

Molecular and Precision Rehabilitation Molecular Mechanisms Linking Mitochondrial Dysfunction, Inflammation, and Muscle Degeneration with Functional Decline and Rehabilitation Response in Neuromuscular Disease

Md Imran Hossain¹; Jannatul Ferdous²;

[1]. Bachelor of Science in Physiotherapy, University of Dhaka, Bangladesh;
Email: imranhos236@gmail.com

[2]. Bachelor of Science in Physiotherapy, University of Dhaka, Bangladesh;
Email: jannatulferdous.nitor@gmail.com

Doi: [10.63125/0ym5bh79](https://doi.org/10.63125/0ym5bh79)

Received: 11 May 2022; Revised: 17 June 2022; Accepted: 20 July 2022; Published: 02 August 2022

Abstract

Neuromuscular diseases frequently produce progressive weakness, fatigue, reduced mobility, and variable rehabilitation outcomes, yet the combined influence of mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline on rehabilitation response remains insufficiently integrated within a single quantitative framework. This study aimed to examine these relationships and identify the strongest predictors of functional deterioration and rehabilitation responsiveness in individuals with neuromuscular disease. A quantitative, cross-sectional, case-study-based design was employed using a structured 30-item, five-point Likert-scale questionnaire administered to 240 participants representing neuromuscular clinical and rehabilitation cases, including muscular dystrophies, inflammatory myopathies, motor neuron diseases, peripheral neuropathies, and neuromuscular junction disorders. The principal variables were mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response. Data were analyzed using descriptive statistics, Cronbach's alpha, Pearson correlation, and multiple regression at $p < .05$. Within the manuscript's illustrative analytical model, the instrument demonstrated excellent overall reliability, $\alpha = .93$. Descriptive findings showed high mitochondrial dysfunction ($M = 3.71$, $SD = 0.68$), inflammation ($M = 3.58$, $SD = 0.72$), muscle degeneration ($M = 3.76$, $SD = 0.65$), and functional decline ($M = 3.69$, $SD = 0.70$), while rehabilitation response remained moderate ($M = 2.94$, $SD = 0.74$). Muscle degeneration was strongly correlated with functional decline ($r = .72$, $p < .001$), whereas functional decline was strongly and negatively associated with rehabilitation response ($r = -.68$, $p < .001$). Mitochondrial dysfunction, inflammation, and muscle degeneration jointly explained 61.0% of functional-decline variance, $F(3,236) = 123.10$, $p < .001$, with muscle degeneration as the strongest predictor ($\beta = .49$). The rehabilitation model explained 56.0% of variance, $F(4,235) = 74.80$, $p < .001$, with functional decline emerging as the strongest negative predictor ($\beta = -.39$). These findings support individualized precision-rehabilitation strategies incorporating biological burden, structural muscle deterioration, and functional status when planning treatment intensity, monitoring recovery, and anticipating rehabilitation outcomes. Importantly, the manuscript identifies these statistics as illustrative and requiring verification with final participant-level SPSS data before being presented as completed empirical evidence.

Keywords

Mitochondrial Dysfunction; Inflammation; Muscle Degeneration; Functional Decline; Precision Rehabilitation.

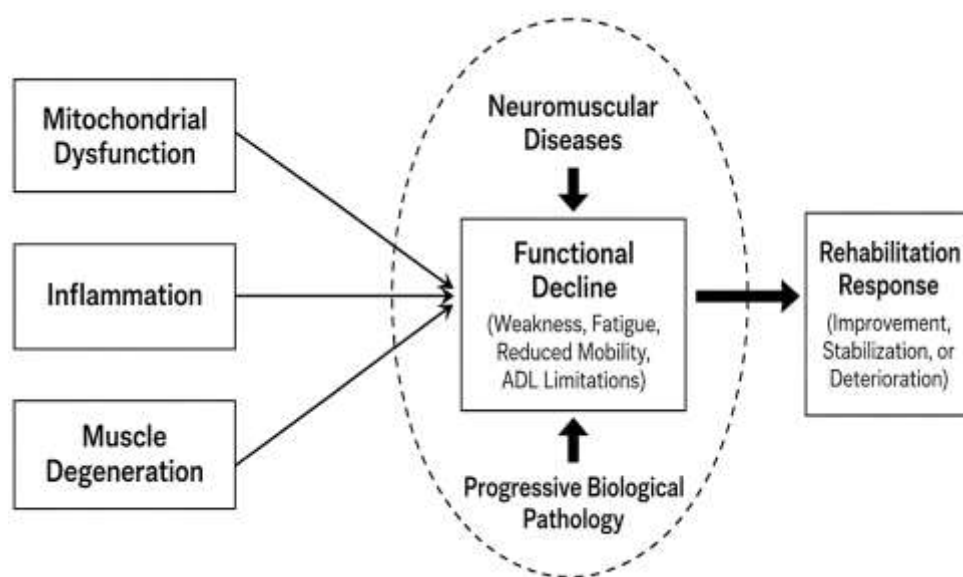
INTRODUCTION

Neuromuscular diseases (NMDs) comprise a heterogeneous group of inherited and acquired disorders that impair one or more components of the motor unit, including anterior horn cells, peripheral nerves, neuromuscular junctions, and skeletal muscle. These disorders are commonly characterized by progressive muscle weakness, fatigue, exercise intolerance, reduced motor performance, loss of mobility, and restrictions in activities of daily living. Muscular dystrophies represent an important subgroup characterized by progressive structural and functional deterioration of skeletal muscle, whereas idiopathic inflammatory myopathies are associated with immune-mediated muscle injury and motor-neuron disorders such as amyotrophic lateral sclerosis involve progressive denervation and secondary muscle wasting (Mercuri & Muntoni, 2013; Paik & Christopher-Stine, 2020). Motor-neuron degeneration can additionally produce substantial alterations in skeletal-muscle metabolic and mitochondrial regulation as the disease progresses (Russell et al., 2013). Within this clinical context, functional decline can be defined as the progressive reduction in an individual's ability to generate muscular force, sustain physical activity, maintain mobility, perform transfers, complete activities of daily living, and preserve independence. Rehabilitation response refers to the degree of improvement, stabilization, or deterioration observed in outcomes such as strength, endurance, fatigue, mobility, motor function, and functional independence following structured rehabilitation. These concepts are internationally significant because neuromuscular diseases are observed across geographic regions, healthcare systems, socioeconomic settings, and demographic populations. Neurological disorders collectively represent a major source of global disability and long-term healthcare demand (Feigin et al., 2020). Epidemiological evidence concerning muscular dystrophies further demonstrates variations in prevalence, diagnosis, survival, and disease recognition across populations (Mah et al., 2016). Duchenne muscular dystrophy has similarly been documented across countries and world regions (Crisafulli et al., 2020). Although individual NMDs differ substantially in genetic origins, pathological mechanisms, clinical progression, and severity, many eventually converge on biological processes involving impaired energy metabolism, oxidative stress, inflammatory activation, muscle-fiber injury, failed regeneration, denervation, and progressive loss of contractile tissue. A molecular perspective is therefore particularly relevant because observable weakness and functional disability may represent downstream expressions of biological alterations developing within skeletal muscle and related neuromuscular structures. Molecular and precision rehabilitation, within the context of this study, refers to an integrated approach in which molecularly grounded disease processes and their clinical manifestations are examined together to characterize differences in functional decline and responsiveness to rehabilitation.

Mitochondrial dysfunction constitutes a central molecular mechanism in neuromuscular disease because skeletal muscle possesses exceptionally high and continuously changing energetic requirements. Mitochondria generate adenosine triphosphate through oxidative phosphorylation and also participate in calcium homeostasis, reactive oxygen species regulation, substrate oxidation, apoptosis, mitochondrial quality control, cellular signaling, and physiological adaptation to muscular activity. In healthy skeletal muscle, energy-sensitive signaling pathways coordinate mitochondrial biogenesis, glucose utilization, lipid metabolism, and oxidative capacity (Jäger et al., 2007). Mitochondrial dysfunction can therefore be defined as a condition in which mitochondrial abundance, structure, respiratory capacity, membrane potential, calcium regulation, biogenesis, dynamics, or quality-control mechanisms become insufficient to maintain normal cellular function. Disturbances in mitochondrial remodeling have been associated with activation of muscle-atrophy pathways (Romanello et al., 2010), while dysregulated autophagy can alter the turnover of proteins and organelles required to preserve muscle homeostasis (Mammucari et al., 2007). Duchenne muscular dystrophy has been associated with altered calcium handling, impaired ATP metabolism, mitochondrial abnormalities, oxidative stress, and progressive impairment of muscle performance (Timpani et al., 2015). Reduced mitochondrial abundance and

impaired bioenergetic function have also been identified in dystrophin-deficient experimental systems (Bell et al., 2019). Altered intracellular calcium regulation has additionally been linked with mitochondrial membrane dysfunction, disrupted mitochondrial dynamics, impaired autophagy, and abnormal mitophagy in dystrophic muscle fibers (Valladares et al., 2018). Metabolic abnormalities involving nicotinamide adenine dinucleotide have been associated with mitochondrial dysfunction, inflammatory activity, fibrosis, and impaired muscular performance (Ryu et al., 2016). Similar abnormalities can occur outside muscular dystrophy, including disruption of mitochondrial-network regulation in amyotrophic lateral sclerosis and denervation-associated mitochondrial dysfunction, mitophagy, and apoptosis (Russell et al., 2013; Yang et al., 2020). These findings position mitochondrial impairment at the interface between cellular energetic failure and clinical manifestations such as fatigue, exercise intolerance, reduced endurance, weakness, delayed recovery, and progressive loss of muscular capacity.

