CLINICAL REVIEW

Mitochondrial Myopathy and Exercise, in Adults

Indexing Metadata/Description

› **Title/condition:** Mitochondrial Myopathy and Exercise, in Adults

› **Synonyms:** Mitochondrial disease in muscle and exercise, in adults; defective mitochondrial respiratory chain in muscle and exercise, in adults; mitochondrial DNA mutation in muscle and exercise, in adults; myopathy, mitochondrial and exercise, in adults; exercise and mitochondrial myopathy in adults

› **Anatomical location/body part affected:** Skeletal muscle fibers/mitochondrial respiratory chain mechanism for oxidative (aerobic) energy production

› **Area(s) of specialty:** Orthopedic Rehabilitation

› **Description**

- Mitochondrial myopathy is a progressive muscle disorder caused by impairment of Adenosine triphosphate (ATP) production(5)
- Mitochondrial disorders can affect different organs (e.g., skeletal muscle, brain, liver, heart, kidney, eye)
- Mitochondrial disorders have a prevalence of ~11.5 in 100,000(9)
- Mitochondria (mt) replicate their own DNA. Mitochondrial DNA (mtDNA) diseases are extremely variable and each has a unique pathogenesis dependent on the involved mutation(s). The focus of this *Clinical Review* is mitochondrial myopathy (mtM) in adults with exercise intolerance and predominantly muscle symptoms, including myalgia. Other types of mtM that involve systemic complications (usually before age 20), such as Kearns-Sayresyndrome, myoclonus epilepsy, mitochondrial encephalomyopathy, or specific mt enzyme deficiencies, are not covered
- The adult form of mtM primarily results from sporadic deletions in mtDNA sequence. The deletions reduce oxidative (aerobic) function of the respiratory chain.(5) Disease severity is highly variable because of the heterogeneity and progressive nature of mtDNA mutations(1)
- Adults with mtM often experience functional disability due to exercise intolerance, muscle pain, and rapid fatigue onset. Symptoms in persons with mtMare mostly due to impaired oxygen utilization for aerobic energy production

› **ICD-10 code:** G71.3 mitochondrial myopathy, not elsewhere classified

(ICD codes provided for reader's reference and not for billing purposes)

› **Reimbursement:** Reimbursement for therapy will depend on insurance contract coverage. No special agencies are applicable for mtM, and no specific issues or information regarding reimbursement has been identified

› **Presentation/signs and symptoms** (3)

- Male or female adult with sudden or gradual onset of exercise-relatedmuscle pain, cramps, and premature fatigue
- Patients with mtM typically report limited tolerance for prolonged, low-intensity endurance-type activity such as walking or cycling, and also for strenuous aerobic activity such as walking or cycling uphill and running(4)
- In physicallyinactive patients, whole-body peak oxygen uptake (VO_2peak) on progressive graded exercise (treadmill or cycle ergometer) testing is significantly below the norm for sex and age

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- Reduced strength
- Sedentary lifestyle

Causes, Pathogenesis, & Risk Factors

› **Causes** [1,5]

- Adult-onset mtM may result from single, large-scale deletions or sporadic point mutations in mtDNA that cause deficiencies in respiratory chain (i.e., electron transport system) enzymes and proteins
- mtDNA deletions usually occur de novo, and in only one family member
- mtDNA defects are inherited only by maternal transmission(i.e., X-linked) because mitochondrial DNA is inherited only from the mother. Men with mutant mtDNA do not pass it on to their biological children. However, defects in nuclear DNA genes can be inherited by autosomal or X-linked transmission, leading to other types of mitochondrial diseases[1]

