The Skeletal Phenotype in Becker Muscular Dystrophy: The Under-Studied Cousin of Duchenne

Rana Halloun [1,2], Stefan Jackowski [1], Maya Scharke [1], Jinhui Ma[1,3], Ken Gaither [4], Thomas Fuerst [4], Hugh McMillan [1,2], James MacDougall [5], Utkarsh Dang, Joanne Donovan[5] and Leanne M. Ward [1,2] for the CANYON Investigators

(1)The Ottawa Pediatric Bone Health Research Group, Ottawa, Ontario, Canada, (2) University of Ottawa, Ottawa, Ontario, Canada, (3) McMaster University, Hamilton, Ontario, Canada, (4) Clario, Philadelphia, Pennsylvania, USA, (5) Edgewise Therapeutics, Boulder, Colorado, USA, (6) Department of Health Sciences, Carleton University

Background

- Becker Muscular Dystrophy (Becker) is an X-linked recessive condition caused, in most cases, by in-frame pathogenic variants in the DMD gene resulting in a decreased functional protein levels
- The phenotype is less severe than Duchenne Muscular Dystrophy and varies significantly depending on the residual level of functional dystrophin
- Progression can be variable; with loss of ambulation occurring as early as the third decade[1]
- Use of mobility assistive devices including wheelchair is common after age 40 [2]
- Sustained use of corticosteroids is not common, due to lack of clear efficacy
- The progressive myopathy of Becker appears to be associated with an increased fracture risk [3,4]
- However, the skeletal site most affected by the Becker myopathy is unknown

Study Objectives

- To determine whether total body and appendicular lean mass by DXA are surrogates for muscle strength
- To describe the multi-site areal bone mineral density (aBMD) phenotype by DXA in Becker
- To identify which BMD site is most sensitive to the myopathy

Methods

Study Design:

- Cross-sectional study of 66 adolescents and adults with genetically-confirmed diagnosis of Becker participating in a multi-centre, Phase 2 clinical trial of sevasemten, a fast skeletal myosin inhibitor (NCT05291091)

Participants:

- Ambulatory
- Not on corticosteroids for at least 6 months
- Ages 12 to 50 years

Clinical Endpoints:

- **Multi-site DXA** for aBMD at the lumbar spine (LS), total hip (proximal), and total body less head (TBLH), converted for age and gender specific Z-scores
- **Body composition** by DXA for total and appendicular lean and fat mass (g), each expressed relative to height squared (kg/m²).
- Muscle Function Tests: North Star Ambulatory Assessment (NSAA), Hand-grip strength (Kg)

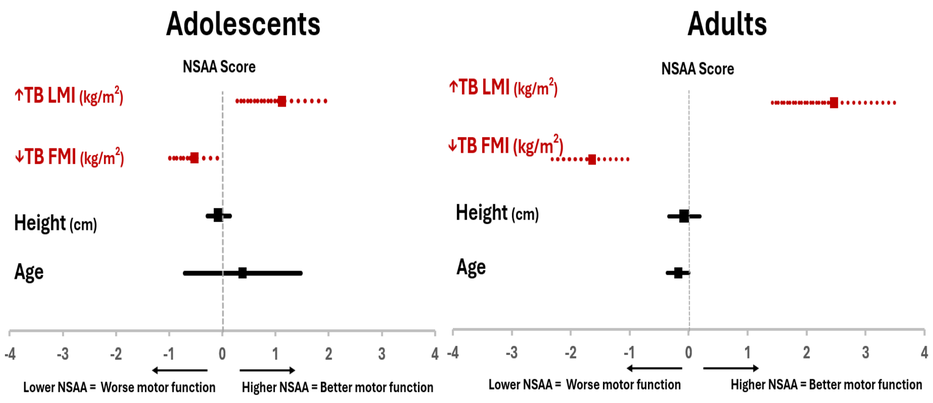
Results

Participant characteristics

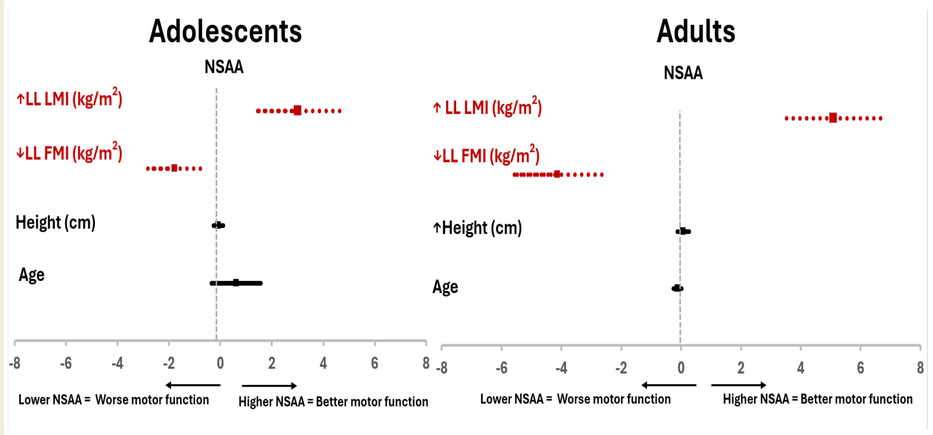
Variable	Adolescents (n=28)	Adults (n=38)
Age (years), median (SD)	15 (1.5)	28.5 (10.2)
(Range)	12 to 17	18 to 50
Height Z-score, median	-0.11 (1.2)	0.18 (0.98)
(SD)		
Range	-2.5 to 2.7	-2.7 to 1.7
BMI (kg/m²), median	21 (5)	27 (3.8)
(SD)		
Range	14 to 38	16 to 32