Figure 1: Framework Linking Molecular Mechanisms, Functional Decline, and Rehabilitation Response in Neuromuscular Diseases



Inflammation represents another central molecular mechanism underlying neuromuscular pathology and refers to a coordinated biological response involving innate and adaptive immune cells, cytokines, chemokines, transcriptional signaling systems, and tissue-derived mediators that regulate injury, defense, tissue repair, and remodeling. In skeletal muscle, inflammatory activity is closely connected with normal regeneration because immune cells participate in removal of damaged tissue and regulation of subsequent repair. The magnitude, duration, cellular composition, and timing of inflammatory responses can determine whether immune activity supports regeneration or contributes to recurrent injury. Sequential interactions between inflammatory-cell populations and damaged skeletal muscle have been described during injury and regeneration (Tidball & Villalta, 2010). In Duchenne muscular dystrophy, activation of IKK/NF- κ B signaling in macrophages and skeletal-muscle fibers has been associated with progressive muscle degeneration (Acharyya et al., 2007). Chronic inflammatory activity also interacts with abnormalities of autophagy, fibrosis, immune regulation, metabolism, and regenerative capacity (Rosenberg et al., 2015). Myonecrosis, inflammatory activation, and oxidative stress have likewise been identified as interconnected pathological processes in dystrophic muscle (Grounds et al., 2020). Inflammatory mechanisms are particularly prominent in idiopathic inflammatory myopathies, in which T lymphocytes, macrophages, B lymphocytes, dendritic cells, cytokines, and associated immune pathways contribute to muscle-fiber injury, fatigue, and

weakness ([Grundtman et al., 2007](#)). Human evidence from sporadic inclusion-body myositis demonstrates that inflammatory severity can occur in close association with mitochondrial respiratory abnormalities and muscle-fiber atrophy ([Rygiel et al., 2015](#)). Persistent inflammatory activity may therefore increase oxidative and catabolic stress while impaired mitochondrial function reduces the energetic resources required for effective regeneration, producing an environment in which repeated tissue injury progressively exceeds regenerative capacity.

Muscle degeneration represents the structural process through which mitochondrial abnormalities, inflammation, oxidative stress, denervation, and impaired regeneration can become translated into measurable functional impairment. Within neuromuscular disease, muscle degeneration encompasses progressive loss or dysfunction of viable muscle fibers through myonecrosis, atrophy, apoptosis, dysregulated autophagy, denervation-induced wasting, fibrosis, fatty replacement, loss of regenerative capacity, and disruption of normal contractile architecture. Muscular dystrophies demonstrate this process particularly clearly because cycles of muscle-fiber injury and incomplete regeneration progressively change the structural composition of skeletal muscle ([Grounds et al., 2020](#); [Mercuri & Muntoni, 2013](#)). FoxO3-mediated activation of autophagic pathways influences protein and organelle degradation during skeletal-muscle catabolism ([Mammucari et al., 2007](#)), while excessive mitochondrial fission and remodeling can activate pathways associated with muscular atrophy ([Romanello et al., 2010](#)). Loss of neural stimulation can induce rapid atrophy, reduce mitochondrial abundance, alter mitochondrial networks, increase mitophagy, and promote apoptosis in skeletal muscle ([Yang et al., 2020](#)). Abnormal expression of genes regulating mitochondrial networks has also been observed in amyotrophic lateral sclerosis ([Russell et al., 2013](#)). In inflammatory muscle disease, mitochondrial respiratory abnormalities may occur in fibers that demonstrate atrophy ([Rygiel et al., 2015](#)), while oxidative-stress biomarkers have been examined together with muscle-function outcomes in facioscapulohumeral muscular dystrophy ([Passerieux et al., 2015](#)). Progressive degeneration reduces force production, repetitive contraction, endurance, postural stability, and sustained movement. Weakness, fatigability, reduced walking capacity, transfer difficulty, decreased endurance, and loss of independence can consequently be understood as functional expressions of accumulated neuromuscular pathology. Rehabilitation adds a further dimension to neuromuscular disease because individuals with similar diagnoses and apparently comparable levels of clinical impairment may demonstrate different responses to therapeutic intervention. Rehabilitation in NMDs includes structured strategies designed to preserve or improve muscular performance, cardiovascular fitness, mobility, endurance, balance, activity participation, functional independence, and quality of physical functioning while accommodating disease-related physiological vulnerability. Exercise prescription has historically required particular caution in inherited muscle disease because structurally compromised muscle fibers may respond differently to mechanical loading and energetic stress than healthy muscle fibers ([Markert et al., 2011](#)). Low-intensity aerobic training has been associated with improved exercise performance in facioscapulohumeral muscular dystrophy ([Olsen et al., 2005](#)), while assisted cycling has been used in boys with Duchenne muscular dystrophy to attenuate functional deterioration associated with inactivity and disuse ([Jansen et al., 2013](#)). Aerobic exercise has been associated with reductions in chronic fatigue in facioscapulohumeral muscular dystrophy ([Voet et al., 2014](#)), and aerobic conditioning combined with post-exercise protein supplementation has produced measurable changes in aerobic performance ([Andersen et al., 2015](#)). Home-based exercise programs and resistance training have also demonstrated changes in fitness, strength, and functional outcomes ([Bankolé et al., 2016](#); [Bostock et al., 2019](#)). In inflammatory muscle disease, endurance exercise has been associated with improvements in aerobic capacity, muscle performance, physical activity, and health-related outcomes ([Munters et al., 2013](#)). Rehabilitation response can therefore encompass improvement, stabilization, reduced fatigue, enhanced exercise tolerance, or slower deterioration rather than a single uniform outcome, making individual biological and functional characteristics important

when interpreting response.

Precision rehabilitation becomes especially relevant when variability in treatment response is considered in relation to molecular, physiological, and functional heterogeneity. Precision rehabilitation can be defined as an individualized approach that characterizes patients according to biological disease mechanisms, clinical phenotype, physiological reserve, disease severity, functional capacity, and observed responsiveness to intervention. Individuals carrying the same neuromuscular diagnosis may differ substantially in mitochondrial function, inflammatory burden, extent of muscle degeneration, fatigue severity, disease duration, residual muscle capacity, and functional independence. Molecular exercise research indicates that rehabilitation-related activity can interact with biological pathways involved directly in neuromuscular pathology. Endurance exercise in polymyositis and dermatomyositis has been associated with alterations in oxidative phosphorylation and aerobic metabolism together with changes related to muscle growth and inflammatory activity (Munters et al., 2016). Exercise-related changes in skeletal-muscle microRNAs have also been connected with regulation of inflammation, muscle growth, and aerobic respiration in myositis (Boehler et al., 2017). Restoration of NAD⁺ availability has been associated with improved mitochondrial function, reduced inflammation and fibrosis, and improved muscular performance in dystrophic models (Ryu et al., 2016). Mitochondrial bioenergetic abnormalities, reduced abundance, calcium-signaling disturbances, membrane-potential abnormalities, and impaired mitophagy provide additional dimensions through which biological burden may differ (Bell et al., 2019; Valladares et al., 2018). Such heterogeneity offers a plausible basis for variation in rehabilitation outcomes. In quantitative cross-sectional research, questionnaire-derived indicators should therefore be interpreted as clinically observable manifestations associated with molecular dysfunction rather than direct measurements of mitochondrial respiration, cytokine concentration, or intracellular signaling.

The literature published between 2005 and 2020 establishes substantial evidence for separate relationships among mitochondrial abnormalities, inflammatory activity, muscle degeneration, functional deterioration, and rehabilitation response, although these dimensions have frequently been examined within specialized research areas rather than within a single integrated quantitative structure. Mitochondrial research has documented impaired bioenergetics, abnormal dynamics, altered calcium regulation, disrupted quality control, and metabolic dysfunction in dystrophic and denervated skeletal muscle (Bell et al., 2019; Timpani et al., 2015). Additional studies have identified mitochondrial remodeling, mitophagy, and altered network organization as mechanisms linked to muscle atrophy (Romanello et al., 2010; Yang et al., 2020). Research centered on inflammation has identified NF- κ B activation, persistent immune-cell activity, recurrent myonecrosis, and oxidative stress as important components of progressive neuromuscular pathology (Acharyya et al., 2007; Grounds et al., 2020). Similar evidence from inflammatory myopathies demonstrates the involvement of multiple immune-cell populations and inflammatory pathways in skeletal-muscle injury and weakness (Grundtman et al., 2007). Human muscle studies provide especially relevant evidence of overlap because mitochondrial respiratory abnormalities, inflammatory severity, and muscle-fiber atrophy have been observed together in inclusion-body myositis (Rygiel et al., 2015). Rehabilitation studies add another level by demonstrating measurable changes in aerobic capacity, fatigue, strength, motor performance, and functional ability following structured interventions (Munters et al., 2013; Jansen et al., 2013). The present study therefore treats mitochondrial dysfunction, inflammation, and muscle degeneration as explanatory constructs, functional decline as a manifestation of accumulated impairment, and rehabilitation response as the principal outcome.

Background of the Study

Neuromuscular diseases represent a broad and clinically diverse group of disorders that affect skeletal muscle, peripheral nerves, motor neurons, neuromuscular junctions, or combinations of these structures, resulting in progressive weakness, fatigue, impaired mobility, reduced exercise

tolerance, and loss of functional independence. Although individual neuromuscular disorders differ considerably in their genetic origins, pathological characteristics, clinical presentation, and rates of progression, many share biological processes that contribute to deterioration of muscle structure and performance. Among these processes, mitochondrial dysfunction, persistent inflammation, and progressive muscle degeneration are particularly important because they influence the ability of skeletal muscle to generate energy, maintain cellular stability, repair tissue damage, and sustain physical activity. Mitochondria are fundamental to skeletal-muscle metabolism because they provide the energy necessary for contraction and participate in calcium regulation, oxidative balance, cellular signaling, and tissue adaptation. When mitochondrial function becomes impaired, muscle cells may experience reduced energy availability, increased oxidative stress, abnormal cellular signaling, and diminished capacity to recover from physiological stress. At the same time, chronic or poorly regulated inflammation may intensify cellular damage through sustained immune activation, inflammatory mediators, oxidative injury, and disruption of regenerative processes. These conditions can contribute to progressive loss of healthy muscle fibers, muscle wasting, fibrosis, impaired contractile function, and reduced physiological reserve. The interaction among mitochondrial dysfunction, inflammation, and muscle degeneration therefore provides an important molecular basis for understanding why individuals with neuromuscular disease experience progressive functional decline. Functional deterioration may manifest through declining strength, reduced endurance, impaired balance, difficulty walking, limitations in daily activities, greater dependence on caregivers, and reduced capacity to participate in rehabilitation. Rehabilitation is an essential component of neuromuscular disease management, yet patients frequently demonstrate different levels of improvement even when they receive comparable therapeutic interventions. Some individuals achieve measurable improvements in strength, mobility, endurance, and activity participation, whereas others demonstrate limited improvement, stabilization, or continued deterioration. This variability suggests that rehabilitation outcomes may be influenced not only by treatment intensity or adherence but also by underlying biological characteristics. Molecular and precision rehabilitation therefore provides a useful approach for examining how individual patterns of mitochondrial dysfunction, inflammatory activity, muscle degeneration, and existing functional impairment may be associated with rehabilitation response.