› **Pathogenesis**

- Mitochondria replicate by a polycistronic (i.e., bacteria-like)mechanism not linked to the cell cycle. The defective mtDNA is found mainly in mature muscle fibers, whereas the satellite cells are much less involved[1]
- The diagnosis of mtM is confirmed by a characteristic finding on microscopy (i.e., crowding of mitochondria along the sarcolemma border, giving a "ragged-red fiber" appearance) and deficits in respiratory chain enzyme (e.g., succinate dehydrogenase and cytochrome oxidase) activity on histochemistry[5,10]
- In mtM, respiratory chain defects impair ATP production from oxidative decarboxylation of fats, carbohydrates, and proteins. Deficits are found at one or more complexes in the respiratory chain [5,10]
  - Complex I (involves NADH coenzyme Q10 [ubiquinone] reductase)
    - No curative treatment, but individuals have shown a positive response when given riboflavin supplementation[11]
  - Complex II (involves succinate dehydrogenase and ubiquinone)
    - There is no definitive treatment and prognosis is poor[11]
  - Complex III (involves cytochromes b, c1 and c)
    - There is no cure for those with Complex III disorders; treatment protocol involves treating the associated symptoms[11]
  - Complex IV (i.e., cytochrome c oxidase)
    - Can involve a wide range of clinical presentations that include failure to thrive, encephalopathy, hypotonia, Leigh syndrome, hepatopathy, and cardiac involvement soon after birth; prognosis is poor[11]
- In mtM, aerobic exercise is limited by deficient oxygen utilization in peripheral muscle, rather than cardiovascular or pulmonary dysfunction that might limit oxygen transport to muscle. Exercise-related symptoms mainly result from a deficient production of ATP[1]
- Satellite cells have a low mutant DNA load compared to the mature muscle fibers that surround them.[1] Whether exercise can trigger the incorporation of satellite cell-derived mtDNA into new mitochondria during adaptive regeneration of muscle warrants further research[1]

› **Risk factors**

- A positive maternal family history of mtM[1,9]
- Genetic and pathological markers for mtM on muscle biopsy[5]

Overall Contraindications/Precautions

› Mitochondrial disease can affect organs other than skeletal muscle, including the heart and brain. Confirm that the patient does not have serious cardiac involvement, epilepsy, or stroke-like symptoms that would contraindicate exercise prescription
› Ensure that the patient does not exercise with complaints of any acute medical condition, such as fever, chills, night sweats, nausea, vomiting, or diarrhea
› DVT
› Avoid exercise that increases symptoms
› Advise patients to stop exercise if muscle pain or cramps become very uncomfortable, and to rest until symptoms subside
› Discontinue exercise program and consult with physician if the patient reports progressive muscle weakness or pain
› Nonfinalized litigation regarding work disability
› Clinicians should follow the guidelines of their clinic/hospital and the physician's orders

› See specific **Contraindications/precautions to examination** and **Precautions/recommendations** under Assessment/Plan of Care

Examination

› **Contraindications/precautions to examination**

- Stop the exam and notify physician if patient has unexplained nonspecific symptoms (e.g., headache, fatigue, dizziness, nausea, blurred vision)
- Notify physician if patient demonstrates poor balance or motor control
- Modify the examination as indicated for patients with severe myalgia

› **History**

- **History of present illness/injury**
  - **Mechanism of injury or etiology of illness:** When did patient note onset of symptoms? Have symptoms progressed over time? What is the reason for referral to PT?
  - **Course of treatment**
    - **Medical management:** Although there is no treatment for mtM, it is important that the medical management address the disease complications, which can include damage to the cardiac, pulmonary, and endocrine system
    - **Medications for current illness/injury:** Pharmacotherapy specific for mtM remains investigational
      - Oral coenzyme Q10 (ubiquinone) may help to alleviate the deficit in Complex I in some cases[5]
      - Elamipretide, an aromatic-cationic tetrapeptide has been shown to increase exercise performance after just 5 days of treatment in patients with primary mitochondrial myopathies[7]
        - Patients were given escalating doses of 0.01, 0.10, and 0.25 mg/kg/h in a 2 – hour intravenous infusion on 5 consecutive days
      - Pharmacological treatment approaches for mitochondrial myopathy may include:[13]
        - Increase respiratory chain flux
          - CoQ_{10} and riboflavin
        - Antioxidants
          - CoQ_{10}, idebenone, alpha-lipoic acid, vitamin C, vitamin E
        - Mitochondrial substrates
          - L-carnitine
    - **Diagnostic tests completed:** Inquire about
      - molecular genetic testing for a mutation in mtDNA
      - electromyography
      - muscle biopsy for histologic or enzymatic evidence of mitochondrial disease
      - exercise stress testing for aerobic capacity (VO2peak)
      - Elevated levels of acylcarnitine is common in patients with mitochondrial myopathy. This may aid in early diagnosis[6]
      - MRI findings of inflammatory changes tomuscleand detection of antimicrobial antibodiesmay contribute todiagnosing for mtM[8]
    - **Home remedies/alternative therapies:** Document any use of home remedies (e.g., ice or heating pack) or alternative therapies (e.g., acupuncture) and whether or not they help
    - **Previous therapy:** Document whether patient has had occupational or physical therapy for this or other conditions and what specific treatments were helpful or not helpful
  - **Aggravating/easing factors** (and length of time each item is performed before the symptoms come on or are eased)
  - **Body chart:** Use body chart to document location and nature of symptoms
  - **Nature of symptoms:** Document nature of symptoms and muscle pain, if present (e.g., constant vs. intermittent, sharp, dull, aching, burning, numbness, tingling)
  - **Rating of symptoms:** Use a visual analog scale (VAS) or 0–10 scale to assess symptoms at their best, at their worst, and at the moment (specifically address if pain is present now and how much)
  - **Pattern of symptoms:** Document changes in symptoms throughout the day and night, if any (a.m., mid-day, p.m., night); also, document changes in symptoms due to weather or other external variables
  - **Sleep disturbance:** If applicable, document number of wakings/night due to muscle pain/cramping

