



Advances in Diagnosis and Management of Metabolic Muscle Disorders

Jelang Jelku D. Sangma^{1,2}

¹Department of Food Science and Nutrition, University of Agricultural Sciences, GKVK, Bangalore, Karnataka, 560065, India

²AICRP-WIA, ICAR (CIWA), Bhubaneswar, College of Community Science, Central Agricultural University, Tura, Meghalaya - 794005, India

Corresponding author: **Jelang Jelku D. Sangma** | E-mail: jelang.jelku3@gmail.com

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Abstract

Metabolic muscle disorders are a heterogeneous group of inherited and acquired conditions resulting from defects in pathways responsible for energy production within skeletal muscle. These disorders impair carbohydrate, lipid, or mitochondrial energy metabolism, leading to symptoms such as exercise intolerance, muscle weakness, cramps, rhabdomyolysis, and progressive myopathy. Recent advances in molecular genetics, imaging, metabolic testing, and therapeutic interventions have significantly improved diagnosis and management strategies. Novel therapies, including enzyme replacement, gene-targeted approaches, and precision metabolic interventions, are reshaping treatment paradigms. This review summarizes current advances in diagnostic techniques, clinical classification, and emerging management strategies for metabolic muscle disorders while highlighting ongoing challenges and future directions in care.

Keywords: Metabolic myopathies, mitochondrial disorders, glycogen storage disease, lipid metabolism defects, muscle weakness, genetic diagnosis, enzyme replacement therapy, metabolic therapy

1. Introduction

Metabolic muscle disorders, also known as metabolic myopathies, arise from abnormalities in biochemical pathways responsible for producing energy required for muscle contraction and maintenance. Skeletal muscle depends on tightly regulated energy production from glycogen, fatty acids, and mitochondrial oxidative phosphorylation. Disruption of these pathways results in inadequate energy supply, particularly during physical exertion, leading to characteristic clinical symptoms [1]. Historically, metabolic muscle disorders were underdiagnosed because symptoms often overlapped with more common neuromuscular or systemic conditions. Patients frequently experienced delayed diagnosis due to nonspecific symptoms such as fatigue or exercise intolerance. However, increasing awareness and advances in diagnostic technologies have improved detection rates and patient outcomes [2]. Recent progress in genetics, metabolomics, and imaging has transformed understanding of these disorders. Additionally, new treatment options, including enzyme replacement and precision dietary strategies, have enhanced quality of life for many patients. As knowledge expands, early diagnosis and personalized management are becoming central goals in clinical care.

2. Classification of Metabolic Muscle Disorders

Metabolic muscle disorders are generally categorized according to the metabolic pathway affected. Three major groups are commonly recognized: glycogen storage disorders, lipid metabolism disorders, and

mitochondrial myopathies. Glycogen storage diseases affecting muscle involve defects in enzymes responsible for glycogen synthesis or breakdown. Conditions such as McArdle disease and Pompe disease impair carbohydrate utilization, causing exercise intolerance and muscle damage. Lipid metabolism disorders involve defective fatty acid oxidation, preventing muscles from efficiently using fats as energy sources, particularly during prolonged exercise or fasting. Examples include carnitine deficiency and multiple acyl-CoA dehydrogenase deficiency. Mitochondrial myopathies result from abnormalities in oxidative phosphorylation within mitochondria, affecting cellular energy production [3]. These disorders may involve muscle alone or present as multisystem diseases affecting the nervous system, heart, and other organs. Correct classification is essential because symptoms, prognosis, and treatment approaches vary widely among different metabolic disorders.

3. Clinical Presentation and Diagnostic Challenges

Metabolic muscle disorders present with a wide spectrum of clinical manifestations, often making early diagnosis difficult. Symptoms typically arise when muscle energy demand exceeds the body's capacity to supply energy due to metabolic pathway dysfunction. Patients commonly report exercise intolerance characterized by early fatigue, muscle pain, stiffness, or cramps during physical activity. In many cases, symptoms are episodic, appearing only during periods of increased metabolic stress such as