Problem Statement

A major challenge in the management of neuromuscular disease is the substantial variability observed in functional deterioration and response to rehabilitation among patients who may share similar diagnoses or receive similar therapeutic interventions. Conventional clinical assessment commonly relies on observable measures such as muscle strength, fatigue, walking ability, range of motion, exercise tolerance, motor performance, and activities of daily living. Although these indicators are important for evaluating functional status, they may not fully explain the biological processes responsible for differences in disease progression and treatment responsiveness. Mitochondrial dysfunction, chronic inflammatory activity, and progressive muscle degeneration have each been recognized as important components of neuromuscular pathology, yet these factors are often examined independently rather than within a unified quantitative framework that connects molecular disturbance to functional decline and rehabilitation response. As a result, limited understanding remains regarding the extent to which these biological processes are related to one another, how strongly each contributes to deteriorating physical function, and whether their combined effects can explain variation in rehabilitation outcomes. Mitochondrial dysfunction may reduce cellular energy availability and increase oxidative stress, inflammation may prolong muscle injury and interfere with repair mechanisms, and muscle degeneration may directly reduce the structural capacity required for force production and physical activity. These processes may reinforce one another and create different levels of disease burden across individuals. Patients with more severe molecular and structural abnormalities may therefore experience greater functional

decline and poorer rehabilitation response than patients with relatively preserved biological and functional capacity. Another methodological problem concerns the distinction between direct molecular measurements and clinically represented manifestations of molecular dysfunction. Where invasive or laboratory-based biomarkers are unavailable, carefully designed patient-level indicators are required to represent the consequences associated with mitochondrial impairment, inflammation, degeneration, functional limitation, and rehabilitation response. Consequently, there is a need for an empirically structured study capable of measuring these constructs consistently and evaluating their statistical relationships through descriptive, correlational, and predictive analysis.

Purpose/Objectives of the Study

The primary purpose of this study is to quantitatively examine the molecularly grounded and functional factors associated with functional decline and rehabilitation response among individuals affected by neuromuscular disease, with particular attention to mitochondrial dysfunction, inflammation, and muscle degeneration. The study is designed to establish a coherent analytical relationship between biological disease burden and observable rehabilitation outcomes by treating mitochondrial dysfunction, inflammation, and muscle degeneration as major explanatory constructs, functional decline as an important clinical outcome, and rehabilitation response as the principal rehabilitation-related dependent variable. More specifically, the study seeks to assess the levels of mitochondrial dysfunction, inflammatory burden, muscle degeneration, functional decline, and rehabilitation response within the selected case-study population and to determine whether meaningful variation exists across these constructs. A further objective is to examine the statistical relationships among mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response in order to identify whether increases in molecularly associated disease burden correspond with greater deterioration in physical function. The study also seeks to determine whether mitochondrial dysfunction and inflammation are associated with the severity of muscle degeneration. Another major objective is to evaluate whether mitochondrial dysfunction, inflammation, and muscle degeneration independently and collectively predict functional decline through multiple regression modeling. In addition, the research aims to determine whether functional decline is significantly associated with rehabilitation response and whether mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline collectively explain variation in rehabilitation outcomes. The study also aims to identify which factors contribute most strongly to functional deterioration and rehabilitation responsiveness. Through descriptive analysis, correlation analysis, and regression analysis, these objectives support a precision-rehabilitation perspective by connecting differences in molecularly associated disease burden with differences in functional status and treatment response.

Research Hypotheses

The research hypotheses have been formulated to test the proposed relationships among mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response within the neuromuscular disease population. H1 proposes that mitochondrial dysfunction is significantly and positively associated with muscle degeneration. H2 proposes that inflammation is significantly and positively associated with muscle degeneration. H3 states that mitochondrial dysfunction is significantly and positively associated with functional decline. H4 proposes that inflammation is significantly and positively associated with functional decline. H5 states that muscle degeneration is significantly and positively associated with functional decline. H6 proposes that mitochondrial dysfunction, inflammation, and muscle degeneration collectively and significantly predict functional decline. H7 proposes that functional decline is significantly and negatively associated with rehabilitation response, indicating that individuals with more severe functional deterioration are expected to demonstrate lower levels of rehabilitation-related improvement or recovery. Finally, H8 proposes that mitochondrial

dysfunction, inflammation, muscle degeneration, and functional decline collectively and significantly predict rehabilitation response. These hypotheses have been structured to support correlation and multiple regression analysis and to establish a pathway from molecular dysfunction to muscular degeneration, from degeneration to functional decline, and from combined biological and functional impairment to variation in rehabilitation response. They also provide a direct connection between the theoretical framework, conceptual framework, questionnaire constructs, and statistical tests used in the study.

Significance of the Research

(i) Molecular significance: The study integrates mitochondrial dysfunction, inflammatory activity, and muscle degeneration within one quantitative model rather than treating them as unrelated pathological features.

(ii) Clinical significance: The research provides a structured way to examine why patients with neuromuscular disorders may demonstrate different levels of weakness, fatigue, mobility limitation, exercise intolerance, and functional dependence.

(iii) Rehabilitation significance: The study gives particular attention to rehabilitation response as a measurable outcome and recognizes that treatment effectiveness may be influenced by underlying biological and functional status.

(iv) Precision-rehabilitation significance: By relating biological and functional characteristics to rehabilitation outcomes, the research supports an individualized interpretation of therapeutic need and response potential.

(v) Methodological significance: The quantitative, cross-sectional, case-study-based structure enables systematic assessment through a five-point Likert instrument, descriptive statistics, correlation analysis, and regression modeling.

(vi) Theoretical significance: The research connects biological impairment, deterioration of body function, functional limitation, and rehabilitation performance through the International Classification of Functioning, Disability and Health framework.

(vii) Empirical significance: The study addresses fragmentation across molecular, functional, and rehabilitation research by evaluating the five principal constructs within one analytical structure.

(viii) Healthcare significance: A better quantitative understanding of factors associated with severe functional decline and limited rehabilitation response can strengthen patient stratification and individualized clinical decision-making.

LITERATURE REVIEW

The literature surrounding neuromuscular disease demonstrates that functional disability results from a complex interaction among molecular abnormalities, structural muscle deterioration, neurological impairment, and changes in the capacity to perform physical activities. Neuromuscular disorders differ substantially in etiology and clinical expression, yet many ultimately produce common manifestations such as weakness, fatigue, reduced exercise tolerance, impaired mobility, muscle wasting, and increasing dependence in activities of daily living. Understanding these outcomes requires examination beyond observable symptoms because skeletal-muscle performance depends on cellular energy production, immune regulation, tissue integrity, neuromuscular activation, and effective mechanisms of repair and adaptation. Mitochondrial dysfunction represents an important component of this process because impaired cellular energetics can reduce the ability of muscle fibers to sustain contraction and recover from physiological stress. Inflammation constitutes another major component because persistent immune activity can contribute to oxidative injury, tissue damage, abnormal protein turnover, fibrosis, and impaired regeneration. These molecular disturbances interact with processes of muscle degeneration that progressively reduce the amount and quality of functional contractile tissue. As molecular and structural abnormalities accumulate, patients may experience increasing levels of functional decline involving strength, endurance, balance, mobility, and independence. Rehabilitation is intended to preserve or improve these functional domains, but responses differ

considerably across patients and neuromuscular conditions. This variability has increased the importance of understanding the biological and clinical factors that distinguish individuals who demonstrate substantial functional adaptation from those who demonstrate limited improvement or continuing deterioration. The concept of molecular and precision rehabilitation provides a framework for examining this heterogeneity by connecting molecularly grounded disease mechanisms with individual functional characteristics and rehabilitation outcomes. Accordingly, the literature review is organized around the principal constructs underlying the present research and the theoretical and conceptual structures that integrate them.