  - **Other symptoms:** Document other symptoms patient may be experiencing that could exacerbate the condition and/or symptoms that could be indicative of a need to refer to physician (dizziness, bowel/bladder/sexual dysfunction, saddle anesthesia)
  - **Respiratory status:** Does patient receive respiratory care or therapy for comorbidities?
  - **Barriers to learning:** Cognitive and behavioral deficits are uncommon
    - **Are there any barriers to learning? Yes__ No__**
    - **If Yes, describe _____**
- **Medical history**
  - **Past medical history**
    - **Previous history of same/similar diagnosis**
    - **Comorbid diagnoses:** Ask patient about other problems, including diabetes, cancer, heart disease, complications of pregnancy, psychiatric disorders, and orthopedic problems
    - **Medications previously prescribed:** Obtain a comprehensive list of medications prescribed and/or being taken (including OTC drugs for pain)
    - **Other symptoms:** Ask patient about comorbid symptoms that may complicate treatment, such as hypoglycemia
- **Social/occupational history**
  - **General inquiry:** What is the level of family support? Any relatives with mtM? Any assistive care required? If so, identify primary caregiver
  - **Patient's goals:** Document what the patient hopes to accomplish with therapy and in general
  - **Vocation/avocation and associated repetitive behaviors, if any:** What is patient's vocation? Does patient desire to participate in regular physical activity?
  - **Functional limitations/assistance with ADLs/adaptive equipment:** The need for assistive/adaptive equipment is uncommon in mtM
  - **Living environment:** Stairs, number of floors in home, with whom patient lives, caregivers, etc. Identify if there are barriers to independence in the home; any modifications necessary?

› **Relevant tests and measures:** (While tests and measures are listed in alphabetical order, sequencing should be appropriate to patient's medical condition, functional status, and clinical setting)

- **Anthropometric characteristics:** Determine height, weight, and BMI. If muscle cramping is worse on one side, assess for bilateral anatomic differences such as leg-length discrepancy
- **Assistive and adaptive devices:** Document any use of assistive and adaptive devices; assess for appropriate fit and use
- **Balance:** Assess static and dynamic balance reactions. mtM is not expected to disturb balance
- **Cardiorespiratory function and endurance:** Document vital signs, including resting heart rate, blood pressure, and respiratory rate. Administer six-minute walk for distance (6MWD) test
- **Circulation:** Assess peripheral pulses and capillary refill time
- **Ergonomics/body mechanics:** Assess for substitute motions
- **Functional mobility:** Assess general mobility. mtM does not usually affect mobility
- **Gait/locomotion:** Assess gait. mtM does not usually disturb gait
- **Joint integrity and mobility:** Assess distal joint integrity in extremities with ligament stress testing
- **Motor function:** Assess motor control, as indicated. mtM does not usually disturb motor control or muscle tone
- **Muscle strength:** Assess general strength with manual muscle testing and note any cramping response. mtM is associated with weakness, in part to muscle disuse[3]
- **Observation/inspection/palpation** (including skin assessment): Observe for changes/deformities in limb muscles. Assess for tenderness in areas of muscle cramping
- **Posture:** Assess general posture and for factors such as leg-length discrepancy that may affect posture
- **Range of motion:** Assess active and passive ROM in the extremities[3]
- **Reflex testing:** Assess deep tendon reflexes. mtM does not usually disturb reflexes
- **Self-care/activities of daily living** (objective testing): Evaluate performance in basic ADLs, as indicated/prescribed. Refer to occupational therapist for history of disability in instrumental ADLs[3]
- **Sensory testing:** Assess sensation (light touch, deep pressure, temperature, and proprioception). mtM does not usually disturb sensation

- **Special test specific to diagnosis**
  - In compliance with medical guidelines, assess heart rate (HR), blood pressure (BP), adverse signs/symptoms, and perceived exertion during incremental graded exercise testing to fatigue on a cycle ergometer or treadmill.[2] The results of testing can be used to estimate the patient's peak HR and VO_2peak, and used in exercise prescription

