Duke University School of Medicine
Doctor of Physical Therapy

The Effect of Exercise in a Pediatric Population with Duchenne Muscular Dystrophy: A Systematic Review of the Literature

Rachel Curran, BS, Nicole Panis, BS, Meghan Barry, BS, Joshua Fries, BS, Laura E. Case, PT, DPT, MS, PCS, C/NDT

Duke University

Background

- Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease affecting 1 in 3,500 boys[1,2]
- Diffuse muscle weakness is caused by deficiency of dystrophin--a subsarcolemmal protein critical for multiple functions, including muscle cell membrane integrity and increasing blood flow to muscles during contraction via neuronal nitric oxide synthase (nNOS)[3-5]
- Risks of exercise must be considered to protect this population from potentially harmful effects, while recognizing potential beneficial aspects of activity to establish the ideal therapeutic balance[6]

Purpose

The aim of this systematic review is to report on benefits and risks of exercise in a pediatric population with DMD. The lack of conclusive evidence and the changing natural history necessitates an updated review to reinvestigate appropriate exercise/activity parameters. The evolving approach to DMD care includes increased focus on cardiac management and appreciation for the effect of abnormal nNOS plus muscle fragility.

Methods

- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines were applied. Three databases were searched: PubMed, CINAHL, and Embase. The quality of each study was then evaluated under the Cochrane criteria checklist.
  - **Inclusion criteria**:
    - Birth-18 years old, human subjects with DMD
    - Published in the last 10 years
    - Physical activity intervention included: aerobic, strength, resistance exercise, respiratory and mastication training, & prescribed functional tasks
  - **Exclusion criteria**:
    - Diagnoses of any other form of MD, broad diagnoses of neuromuscular disease, mixed populations
    - Confounding physical and cognitive conditions
    - Mean study population older than 18 years
    - Non-human subjects, non-English text

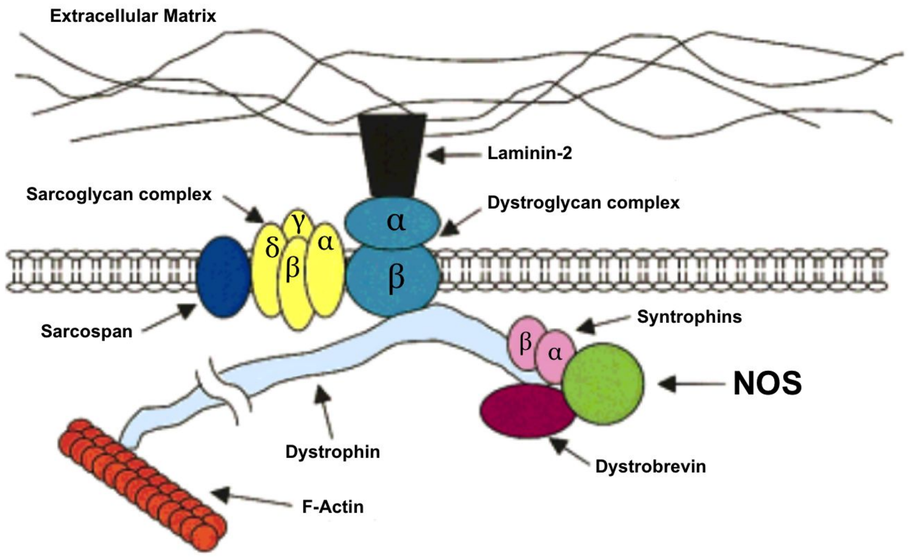

Figure 1 in Rando TA. Role of nitric oxide in the pathogenesis of muscular dystrophies: a "two hit" hypothesis of the cause of muscle necrosis. *Microsc Res Tech.* 2001;55(4): 223-235. Used with permission.[5]

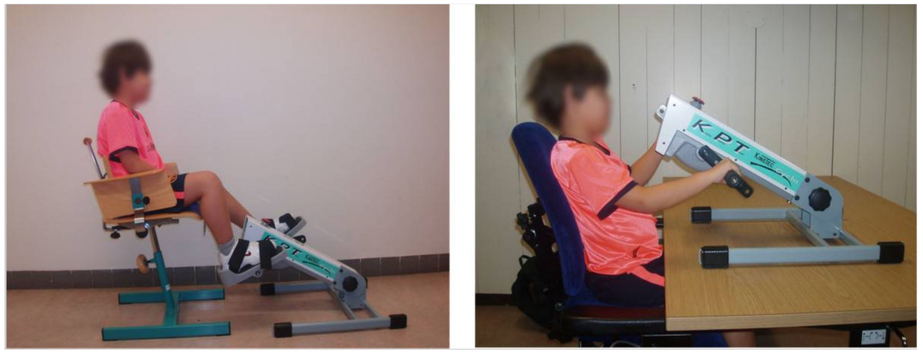

Figure 3: Posture during dynamic leg and arm training
From: Jansen, M., de Groot, I.J., van Alfen, N. et al. BMC Pediatr (2010) 10: 55. doi:10.1186/1471-2431-10-55. Permission in accordance with Open Access under Creative Commons Public License[7]

