Mitochondrial Disease Version 2.0 NINDS CDE Project
Exercise Physiology Subgroup Summary

The NINDS Mitochondrial Disease v2.0 Common Data Element (CDE) Exercise Physiology Subgroup targeted patients with symptoms of mitochondrial dysfunction in skeletal muscle as a dominant clinical manifestation and considered CDEs that capture the impact of impaired skeletal muscle mitochondrial function to be within their purview.

Given the dependency of skeletal muscle on oxidative metabolism for sustained energy production, mitochondrial myopathies commonly manifest as exercise intolerance, defined as the development of muscle fatigue and lactic acidosis during levels of sustained physical exertion that healthy persons easily tolerate (Taivassalo et al., 2003). Tachycardia and dyspnea are also often associated with exercise intolerance; these symptoms are attributable to exaggerated increases in cardiac output and in ventilation relative to metabolic rate that accompany impaired oxidative phosphorylation in skeletal muscle with restricted extraction of oxygen from arterial blood (Taivassalo et al., 2003, Heinicke et al., 2011). Generalized or fixed muscle weakness, defined as an inability to generate normal muscle force during brief muscle contractions, may also occur and contribute to exercise intolerance because any absolute motor task would be completed at a higher relative intensity. Rarely rhabdomyolysis, attributable to muscle necrosis with elevated serum creatine kinase and myoglobinuria may be seen in mitochondrial myopathies; however, this has not been reported in any of the studies evaluating the therapeutic efficacy of endurance or resistance exercise in those with primary mitochondrial myopathy.

The subgroup recommends objective, quantitative assessment of muscle fatigue during sustained physical activity and of muscle strength to capture the dominant symptoms of mitochondrial disease in skeletal muscle. The transition from predominantly anaerobic to oxidative metabolism to support muscle contractile energy demands occurs within the first minutes of exercise, and within 3-5 minutes, oxidative steady state is normally achieved. Accordingly, physical activity maintained for this period or greater is appropriate for assessing muscle oxidative metabolism.

The outcomes below are v2.0 recommendations for primary mitochondrial myopathy clinical trial readiness by the Exercise Physiology Subgroup.

References

Heinicke K, Taivassalo T, Wyrick P, Wood H, Babb TG, Haller RG. Exertional dyspnea in mitochondrial myopathy: clinical features and physiological mechanisms. Am J Physiol Regul Integr Comp Physiol. 2011 Oct;301(4):R873-84.

Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. Brain. 2003 Feb;126(Pt 2):413-23.

Summary of Recommendations

Subdomain	Instrument/CRF Name	Classification	Purpose, Instrument Use
Digital Technology	Exercise Wearables	Supplemental – Highly Recommended; Exploratory	Exploratory metrics
Exercise Physiology	Staged Exercise Tolerance Test	Supplemental – Highly Recommended	Measurement of mitochondrial capacity (VO_2)
Imaging Diagnostics	2D Speckle Tracking (Strain) Echocardiography Imaging	Exploratory	
	Cardiac Magnetic Resonance Imaging (MRI)	Supplemental	
	Echocardiogram	Supplemental – Highly Recommended	
	Phosphorus Magnetic Resonance Spectroscopy (31P-MRS)	Exploratory	
Motor Function	2 Minute Walk Test	Exploratory	Clinical outcomes
	6 Minute Walk Test	Supplemental	Clinical outcomes
	Borg Rating of Perceived Exertion (RPE) Scale	Supplemental – Highly Recommended	Clinical outcomes
	Mitochondrial Myopathy Composite Assessment Tool (MM-COAST)	Supplemental – Highly Recommended	Clinical outcomes
Muscle Strength Testing	Maximum Voluntary Isometric Contraction (MVIC)	Supplemental	
NIH Resources	Quality of Life in Neurological Disorders (Neuro-QOL)	Supplemental – Highly Recommended	Impact of disease on QoL
Non-Imaging Diagnostics	Electrocardiogram (ECG)	Supplemental – Highly Recommended; Supplemental	Suggested prior to exercise testing or training to rule out conduction issues or evidence of cardiac hypertrophy
	Holter Examination	Supplemental	
Pulmonary Function Testing/Respiratory Status	Pulmonary Function	Supplemental – Highly Recommended; Supplemental	Measurement of mitochondrial capacity (VO_2)
Quality of Life/Patient Reported Outcomes	Short Form 36-Item Health Survey (SF-36)	Supplemental – Highly Recommended	Impact of disease on QoL