strenuous exercise, prolonged fasting, infections, or exposure to cold environments [4]. A particularly serious complication is rhabdomyolysis, in which muscle fibers break down, releasing myoglobin into the bloodstream. This can lead to dark-colored urine and, in severe cases, acute kidney injury. Some patients experience recurrent episodes triggered by physical exertion, making lifestyle adaptation necessary. Clinical patterns often provide clues to the underlying metabolic defect. Individuals with glycogen metabolism disorders usually experience symptoms during short bursts of intense activity such as sprinting or lifting heavy objects. In contrast, patients with fatty acid oxidation defects struggle during prolonged, endurance-type activities or fasting states when fat metabolism becomes the primary energy source. Mitochondrial disorders often present with chronic fatigue, progressive muscle weakness, and involvement of multiple organ systems, including neurological, cardiac, or endocrine abnormalities [5]. Diagnostic challenges arise because symptoms overlap with more common neuromuscular conditions, inflammatory muscle diseases, or even psychological fatigue syndromes. Moreover, patients may appear normal between episodes, and laboratory findings can be inconclusive outside of symptomatic periods. Careful clinical history, attention to symptom triggers, and multidisciplinary evaluation are therefore essential in establishing an accurate diagnosis.

Table 1. Classification and Clinical Features of Major Metabolic Muscle Disorders

Disorder Category	Representative Diseases	Primary Metabolic Defect	Key Clinical Features	Common Triggers
Glycogen storage disorders (muscle type)	McArdle disease, Pompe disease, Tarui disease	Defective glycogen breakdown or utilization	Exercise intolerance, muscle cramps, early fatigue, rhabdomyolysis, progressive weakness	Short, high-intensity exercise
Lipid metabolism disorders	Carnitine deficiency, CPT II deficiency, fatty acid oxidation defects	Impaired fatty acid transport or oxidation	Muscle pain, fatigue during prolonged exercise, recurrent rhabdomyolysis	Fasting, prolonged exercise, illness
Mitochondrial myopathies	MELAS, MERRF, mitochondrial DNA disorders	Defective oxidative phosphorylation	Muscle weakness, fatigue, neurological and systemic involvement	Exercise stress, infections
Mixed or multisystem metabolic disorders	Multiple acyl-CoA dehydrogenase deficiency, metabolic syndromes	Multiple energy pathways affected	Variable muscle weakness, metabolic crises, systemic symptoms	Metabolic stress, fasting, infection

Table 2. Diagnostic and Management Approaches in Metabolic Muscle Disorders

Approach	Diagnostic or Therapeutic Role	Examples/Methods	Clinical Benefit
Biochemical blood tests	Initial metabolic evaluation	Creatine kinase, lactate, acylcarnitine profiles	Detects metabolic abnormalities
Genetic testing	Identification of causative mutations	Next-generation sequencing, gene panels	Enables accurate diagnosis and counseling
Muscle imaging	Structural and metabolic evaluation	MRI, MR spectroscopy	Non-invasive assessment of muscle involvement
Muscle biopsy	Enzyme and histological analysis	Histochemistry, enzyme assays	Confirms metabolic defects
Dietary management	Metabolic pathway optimization	Carbohydrate planning, fat modification	Reduces symptom frequency
Exercise therapy	Functional improvement	Supervised aerobic conditioning	Enhances endurance and muscle strength
Enzyme replacement therapy	Corrects enzyme deficiency	Pompe disease treatment	Improves muscle and respiratory function
Emerging gene therapies	Targets underlying genetic defects	Experimental gene replacement/editing	Potential future curative treatment

4. Advances in Diagnostic Techniques

Advances in diagnostic technology have significantly improved detection and classification of metabolic muscle disorders. Traditionally, diagnosis relied heavily on invasive muscle biopsies combined with enzyme assays. While biopsies remain valuable in selected cases, newer diagnostic tools now allow less invasive and more precise identification of disease mechanisms [6]. Biochemical testing continues to serve as an important first step, including measurement of serum creatine kinase levels, lactate concentration, acylcarnitine profiles, and metabolic intermediates. However, results may fluctuate, and normal values do not exclude disease, necessitating further investigation. Exercise testing has become a useful diagnostic aid. Non-invasive cardiopulmonary exercise testing evaluates oxygen consumption and metabolic responses, while forearm exercise testing can reveal abnormal lactate or ammonia responses indicating glycolytic pathway defects. Imaging technologies, particularly muscle MRI and magnetic resonance spectroscopy, provide insight into muscle structure and metabolism without invasive procedures. MRI can detect patterns of muscle involvement characteristic of certain metabolic disorders, while spectroscopy assesses metabolic function in living tissue.

The most transformative development has been the introduction of next-generation sequencing technologies. Genetic panels and whole-exome sequencing allow identification of disease-causing mutations quickly and cost-effectively.

Genetic diagnosis enables earlier intervention, family screening, and personalized management. Complementary approaches such as metabolomics and proteomics are further refining diagnostic precision by identifying metabolic signatures associated with specific disorders [7].