Comprehensive Overview of Selected Articles

ARTICLE	POPULATION*	INTERVENTION	COMPARATOR	OUTCOMES	STUDY TYPE	LEVEL OF EVIDENCE
Alemdaroglu, I., et al. (2015)[8]	X = 12, 9.50 years old (SD=1.38)	UE ergometry (40min 3d/week, for 8 weeks)	PROM, AAROM, AROM, or resistive ROM assigned based on UE baseline	Strength (hand-held dynamometer), **grip strength, UE functional performance (AREA, timed functional tests), NSAA for ambulatory status	Controlled trial with randomization	1b
Garrood, P., et al. (2009)[9]	X = 11, 8.2 years old (range 6.6 to 9.9)	Step test protocol 20 steps on/off 20cm bench	Step test protocol 20 steps on/off 20cm bench in healthy control subjects	Signal intensities of lower limbs (MR imaging)	Case Control	3b
Jansen, M., et al. (2013)[10]	X = 11, 10.8 years old (SD=2.4)	Low intensity assisted bicycle training of arms and legs (15min 5d/week, for 24 weeks)	Usual care	UE and LE Function (MFM, A6MCT)	Randomized control design	1b
Rodrigues, M. R., et al. (2014)[11]	X = 26, 9.5 years old (SD=2.2)	Yoga hatha breathing exercises (10 months)	None	Pulmonary function (Spirometry measures of FVC, FEV_1, MEP, MIP)	Prospective open-label study	4
Toussaint, M., et al. (2008)[12]	X = 50, 21.6 years old (SD=5.7)	Level of unloading of respiratory muscles using n-NIPPV and d-NIPPV	Level of unloading of respiratory muscles using n-NIPPV and d-NIPPV at varying stages of respiratory involvement	Modified BORG dyspnea score, 7 point Symptoms Scale, respiratory loading dosage (T_{lim}, $TT_{0.1}$)	Case control	3b
Van Bruggen, H.W., et al. (2015)[13]	X = 17, 16.6 years old (SD=6.1)	Chewing gum protocol (30min 5d/wk, for 4 weeks)	Chewing gum protocol in healthy control subjects (30min 5d/wk, for 4 weeks)	MFM, anterior MVBF (VU University Bite Force Gauge), mixing ability (histogram analysis of chewed wax et)	Controlled pilot study	3b
Van Ginderdeuren, E., et al. (2016)[14]	X = 8, 9-12 years old	2 MVC of biceps brachii, 2 min recovery, 1 min of sustained 60% MVC, 10 min recovery	2 MVC of biceps brachii, 2 min recovery, 1 min of sustained 60% MVC, 10 min recovery in healthy control subjects	Oxygenation changes (NIRS), myoelectrical activity changes (sEMG), 6MWT	Controlled trial	3b

*All subjects male, diagnosed with Duchenne Muscular Dystrophy, ** "Grip Track" module

Abbreviations: AAROM= Assisted Active Range of Motion; A6MCT= Assisted 6 Minute Cycling Test; AREA= Arm Elevation Assessment; AROM= Active Range of Motion; FEV1= Forced Expiratory Volume in One Second; FVC= Forced Vital Capacity; MEP= Maximal Expiratory Pressure; MFM= Motor Function Measure; MIP= Maximum Inspiratory Pressure; MVBF= Maximum Voluntary Bite Force; MVC= Maximum Ventilatory Capacity; n-NIPPV = Nocturnal Non-Invasive Positive Pressure Ventilation; d-NIPPV = Diurnal Non-Invasive Positive Pressure Ventilation; NIRS= Near-Infrared Spectroscopy; NSAA= NorthStar Ambulatory Assessment; PROM= Passive Range of Motion; ROM= Range of Motion; sEMG= Surface Electromyography; UE=Upper Extremity; 6MWT= 6 Minute Walk Test, $TT_{0.1}$ = non-invasive tension time index, T_{lim}= respiratory endurance

Results

Seven selected articles report on changes in strength, function, imaging/biomarkers, and respiratory function after exercise.

EXERCISE EFFECT	OUTCOME MEASURED	RESULTS
Benefit of exercise	Strength	**0/2 studies reported benefit in strength**
	Function	**3/3 studies reported benefit in function** - AREA score and t-shirt donning/removing tests[8] - D1 and D3 of MFM[10] - Reduced mixing index indicating improved masticatory performance[13]
	Imaging/ Biomarkers	**0/2 studies reported benefit via imaging/biomarkers**
	Respiratory Function	**1/2 studies reported benefit in respiratory function** - Improved FVC and FEV_1[11]
Risk of exercise	Strength	**0/2 studies reported risk to strength**
	Function	**0/3 studies reported risk to function**
	Imaging/ Biomarkers	**2/2 studies reported risk via imaging/biomarkers** - Increased contrast enhancement of TA[9] - Smaller ΔTOI with isometric contraction[14]
	Respiratory Function	**1/2 studies reported risk in respiratory function** - Improved Borg dyspnea score, rib cage flexibility, and T_{lim} with respiratory muscle unloading[12]

Abbreviations: AREA = Arm Elevation Assessment; D1 = Standing and Transfers Function on MFM; D3 = Distal Motor Function Portion of MFM; FEV_1 = Forced Expiratory Volume at One Second; FVC = Forced Ventilatory Capacity; MFM = Motor Function Measure; TA = Tibialis Anterior; T_{lim} = Respiratory Muscle Endurance Time; TOI = Muscle Tissue Oxygenation Index

Conclusions

- Continued caution for protection of this vulnerable population
- Safe and effective implementation of exercise/activity requires:
  - definition by type, dosage, and frequency
  - consideration of individual's current disease status
- Evidence supports the use of low-intensity, assisted, and submaximal activity, while avoiding overexertion to best protect the vulnerable state of the muscle tissue, all systems contributing to exercise capacity, and each individual with DMD

Clinical Relevance

- Further study is necessary to better recommend exercise and activity parameters in clinical practice
- Approval of actual disease-modifying drugs has begun for those with DMD, and will require additional study of potential changes in exercise capacity, and potential effects of exercise combined with anticipated and exciting increases in emerging treatments

Acknowledgements / References

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