordinated movements such as agility drills may be more appropriate and potentially more effective. To study the effects of exercise interventions on skeletal muscle, large multi-site randomized controlled trials using targeted outcomes and interventions are needed.

To prevent impairments, functional limitations, and long-term effects of SCD and MSS CCS, strategies to identify those at risk are needed. Therefore, to increase appropriate physical therapy referrals for children, adolescents, and young adults at risk for skeletal muscle impairments, gross motor performance limitations, and reduced quality of life, screening tools that include a collection of sensitive outcome measures need to be

developed. In addition, multidisciplinary and prospective surveillance models designed to regularly monitor physical impairments and functional limitations, provide immediate access to rehabilitation services for identified needs, and educate patients and family members on early identification and prevention of known adverse effects would be beneficial to children with SCD and MSS CCS.[260]

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