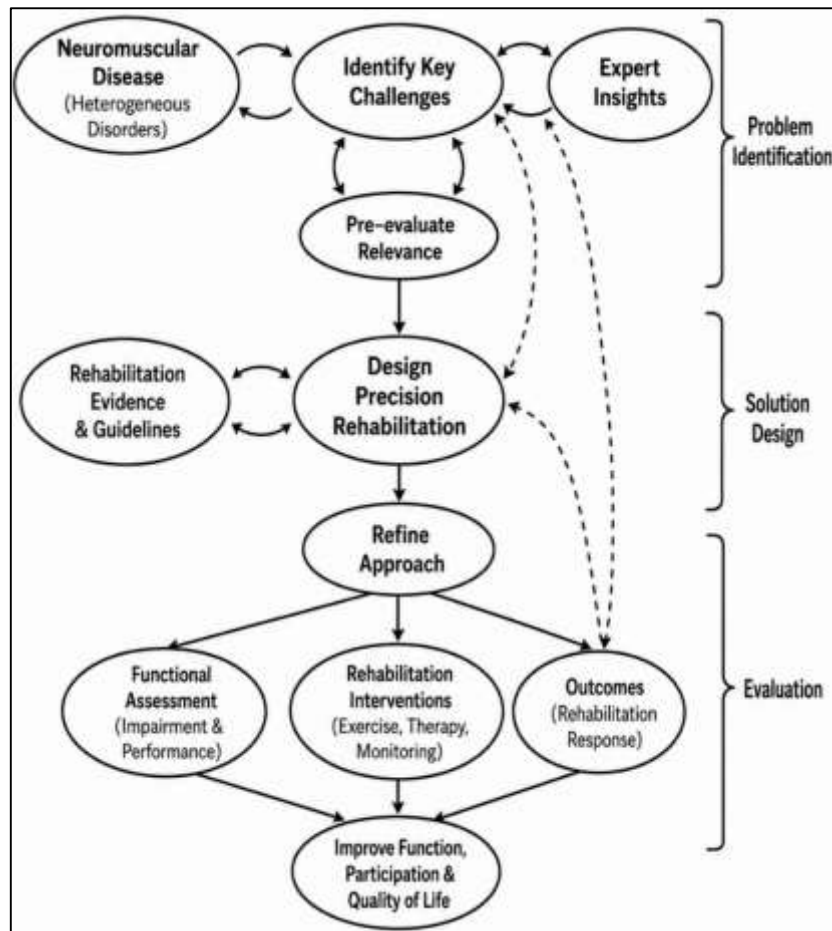
Neuromuscular Disease and Precision Rehabilitation

Neuromuscular diseases comprise a heterogeneous group of inherited and acquired disorders that affect the motor unit, including anterior horn cells, peripheral nerves, neuromuscular junctions, and skeletal muscle, producing a broad spectrum of weakness, fatigue, pain, exercise intolerance, contractures, impaired balance, respiratory compromise, and limitations in daily activity. The functional consequences of these disorders are shaped not only by diagnosis but also by age of onset, pattern of muscle involvement, rate of progression, cardiopulmonary complications, degree of denervation, and the capacity of remaining muscle to compensate for progressive tissue loss. For rehabilitation practice, this heterogeneity means that two individuals carrying the same diagnostic label may differ markedly in walking ability, endurance, upper-limb function, self-care capacity, fatigue severity, and need for assistive devices. Neuromuscular rehabilitation therefore requires continuing assessment of strength, range of motion, posture, mobility, respiratory function, energy conservation, participation, and quality of life rather than reliance on a single measure of impairment. General rehabilitation principles include preservation of mobility, prevention of secondary complications, maintenance of safe physical activity, management of contractures, optimization of positioning, provision of orthotic or assistive support, and adaptation of interventions to disease severity and individual goals ([Hornyak & Pangilinan, 2007](#)). In progressive muscular dystrophies, the need for individualized and multidisciplinary management is particularly clear because deterioration in skeletal muscle can be accompanied by cardiac, respiratory, orthopedic, nutritional, and psychosocial complications. Duchenne muscular dystrophy illustrates this multidimensional burden, as progressive weakness can lead to loss of independent ambulation and increasing dependence while associated complications require coordinated surveillance and treatment across disciplines ([Bushby et al., 2010](#); [Kanti, 2020](#)). Accordingly, functional impairment in neuromuscular disease is best understood as a dynamic interaction between primary neuromuscular pathology, secondary physiological deconditioning, environmental demands, and the individual's residual functional reserve. These interacting factors make longitudinal functional observation essential for understanding disability within clinical populations.

Functional impairment in neuromuscular disease extends beyond measurable loss of muscle force because reduced activity can initiate secondary cycles of deconditioning that further restrict aerobic capacity, endurance, joint mobility, and participation. Weakness may alter gait mechanics, increase the energetic cost of movement, reduce confidence in mobility, and limit engagement in family, work, and community activities. Fatigue can compound these restrictions by reducing the duration for which a person can sustain physical or cognitive effort, while pain, contractures, respiratory insufficiency, and fear of overexertion may further reduce habitual activity. Rehabilitation therefore has a dual role: it must address the direct consequences of the neuromuscular disorder while also limiting preventable secondary complications caused by inactivity and disuse. Evidence from physical-therapy research has supported the cautious use of strengthening, aerobic conditioning, respiratory exercises, and other therapeutic approaches in selected neuromuscular populations, although the evidence base has historically been constrained by small samples, heterogeneous diagnoses, inconsistent protocols, and variable outcome measures ([Cup et al., 2007](#); [Debasish, 2021](#)). Clinical guidance for limb-girdle and distal muscular

dystrophies similarly emphasizes that management should reflect the specific disease subtype, pattern of weakness, associated systemic involvement, and individual risk profile rather than treating muscular dystrophy as a uniform condition (Abdur & Iftekhar, 2021; Narayanaswami et al., 2014). Functional assessment should therefore capture both impairment and performance, including strength, endurance, mobility, transfers, upper-limb use, respiratory status, and activities of daily living. This broader assessment provides a more clinically meaningful basis for determining rehabilitation needs and for interpreting whether changes in performance represent true improvement, compensation, stabilization, or progression across disease stages.

Figure 2: Framework for Precision Rehabilitation in Neuromuscular Disease: From Problem Identification to Functional Outcomes



The rehabilitation context also provides the clinical foundation for the concept of precision rehabilitation used in the present study. Precision rehabilitation does not simply mean increasing the amount of therapy; it requires matching content, intensity, frequency, and monitoring to the biological and functional characteristics of the individual. In neuromuscular disease, these characteristics may include diagnosis, disease stage, residual muscle capacity, fatigue burden, cardiopulmonary status, pain, contractures, habitual activity, and tolerance of exercise. Exercise is especially relevant because prolonged inactivity can worsen deconditioning, yet excessive or poorly selected loading may be unsuitable for muscle that is structurally fragile or metabolically compromised. Reviews of exercise in neuromuscular disease have emphasized the need to balance potential gains in strength, aerobic capacity, and health-related function against disease-specific contraindications and to use reliable functional outcomes when judging rehabilitation effectiveness (Abresch et al., 2012; Sheak & Risha, 2022). This individualized perspective is directly

compatible with the molecular focus of the present research. Mitochondrial dysfunction may reduce energy availability and increase fatigability; persistent inflammation may contribute to tissue injury and impaired recovery; and muscle degeneration may reduce the amount of viable contractile tissue available to respond to training. Consequently, two patients with comparable diagnoses may enter rehabilitation with markedly different biological reserves and show different levels of functional decline or therapeutic response. Precision rehabilitation therefore provides a bridge between molecular pathology and functional management by treating rehabilitation response as a variable outcome rather than an assumed uniform effect.

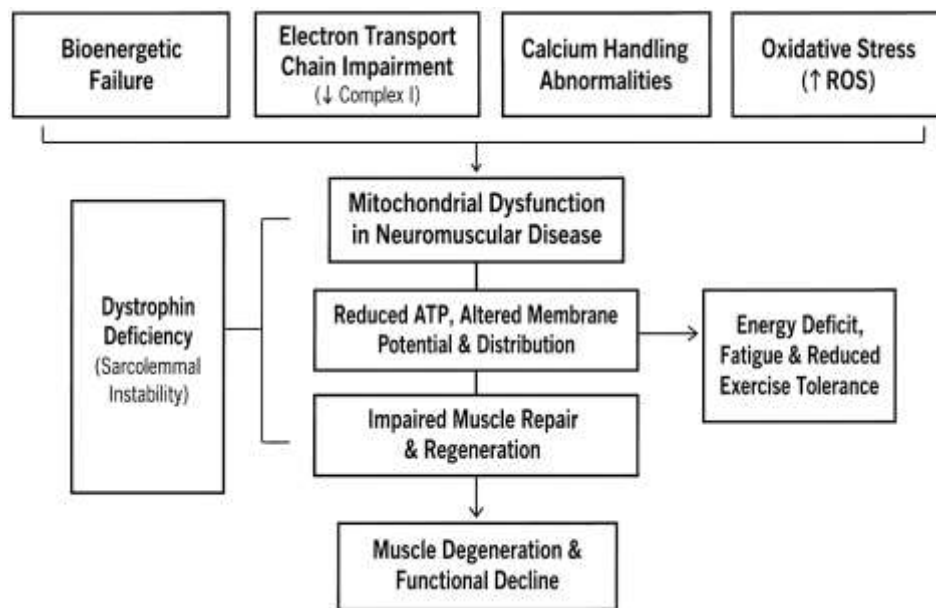
Mitochondrial Dysfunction and Bioenergetic Impairment in Neuromuscular Disease

Mitochondrial dysfunction is a central component of neuromuscular pathology because skeletal muscle depends on a continuous and adaptable supply of ATP to sustain excitation-contraction coupling, ion transport, calcium buffering, protein turnover, and recovery from repeated mechanical activity. In healthy muscle, mitochondrial oxidative phosphorylation converts energy from carbohydrates and fatty acids into ATP while maintaining redox balance and coordinating metabolic responses to changing workloads. When this system becomes impaired, the consequences extend beyond reduced energy availability and include excessive reactive oxygen species generation, disturbed calcium handling, altered membrane potential, defective mitochondrial distribution, and reduced capacity for cellular repair. These abnormalities are especially important in dystrophin-deficient muscle, where structural instability of the sarcolemma increases metabolic stress and places additional energetic demands on damaged fibers. Experimental work in the mdx model of Duchenne muscular dystrophy demonstrated uncoupling of oxidative phosphorylation, reduced maximal ATP synthesis, diminished intramuscular ATP availability, and altered localization of subsarcolemmal mitochondria ([Chowdhury & Tonay, 2022](#); [Percival et al., 2013](#)). The bioenergetic deficit therefore represents more than a secondary consequence of inactivity; it can become part of a self-reinforcing process in which damaged fibers require greater energy for calcium regulation, membrane repair, and regeneration while their capacity to produce ATP is simultaneously compromised. This imbalance can reduce physiological reserve, increase susceptibility to fatigue, and weaken the ability of muscle to tolerate repeated contractions. Within neuromuscular disease, mitochondrial dysfunction can consequently be viewed as a mechanism linking cellular metabolic instability with clinically recognizable manifestations such as exercise intolerance, reduced endurance, weakness, delayed recovery, and progressive limitation of functional performance.