Relationship Between Motor Function Assessments and Lean and Fat Mass Indices

1A: NSAA and Total Lean and Fat Mass Indices



1B: NSAA and Lower Limb Lean and Fat Mass Indices



1C: Hand-Grip Strength and Upper Limb Lean and Fat Mass Indices

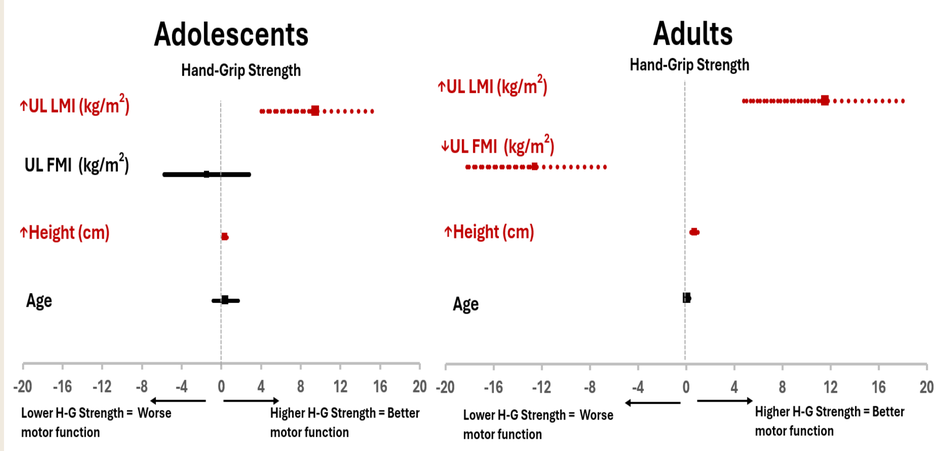


Figure 1: A multivariate linear regression model adjusted for height and age showing the relation between **(A)** total body lean, fat mass with motor function **(B)** lower body composition parameters with motor function **(C)** upper limb body composition parameters and upper limb motor function. Statistically significant variables ($p<0.05$) are outlined in red and dashed. **TB LMI** total body lean mass index, **TB FMI** total body fat mass index, **NSAA** North Star Ambulatory **LL LMI** lower limb LMI, **LL FMI** lower limb FMI **UL LMI** upper limb lean mass index, **UL FMI** upper limb fat mass index

Results (Continued)

Bone Mineral Density Phenotype:

- The aBMD Z-score was lowest at the total hip (-1.7 ± 1.1), followed by the TBLH (-1.5 ± 1.2) and highest at the LS (-0.3 ± 1.3)
- A one sample t -test, comparing the multi-site DXA parameters to the healthy population noted that the median total hip and TBLH Z-scores were significantly lower than the healthy average ($p<0.001$ for both) (Figure 2)
- 42% of the cohort had hip aBMD Z-scores below -2, which is considered in the osteoporotic range

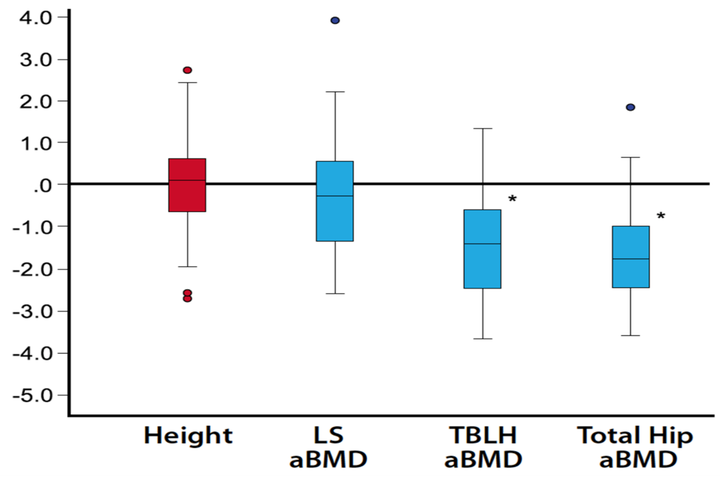


Figure 2: A one-sample t-test comparing multi-site areal bone mineral density (aBMD) Z-scores to the expected mean of the healthy reference population. * indicate statistically significant variables ($p< 0.05$). Error bars represent 95% confidence intervals. **LS aBMD** lumbar spine areal bone mineral density, **TBLH** total body less head

Conclusions

- Total body and appendicular lean mass by DXA were highly associated with motor function
- In contrast, increased total body and appendicular fat mass index were associated with worse motor function
- These data suggest that body composition by DXA may be considered surrogate endpoints for muscle strength in clinical practice and in clinical trials
- **Even with preserved ambulation**, mean multi-site BMD Z-scores were below the healthy average
- Total hip BMD Z-score **was the most sensitive site** for the dystrophinopathy changes, with the lowest mean Z-scores
- Total hip BMD should be included in bone health assessment for individuals with Becker

References:

1. Nakamura A, et al. Neurol Genet. 2024 Dec 17;11(1)
2. Riguzzi P, et al. Poster presented at WMS. 2024. #320P
3. Söderpalm AC, et al. Acta Paediatr. 2012 Apr;101(4):424-32.
4. Barp A, et al. Muscle Nerve. 2022 Jul;66(1):63-70.