5. Current Management Approaches

Management of metabolic muscle disorders primarily focuses on minimizing symptoms, preventing metabolic crises, and improving quality of life. Because many of these conditions are genetic and currently incurable, treatment strategies emphasize metabolic optimization and lifestyle modification. Exercise recommendations are carefully tailored to individual metabolic limitations. Moderate, supervised aerobic exercise often improves mitochondrial efficiency and overall endurance while reducing muscle injury risk. Conversely, high-intensity exertion may be discouraged in certain glycogen storage disorders due to risk of rhabdomyolysis [8]. Dietary interventions are central to management. Patients with glycogen storage diseases may benefit from controlled carbohydrate intake and pre-exercise carbohydrate supplementation to maintain glucose availability. Individuals with fatty acid oxidation disorders often require avoidance of prolonged fasting and may benefit from supplementation with medium-chain triglycerides that bypass defective metabolic pathways. Carnitine supplementation is sometimes used to improve fatty acid transport in selected cases [9].

Supportive care also includes hydration management, prompt treatment of infections, and avoidance of medications or conditions that may worsen metabolic stress. Physical therapy programs help preserve muscle function, prevent contractures, and maintain mobility. Because many metabolic muscle disorders involve multiple organ systems, coordinated care involving neurologists, metabolic specialists, cardiologists, dietitians, and rehabilitation professionals is essential for optimal long-term outcomes.

6. Emerging Therapies and Precision Medicine

Rapid progress in molecular medicine has created promising therapeutic opportunities aimed at correcting underlying metabolic defects rather than simply managing symptoms. One of the most successful advances is enzyme replacement therapy (ERT), particularly in Pompe disease, where replacement of deficient acid alpha-glucosidase significantly improves survival and muscle function, especially when initiated early. Gene therapy is emerging as a potential transformative approach [10]. Advances in viral vector technology allow delivery of functional genes into muscle cells to correct metabolic deficiencies. Several clinical trials are exploring gene replacement strategies for metabolic myopathies and mitochondrial disorders, although long-term safety and durability remain under investigation. Precision medicine approaches use genetic and metabolic information to tailor interventions to individual patients. Pharmacological agents targeting mitochondrial function, antioxidant pathways, and metabolic enhancement are under study, aiming to improve cellular energy production and reduce oxidative stress. Research is also exploring small-molecule therapies that enhance residual enzyme activity or bypass defective metabolic steps. Nutritional supplementation targeting mitochondrial cofactors and metabolic intermediates is being investigated as adjunct therapy. While many of these treatments remain experimental, ongoing clinical trials provide hope for disease-modifying therapies in conditions previously considered untreatable.

7. Challenges and Future Directions

Despite advances in diagnosis and therapy, significant challenges persist in the management of metabolic muscle disorders. Delayed or missed diagnoses remain common, partly due to variability in symptoms and limited awareness among healthcare providers. Improved education and screening strategies are needed to identify patients earlier in the disease course. Access to advanced genetic testing and specialized care varies globally, leading to disparities in diagnosis and treatment. High costs associated with enzyme replacement therapies and emerging gene therapies also pose challenges for healthcare systems and patients [11]. Another challenge involves understanding long-term disease progression and therapy outcomes. Many new treatments require extended follow-up studies to evaluate safety, durability, and effectiveness across different patient populations [12].

Future research aims to develop newborn screening programs, improved biomarkers for early detection, and novel therapies targeting metabolic pathways. Advances in gene-editing technologies and regenerative medicine may eventually provide curative strategies for certain disorders. Integration of personalized medicine, digital health monitoring, and multidisciplinary clinical care will likely shape future management strategies.

8. Conclusion

The field of metabolic muscle disorders has undergone significant transformation due to advances in molecular diagnostics, metabolic research, and therapeutic innovation. Improved understanding of disease mechanisms has enabled earlier diagnosis and more targeted management strategies, reducing disease burden for many patients. Genetic testing and metabolic profiling have replaced many traditional diagnostic limitations, while enzyme replacement and emerging gene-based therapies offer promising avenues for disease modification. Lifestyle management, nutritional interventions, and structured rehabilitation remain foundational components of patient care and progress will depend on expanding diagnostic access, improving therapeutic affordability, and advancing precision medicine approaches. With sustained interdisciplinary collaboration and technological innovation, outcomes for individuals affected by metabolic muscle disorders are expected to improve substantially in the coming decades.

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