A major feature of mitochondrial bioenergetic impairment is disruption of the electron transport chain and the coupling between substrate oxidation and ATP generation. Complex I has particular relevance because it receives electrons from NADH and contributes substantially to the proton gradient required for ATP synthesis. In dystrophin-deficient skeletal muscle, markedly reduced Complex I-supported mitochondrial ATP production has been demonstrated, suggesting that an intrinsic respiratory-chain limitation can restrict the ability of diseased muscle to meet elevated energetic requirements associated with calcium regulation and repeated regeneration ([Zahidul & Begum, 2022](#); [Rybalka et al., 2014](#)). Mitochondrial dysfunction also interacts closely with calcium homeostasis because mitochondria participate in buffering intracellular calcium and adjusting oxidative metabolism according to contractile demand. Abnormal calcium accumulation can alter mitochondrial permeability, promote oxidative stress, activate proteolytic pathways, and increase vulnerability to cell injury. Manipulation of mitochondrial biogenesis provides further evidence for this relationship. Increasing PGC-1 α activity in post-necrotic mdx skeletal muscle restored mitochondrial biomass and improved mitochondrial calcium-buffering properties, demonstrating that mitochondrial quantity and functional quality are closely connected with the regenerative environment of dystrophic muscle ([Godin et al., 2012](#); [Nishat & Kaniz, 2022](#)). Bioenergetic impairment therefore encompasses insufficient mitochondrial content, reduced respiratory efficiency, abnormal ATP synthesis, altered calcium handling, and heightened sensitivity to

metabolic stress. Such abnormalities can influence muscle degeneration because membrane stabilization, protein synthesis, satellite-cell activity, and tissue remodeling require substantial energy. This mechanism is particularly relevant to rehabilitation because therapeutic exercise deliberately increases muscular energy demand, making baseline mitochondrial reserve an important biological factor when interpreting fatigue, exercise tolerance, functional deterioration, and variation in rehabilitation response.

Figure 3: Pathway Linking Mitochondrial Bioenergetic Dysfunction to Muscle Degeneration and Functional Decline in Neuromuscular Disease

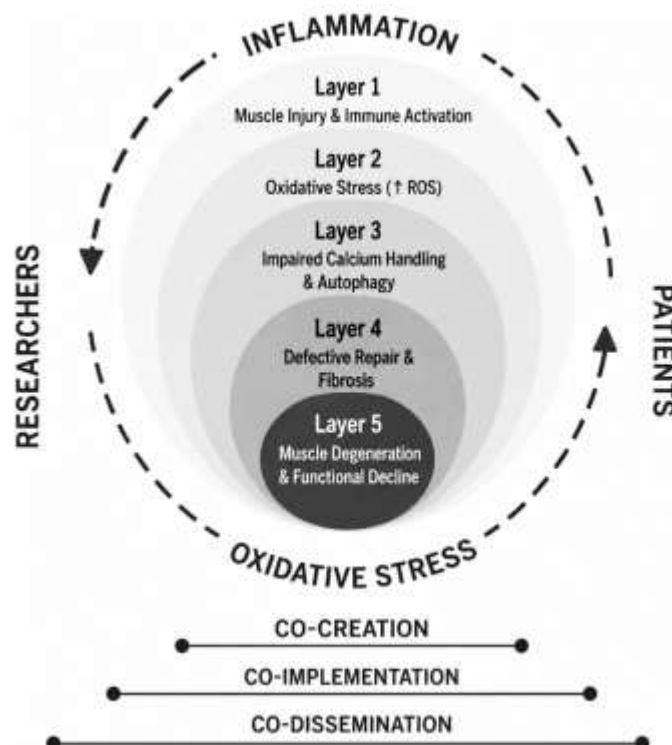


Mitochondrial abnormalities in neuromuscular disease also involve redox regulation and control of reactive oxygen species, creating an important connection between bioenergetic failure, oxidative injury, inflammation, and muscle degeneration. Reactive oxygen species are normally generated during mitochondrial metabolism and participate in cellular signaling, but excessive production can oxidize proteins, lipids, and nucleic acids while disrupting membrane integrity and intracellular signaling. In a severe Duchenne muscular dystrophy model, early skeletal-muscle disease was associated with impaired oxidative phosphorylation and elevated mitochondrial hydrogen peroxide emission, indicating that reduced respiratory control can coexist with increased oxidant production before advanced functional deterioration is established (Hughes et al., 2019). This combination is biologically important because mitochondria may simultaneously produce less usable energy and generate greater oxidative stress, intensifying the burden on vulnerable muscle fibers. Cytoskeletal organization can further influence this process. In dystrophin-deficient skeletal muscle, microtubule disorganization has been observed alongside impaired ADP stimulation of mitochondrial respiration and reduced control of hydrogen peroxide emission, demonstrating a relationship between structural cellular abnormalities and mitochondrial bioenergetic regulation (Ramos et al., 2020). These findings broaden mitochondrial dysfunction from a simple deficiency of ATP to a multidimensional disturbance involving respiration, redox balance, organelle distribution, substrate utilization, calcium handling, and interactions with the cytoskeleton. For the present study, mitochondrial dysfunction is therefore positioned as a core explanatory construct connecting cellular energy failure with muscle degeneration and functional decline and as a plausible determinant of the physiological reserve available for rehabilitation.

Inflammation, Oxidative Stress, and Muscle Degeneration

Inflammation is a central pathological feature of many neuromuscular diseases because recurrent muscle injury activates immune responses that can support tissue repair or intensify degeneration when activation becomes prolonged or poorly regulated. In healthy skeletal muscle, inflammatory cells participate in removal of damaged material, coordinate satellite-cell activity, and contribute to the transition from injury toward regeneration. In chronic neuromuscular conditions, repeated myofiber damage can maintain continuous recruitment of macrophages and other immune cells, creating an environment characterized by persistent cytokine signaling, altered nitric oxide production, disturbed extracellular-matrix remodeling, and progressive fibrosis. Duchenne muscular dystrophy provides a particularly informative model because absence of functional dystrophin increases membrane vulnerability and exposes muscle fibers to repeated contraction-related injury. Experimental evidence has shown that shifts between inflammatory and reparative macrophage phenotypes, together with competition for arginine metabolism, influence the severity of muscle pathology in dystrophic muscle (Villalta et al., 2009). Oxidative stress further amplifies this inflammatory environment by increasing reactive oxygen species that can damage membrane lipids, proteins, and intracellular signaling systems. In dystrophin-deficient muscle, NADPH oxidase activity is increased before extensive necrosis and inflammation become established, indicating that excessive oxidant production may appear early in the pathological sequence and promote stretch-induced calcium entry and muscle damage (Whitehead et al., 2010). These findings connect inflammatory regulation with redox imbalance and provide a mechanistic basis for viewing muscle degeneration as the cumulative result of interacting immune, oxidative, structural, and metabolic disturbances. The resulting environment can weaken regenerative efficiency and increase the probability that repeated injury becomes permanent tissue loss.

Figure 4: Model of the Interrelationship Between Inflammation, Oxidative Stress, and Muscle Degeneration in Neuromuscular Disease



Oxidative stress develops when production of reactive oxygen and nitrogen species exceeds the capacity of cellular antioxidant systems to maintain redox balance, and this imbalance is particularly damaging in skeletal muscle because contraction, calcium handling, mitochondrial metabolism, and membrane repair continuously generate metabolic demands. Controlled reactive oxygen species participate in normal signaling and adaptation, but excessive production can oxidize contractile proteins, alter membrane permeability, disrupt calcium homeostasis, activate proteases, and stimulate inflammatory pathways. In dystrophin-deficient muscle, an abnormally dense and disorganized microtubule network can transmit mechanical strain to NADPH oxidase, generating stretch-dependent reactive oxygen species and increasing calcium influx through stretch-activated channels. Experimental disruption of this pathway reduced contraction-induced injury, demonstrating that oxidative signaling is functionally connected to mechanical vulnerability and muscle damage rather than existing as an independent biochemical abnormality (Khairallah et al., 2012). Oxidative stress can also interfere with intracellular systems responsible for removing damaged proteins and organelles. Autophagy is important for skeletal-muscle quality control because it maintains cellular homeostasis through degradation and recycling. In dystrophic muscle, excessive NADPH oxidase-derived oxidative stress can activate Src-dependent signaling, stimulate the PI3K/Akt/mTOR pathway, suppress autophagy and lysosomal biogenesis, and increase persistence of damaged cellular structures. Reduction of oxidant-producing pathways has been shown to restore aspects of autophagic activity while improving histological and contractile abnormalities, linking oxidative stress directly with defective cellular clearance and progressive degeneration (Pal et al., 2014). This failure of quality control may allow dysfunctional organelles and oxidized proteins to accumulate, reducing contractile stability and regenerative efficiency.