Assessment/Plan of Care

› **Contraindications/precautions**
- Patients with mtM are at risk for exercise-related muscle pain and cramps. Ensure that patient is aware of the potential for muscle pain and cramps and educated on prevention. Discharge criteria should include independence with prevention strategies for avoiding exercise-related myalgia
- There is no evidence to support the use of modalities or electrotherapy for treating myalgia or cramps in mtM. However, clinicians should use their professional judgment and follow the guidelines of their clinic/hospital for the use of modalities and electrotherapy, as well as the physician's order. (Note: This review does not cover the treatment of coexisting/comorbid conditions in mtM)

› **Diagnosis/need for treatment:** mtM phenotype with history of exercise-related myalgia, muscle cramps, and weakness. Functional disabilities related to exercise intolerance. Poor physical fitness associated with exercise avoidance/individualized exercise prescription with patient education is indicated for improving exercise capacity

› **Rule out:** Other types of mtM disease (e.g., Kearns-Sayresyndrome, myoclonus epilepsy, or mitochondrial encephalomyopathy); glycogen storage disease type V (GSDV); muscular dystrophy; myoclonic dystrophy

› **Prognosis:**
- Due to the dysfunction of multiple organ systems, clinical phenotype and prognosis is variable[5]

› **Referral to other disciplines:** Clinical exercise testing laboratory for measurement of VO_2peak; aquatic exercise therapist for patients with orthopedic problems on weight bearing; nutritionist for advice on supplements; acupuncturist for pain

› **Other considerations:** Oral coenzyme Q10 supplementation may improve aerobic capacity and post-exercise lactate levels[5]

› **Treatment summary**
- Authors of a study conducted in Denmark concluded that aerobic exercise improves oxidative capacity in patients with mtDNA mutations and is considered safe for them to perform[12]
- Exercise therapy has been shown to be an effective treatment option for those with mitochondrial disease. Aerobic exercise can increase mitochondrial production by stimulating mitochondrial biogenesis, resulting in an increase in muscle mitochondrial enzyme activity and muscle strength[13]

Problem	Goal	Intervention	Expected Progression	Home Program
Impaired ROM	Improve ROM	**Exercise therapy** Stretching exercise[3]	Progress as able	Provide written instructions

Exercise avoidance secondary to muscle pain and premature fatigue	Reduce frequency and intensity of exercise-related muscle pain	**Physical agents and electrotherapeutic modalities** Evidence is lacking to support the use of modalities for treatment of symptoms in mtM **Patient education** Educate patient on modifications to exercise program to minimize symptoms	N/A	N/A
Reduced aerobic fitness and muscle strength due to exercise avoidance	Improve functional capacity in daily and recreational activities	**Exercise therapy** Aerobic and resistance exercise training[3] (See program components in *Treatment summary*, above)	Begin with moderate-intensity exercise and progress as tolerated. Allow up to 12 weeks to achieve goals	Patient education on aerobic and resistance exercises that can be performed at home. Instructions to avoid muscle pain by modifying exercise, as needed. Correct use of exercise equipment

Desired Outcomes/Outcome Measures

› Increased aerobic work tolerance
  • Maximum workload and estimated VO2peak on progressive cycle ergometer exercise test[2]
› Increased muscle strength
  • 1-RM on weight-lifting machines
› Improved function in daily physical activity
  • Patient satisfaction
  • Health Related Quality of Life questionnaire (e.g., SF-36)
› Decreased exercise-related muscle pain
  • VAS

Maintenance or Prevention

› Continue physical activity in the community to maintain aerobic fitness and strength.
› Cessation of aerobic training is associated with reversal of benefits

Patient Education

See *Facts About Mitochondrial Myopathies* at the MDA.org website, https://www.mda.org/disease/mitochondrial-myopathies

Coding Matrix

References are rated using the following codes, listed in order of strength:

M	Published meta-analysis	**RV**	Published review of the literature	**PP**	Policies, procedures, protocols
SR	Published systematic or integrative literature review	**RU**	Published research utilization report	**X**	Practice exemplars, stories, opinions
RCT	Published research (randomized controlled trial)	**QI**	Published quality improvement report	**GI**	General or background information/texts/reports
R	Published research (not randomized controlled trial)	**L**	Legislation	**U**	Unpublished research, reviews, poster presentations or other such materials
C	Case histories, case studies	**PGR**	Published government report	**CP**	Conference proceedings, abstracts, presentation
G	Published guidelines	**PFR**	Published funded report		

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