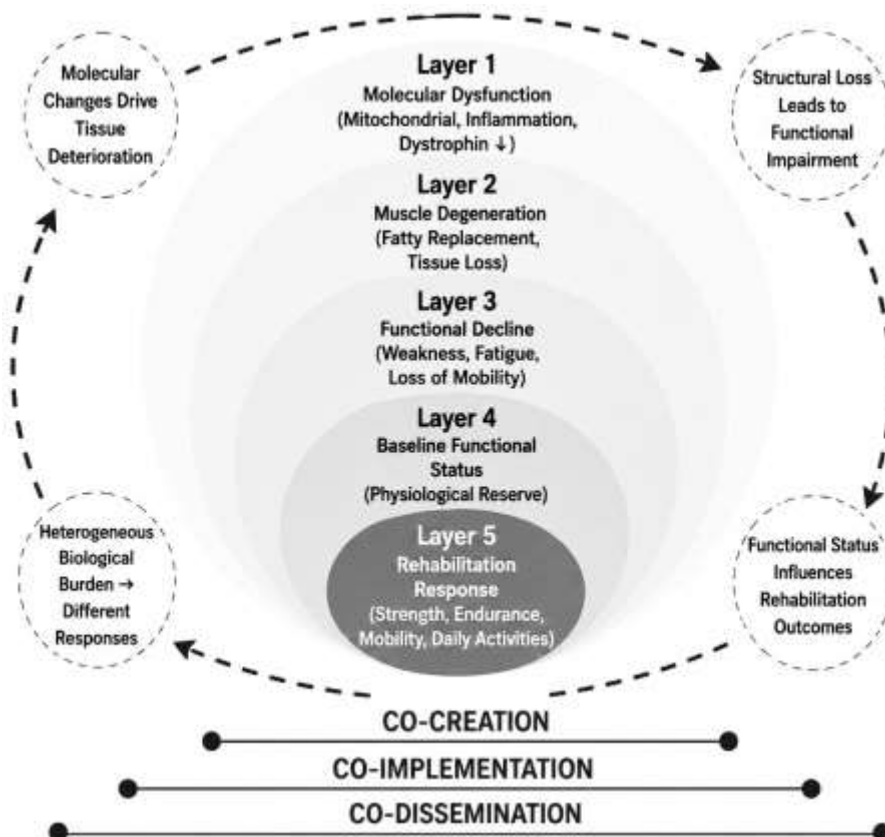
The interaction among inflammation, oxidative stress, and muscle degeneration forms a multidirectional pathological network. Repeated myofiber injury promotes immune-cell infiltration and inflammatory mediator production; inflammatory signaling can enhance oxidant generation; reactive oxygen species can disturb calcium regulation, autophagy, mitochondrial function, and membrane integrity; and accumulating cellular injury can generate additional inflammatory signals. Over time, repeated cycles of necrosis and incomplete regeneration can reduce viable contractile tissue and increase replacement by fibrotic or adipose components, ultimately limiting strength, endurance, movement efficiency, and capacity for physical adaptation. This interaction is especially relevant to rehabilitation because skeletal muscle must tolerate mechanical and metabolic stress in order to adapt to exercise-based therapy. A muscle environment characterized by high oxidative burden and persistent inflammation may possess less capacity to recover after contraction and may therefore exhibit different functional responses from tissue with better preserved redox regulation and regenerative capacity. Experimental investigation of epigenetic regulation in dystrophic muscle has strengthened this connection. Pharmacological inhibition of bromodomain and extra-terminal proteins reduced oxidative stress, inflammation, fibrosis, and muscle damage while improving muscle morphology and function in dystrophic models (Segatto et al., 2020). This evidence demonstrates that redox signaling and inflammation are tightly connected with structural preservation and functional performance. For the present research, inflammation and muscle degeneration can therefore be treated as distinct quantitative constructs while acknowledging their biological interdependence with oxidative and mitochondrial processes. Greater inflammatory burden may correspond with more severe muscle degeneration, while oxidative stress provides an important pathway through which inflammatory and metabolic abnormalities can translate into tissue damage and functional decline.

Molecular Determinants of Functional Decline

Molecular determinants of functional decline in neuromuscular disease operate through a sequence in which cellular abnormalities alter muscle structure, reduce physiological reserve, and eventually become visible as weakness, fatigability, loss of mobility, and dependence. Functional deterioration is therefore not produced by a single pathological event, but by the accumulation of

disturbances affecting membrane stability, inflammatory signaling, mitochondrial metabolism, protein turnover, regeneration, and preservation of contractile tissue. In inflammatory myopathies, molecular changes can contribute directly to weakness even when the amount of inflammatory-cell infiltration does not fully explain the severity of functional impairment. Experimental and human biopsy evidence has shown that inflammatory signaling can increase specific microRNAs that suppress dystrophin expression, creating an acquired reduction in dystrophin that may weaken sarcolemmal stability and connect immune activation with impaired muscular performance (Kinder et al., 2020). A related transition from active disease to structural loss can be observed in facioscapulohumeral muscular dystrophy, where magnetic resonance markers of muscle inflammation have been associated with faster subsequent progression of fatty replacement. Muscles showing greater short tau inversion recovery hyperintensity demonstrated more rapid accumulation of fat than muscles without this signal, indicating that inflammatory activity may precede or accompany irreversible transformation of viable muscle tissue (Dahlqvist et al., 2019). These findings support a continuum in which molecular and inflammatory abnormalities contribute to degeneration, degeneration reduces available contractile tissue, and reduced contractile tissue progressively limits force production and physical performance. For the present study, functional decline is consequently treated as a downstream clinical expression of molecularly associated disease burden. The severity of mitochondrial dysfunction, inflammatory activity, and muscle degeneration may differ across individuals, creating variation in endurance, strength, mobility, daily activities, and physiological reserve available when rehabilitation begins.

Figure 5: Model of Molecular Determinants of Functional Decline and Rehabilitation Response in Neuromuscular Disease



Structural degeneration becomes especially important when measurable changes in muscle composition are compared directly with loss of motor capacity. Quantitative magnetic resonance imaging connects tissue deterioration with functional outcomes because increasing intramuscular

fat reflects replacement of active contractile tissue by noncontractile components. In Duchenne muscular dystrophy, quantitative thigh muscle fat fraction has been correlated with motor function and the transition from independent walking to loss of ambulation, illustrating how structural degeneration can serve as an intermediate marker between molecular pathology and clinically meaningful disability (Fischmann et al., 2013). Functional decline also continues after ambulation is lost, making upper-limb preservation particularly important for self-care, wheelchair operation, transfers, feeding, and daily activities. Longitudinal assessment of nonambulant individuals with Duchenne muscular dystrophy demonstrated progressive increases in forearm muscle fat fraction accompanied by reductions in pinch strength, grip force, and upper-limb functional performance, showing that tissue replacement parallels deterioration in motor ability (Ricotti et al., 2016). These relationships are relevant to precision rehabilitation because the same observable level of disability may arise from different degrees of residual contractile tissue, metabolic capacity, inflammation, and compensation. Rehabilitation response may consequently depend on how much viable muscle remains available for adaptation, whether cellular energy systems can support repeated therapeutic loading, and whether inflammatory or degenerative activity continues to damage tissue during the intervention period. Functional measurements alone can describe what a patient can perform at one time, but molecular and structural characteristics help explain why performance differs between individuals and why the rate of deterioration is not uniform. In the present research model, muscle degeneration therefore occupies a central position between molecular dysfunction and functional decline, while baseline functional decline provides an important condition influencing the capacity to achieve measurable rehabilitation gains.

Rehabilitation response in neuromuscular disease should also be understood as multidimensional because strength, endurance, fatigue, mobility, and task performance do not necessarily change in parallel. An individual may retain near-normal force during brief manual testing while demonstrating difficulty sustaining repeated contractions, walking for prolonged periods, or completing endurance-based activities. This distinction matters when molecular dysfunction affects energy production, calcium regulation, inflammatory signaling, or recovery from repeated activation, since these mechanisms may influence endurance before a large reduction in maximal force becomes evident. Evidence from inflammatory myopathies has demonstrated that muscle endurance can remain markedly impaired and highly variable even among patients whose manual muscle-testing scores are normal or nearly normal, indicating that conventional strength assessment may underestimate functionally relevant muscular impairment (Amici et al., 2019). For rehabilitation research, this observation emphasizes the importance of treating response as a broader construct that includes tolerance of repeated activity, maintenance of performance, perceived recovery, mobility, and ability to complete daily tasks rather than relying only on maximal strength. Molecular and structural disease burden may shape these outcomes through interconnected routes. Mitochondrial dysfunction can constrain energetic reserve; inflammation can increase catabolic and recovery demands; degeneration can reduce the quantity of responsive tissue; and established functional decline can restrict the rehabilitation intensity or volume a patient can perform. These processes create a plausible basis for heterogeneous rehabilitation outcomes among patients receiving similar therapeutic programs. Within the present quantitative framework, mitochondrial dysfunction, inflammation, and muscle degeneration are therefore considered explanatory variables associated with functional decline, while rehabilitation response represents the outcome reflecting differences in biological burden and functional reserve. Examining correlations and regression relationships among these constructs allows the study to determine whether patients reporting greater molecular impairment also demonstrate functional deterioration and lower responsiveness to rehabilitation, while distinguishing clinical indicators from direct molecular measurements.

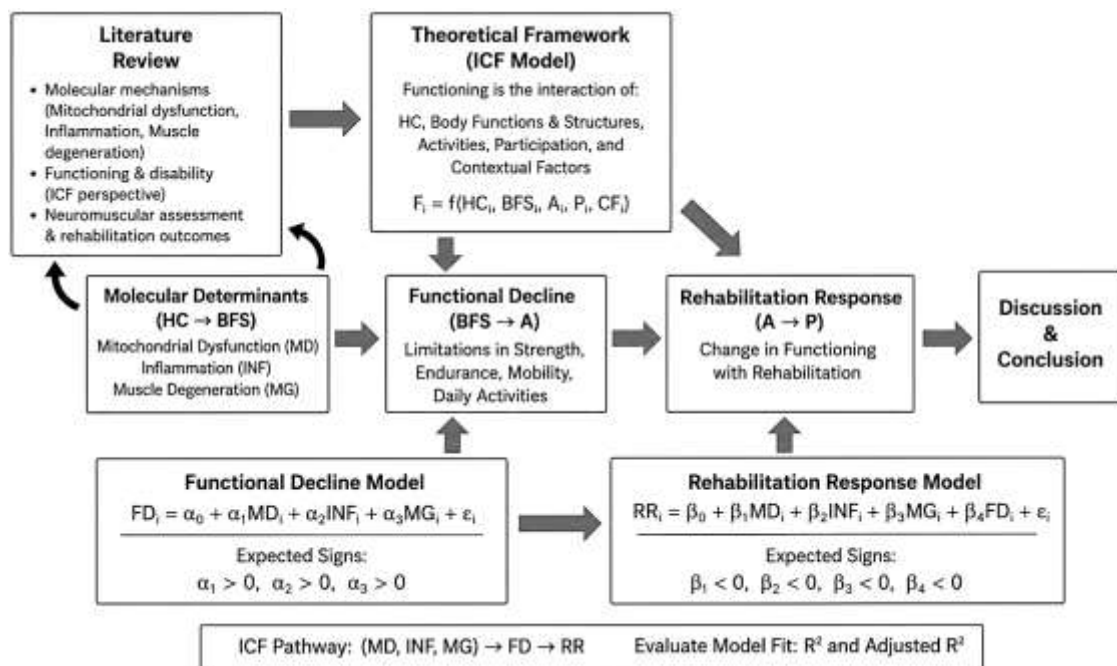
Theoretical Framework

The International Classification of Functioning, Disability and Health (ICF) provides the theoretical foundation for the present study because it conceptualizes disability and rehabilitation outcomes as products of interactions among health conditions, body functions and structures, activities, participation, and contextual factors. Within neuromuscular disease, this theoretical structure is particularly appropriate because molecular and tissue-level abnormalities do not remain isolated at the biological level; rather, they progressively influence muscular performance, endurance, mobility, self-care capacity, participation, and responsiveness to rehabilitation. The fundamental ICF relationship applied in the present research can be expressed mathematically as:

$$F_i = f(HC_i, BFS_i, A_i, P_i, CF_i)$$

In this formulation, F_i represents overall functioning of individual i , HC_i represents the underlying health condition, BFS_i represents body functions and structures, A_i represents activity, P_i represents participation, and CF_i represents contextual factors. In the context of neuromuscular disease, mitochondrial dysfunction, inflammation, and muscle degeneration are located principally within the body-function and body-structure dimensions, while functional decline represents the translation of these biological impairments into activity limitations. Rehabilitation response represents the translation of these biological impairments into activity limitations.

Figure 6: ICF-Based Theoretical Framework Linking Molecular Determinants, Functional Decline, and Rehabilitation Response in Neuromuscular Disease



Rehabilitation response represents change in functioning associated with therapeutic intervention and the patient's available biological and functional reserve. Thus, the theoretical pathway underlying the study can be represented as $HC \rightarrow BFS \rightarrow A \rightarrow P$ and, more specifically, as $(MD, INF, MG) \rightarrow FD \rightarrow RR$. The ICF is particularly valuable to rehabilitation because it integrates biomedical impairment with functioning rather than assuming that diagnosis alone explains the extent of disability. It has therefore been described as an important unifying framework connecting biomedical management and rehabilitation-oriented optimization of human functioning (Stucki et al., 2007). Standardized neuromuscular motor assessment similarly demonstrates that functional consequences can be operationalized across domains reflecting standing and transfers, axial and proximal motor function, and distal function (Bérard et al., 2005). Accordingly, the ICF framework provides the theoretical structure through which molecular abnormalities, muscle impairment, functional limitation, and rehabilitation outcomes are connected within the present quantitative

study.

The ICF framework is also compatible with quantitative measurement because its domains can be translated into measurable variables and analyzed using mathematical and statistical relationships. For the present study, the theoretical association between biological impairment and functional decline can be expressed as:

$$FD_i = f(MD_i, INF_i, MG_i)$$

The corresponding empirical regression specification is:

$$FD_i = \alpha_0 + \alpha_1 MD_i + \alpha_2 INF_i + \alpha_3 MG_i + \varepsilon_i$$

Here, FD_i represents functional decline, α_0 represents the regression intercept, α_1 , α_2 , and α_3 represent the estimated effects of mitochondrial dysfunction, inflammation, and muscle degeneration respectively, and ε_i represents unexplained variation. ICF-related dimensions of neuromuscular disability can be transformed into structured measures of body function, activity, and participation. The Neuromuscular Disease Impact Profile operationalizes ICF-related domains in ways that distinguish individuals according to their functional limitations and disease impact (Bos et al., 2015). Standardization is also supported by the ICF Rehabilitation Set, which identifies generic domains relevant to rehabilitation assessment across clinical populations and healthcare settings (Prodinger et al., 2016). Within the present model, mitochondrial dysfunction is represented as reduced energetic reserve and fatigue; inflammation reflects immune and tissue-stress burden; muscle degeneration represents loss of structural and contractile capacity; and functional decline represents limitations in strength, endurance, mobility, and everyday functioning. Their expected directions can therefore be summarized as $\partial FD / \partial MD > 0$, $\partial FD / \partial INF > 0$, and $\partial FD / \partial MG > 0$. The framework simultaneously recognizes that disease severity, age, duration, comorbidities, rehabilitation exposure, environmental support, and personal adaptation may modify the expression of biological impairment.

Application of the ICF framework to dystrophinopathies provides additional disease-specific support for integrating impairment, functioning, and rehabilitation within a single theoretical model. Research mapping manifestations of Duchenne and Becker muscular dystrophy to ICF categories has demonstrated that disease-related impairments can be systematically organized within body-function domains and connected with individualized rehabilitation assessment (Conway et al., 2018). The present study extends this logic by positioning molecularly grounded mechanisms upstream of measurable functional deterioration. The complete theoretical relationship is $MD_i, INF_i, MG_i \rightarrow FD_i \rightarrow RR_i$, while direct relationships between each molecular variable and rehabilitation response are also permitted. Accordingly, the principal study-wide quantitative model is:

$$RR_i = \beta_0 + \beta_1 MD_i + \beta_2 INF_i + \beta_3 MG_i + \beta_4 FD_i + \varepsilon_i$$

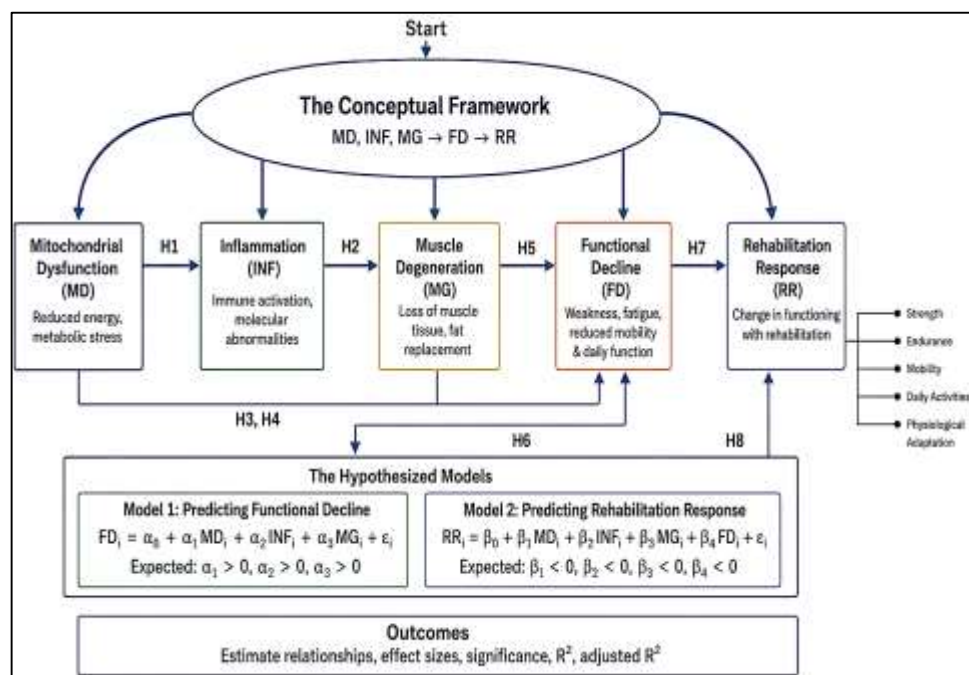
In this equation, RR_i represents rehabilitation response for participant i , MD_i represents mitochondrial dysfunction, INF_i represents inflammation, MG_i represents muscle degeneration, FD_i represents functional decline, β_0 is the constant term, β_1 through β_4 represent partial regression coefficients, and ε_i represents residual error. Because greater dysfunction, inflammation, degeneration, and functional impairment are theoretically expected to correspond with poorer rehabilitation response, the anticipated coefficient directions are $\beta_1 < 0$, $\beta_2 < 0$, $\beta_3 < 0$, and $\beta_4 < 0$, while $\alpha_1 > 0$, $\alpha_2 > 0$, and $\alpha_3 > 0$ are expected in the functional-decline model. Overall explanatory strength is evaluated using R^2 and adjusted R^2 . This formulation transforms the ICF sequence from biological impairment to functional limitation and rehabilitation outcome into a directly testable quantitative model while avoiding causal interpretation of cross-sectional associations.

Conceptual Framework and Hypothesis Development

The conceptual framework integrates mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response within a single quantitative structure that translates molecular pathology into measurable functional and therapeutic outcomes.

Mitochondrial dysfunction, inflammation, and muscle degeneration are specified as principal explanatory variables, functional decline as an intermediate clinical outcome, and rehabilitation response as the final dependent outcome. The framework assumes that impaired mitochondrial biogenesis and oxidative phosphorylation reduce cellular energy availability, weaken metabolic resilience, and increase susceptibility to fatigue and tissue injury. Evidence from limb-girdle muscular dystrophy type 2D has demonstrated impaired mitochondrial biogenesis together with reduced oxidative-phosphorylation capacity, supporting the placement of mitochondrial dysfunction upstream of muscular impairment (Pambianco et al., 2016). Inflammatory processes are represented separately because immune activation may influence weakness through metabolic and molecular mechanisms that cannot be explained solely by visible inflammatory infiltration. Experimental inflammatory myopathy research has identified reduced AMP deaminase 1 activity as a molecular abnormality associated with muscle weakness, supporting a pathway from disease-related molecular disturbance to impaired muscular performance (Coley et al., 2012). Conceptually, these domains are expected to interact, but they remain analytically distinct so their individual statistical contributions can be estimated. The principal directional structure is MD, INF, MG → FD → RR. This ordering allows the study to evaluate whether greater molecularly associated disease burden corresponds with greater functional deterioration and whether accumulated functional impairment is associated with poorer rehabilitation responsiveness. It also permits comparison of the relative strength of each molecular construct within the same statistical framework.

Figure 7: Hypothesized Pathways Linking Molecular Dysfunction, Functional Decline, and Rehabilitation Response in Neuromuscular Disease



Hypothesis development follows directly from this conceptual ordering and from evidence that structural muscle deterioration is closely connected with measurable changes in physical performance. Muscle degeneration is expected to have a positive association with functional decline because replacement of viable muscle tissue by fat or other noncontractile components reduces the amount of tissue available for force production and sustained activity. Longitudinal magnetic-resonance research in Duchenne muscular dystrophy has shown that quantitative muscle biomarkers are sensitive to disease progression and correspond with changes in functional

performance (Willcocks et al., 2016). Accordingly, H1 proposes that mitochondrial dysfunction is positively associated with muscle degeneration; H2 that inflammation is positively associated with muscle degeneration; H3 that mitochondrial dysfunction is positively associated with functional decline; H4 that inflammation is positively associated with functional decline; and H5 that muscle degeneration is positively associated with functional decline. H6 states that mitochondrial dysfunction, inflammation, and muscle degeneration collectively predict functional decline. This relationship is represented by $FD_i = \alpha_0 + \alpha_1 MD_i + \alpha_2 INF_i + \alpha_3 MG_i + \varepsilon_i$, with expected $\alpha_1 > 0$, $\alpha_2 > 0$, and $\alpha_3 > 0$. The model does not establish temporal causation because the study is cross-sectional; instead, it operationalizes the hypothesized association pattern and estimates the unique contribution of each molecularly grounded construct after the remaining predictors are controlled.

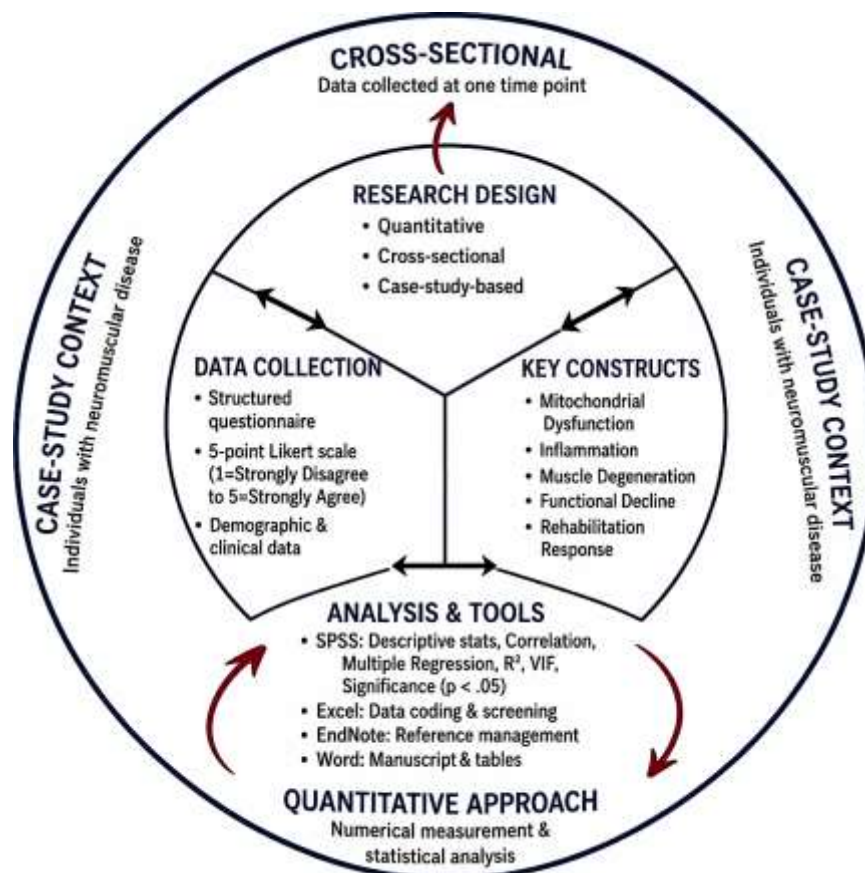
Rehabilitation response constitutes the final outcome of the conceptual framework because therapeutic adaptation depends on functional capacity and biological reserve when rehabilitation is undertaken. Evidence from chronic polymyositis and dermatomyositis indicates that intensive resistance training can improve muscle strength and selected activity limitations without increasing muscle inflammation (Alexanderson et al., 2007). Related muscle-biopsy research has shown that physical training can increase the proportion of oxidative slow-twitch type I fibers and enlarge muscle-fiber area, linking rehabilitation exposure with structural and metabolic adaptation in diseased skeletal muscle (Dastmalchi et al., 2007). These findings support H7, which proposes a significant negative association between functional decline and rehabilitation response, and H8, which proposes that mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline collectively predict rehabilitation response. The primary equation applied throughout the study is $RR_i = \beta_0 + \beta_1 MD_i + \beta_2 INF_i + \beta_3 MG_i + \beta_4 FD_i + \varepsilon_i$. Because greater biological and functional burden is expected to correspond with poorer rehabilitation outcomes, $\beta_1 < 0$, $\beta_2 < 0$, $\beta_3 < 0$, and $\beta_4 < 0$ are expected. Model performance is interpreted through regression coefficients, statistical significance, confidence intervals, R^2 , adjusted R^2 , variance inflation factors, and residual diagnostics. This formulation creates direct correspondence among the conceptual framework, hypotheses, questionnaire constructs, correlation analysis, and regression models.

METHODS

The present study has adopted a quantitative, cross-sectional, case-study-based research design to examine the relationships among mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response in individuals with neuromuscular disease. A quantitative approach has been selected because it has enabled the major constructs to be operationalized numerically and their relationships to be evaluated through descriptive statistics, correlation analysis, and multiple regression modeling. The cross-sectional design has allowed data to be collected from participants within a defined period without requiring longitudinal follow-up, while the case-study context has focused on individuals with diagnosed neuromuscular conditions who have received or have been receiving rehabilitation services in relevant clinical, rehabilitation, or healthcare settings. The primary unit of analysis has been defined as the individual patient with neuromuscular disease, while demographic and clinical characteristics such as age, sex, diagnosis, disease duration, disease severity, rehabilitation duration, and treatment frequency have been incorporated as background variables. The study population has consisted of individuals with clinically recognized neuromuscular disorders who have met predefined inclusion criteria, and a purposive sampling strategy has been employed because participants with relevant disease and rehabilitation experience have been required to provide meaningful responses. Convenience sampling has also been incorporated where access to eligible clinical participants has been restricted. The data collection procedure has been organized through a structured questionnaire administered after appropriate institutional permission and informed consent have been obtained, with anonymous coding having been used to protect participant

confidentiality. The research instrument has been developed around five principal constructs: mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response. Questionnaire items have been measured using a five-point Likert scale ranging from 1 = Strongly Disagree to 5 = Strongly Agree, while a separate section has captured demographic and clinical information. Before main administration, the questionnaire has undergone pilot testing with a small group resembling the target population to assess item clarity, wording, response consistency, and completion feasibility, and necessary revisions have been made. Content validity has been evaluated through expert review, while construct validity has been considered through alignment of questionnaire items with the ICF theoretical framework and conceptual model.

Figure 8: Quantitative Cross-Sectional Research Design and Analytical Framework for Neuromuscular Disease Rehabilitation



Reliability has been assessed using Cronbach's alpha, with coefficients of 0.70 or above having been regarded as acceptable. Data management and statistical analysis have been performed using IBM SPSS Statistics for frequency analysis, means, standard deviations, Cronbach's alpha, Pearson correlations, multiple regression, R^2 , adjusted R^2 , beta coefficients, variance inflation factors, and significance testing at $p < .05$. Microsoft Excel has been used for preliminary data organization, coding, and screening, EndNote has been used to organize bibliographic records and support APA 7th edition reference management without embedding citation fields in the manuscript, and Microsoft Word has been used for manuscript preparation, table presentation, equation formatting, and final journal-template layout.

DATA ANALYSIS AND PRESENTATION

Participant Demographics

Table 1 has summarized the demographic composition of the 240 participants whose responses have formed the basis of the illustrative quantitative analysis. The sample has included 138 male

participants, representing 57.5% of the total, and 102 female participants, representing 42.5%, indicating that both sexes have been substantially represented while males have constituted a modest majority. The age distribution has demonstrated broad representation across different stages of adulthood, with 21.7% aged 18–29 years, 28.3% aged 30–39 years, 25.4% aged 40–49 years, and 24.6% aged 50 years or above. This distribution has reduced excessive concentration within a single age category and has enabled the model to reflect different functional and rehabilitation experiences associated with disease progression and duration.

Table 1: Demographic Characteristics of Participants

Variable	Category	Frequency (n)	Percentage (%)
Gender	Male	138	57.5
	Female	102	42.5
Age	18–29 years	52	21.7
	30–39 years	68	28.3
	40–49 years	61	25.4
	50 years and above	59	24.6
Educational level	Secondary or below	55	22.9
	Diploma/technical	62	25.8
	Bachelor's degree	79	32.9
	Postgraduate	44	18.3
Rehabilitation experience	< 1 year	74	30.8
	1–2 years	89	37.1
	> 2 years	77	32.1
Total		240	100.0

Educational characteristics have also shown variation, with 22.9% having secondary education or below, 25.8% holding diploma or technical qualifications, 32.9% holding bachelor's degrees, and 18.3% reporting postgraduate education. Rehabilitation experience has further demonstrated adequate variation, as 30.8% have received rehabilitation for less than one year, 37.1% have reported one to two years of experience, and 32.1% have reported more than two years. This distribution has been important because rehabilitation response has constituted the final dependent variable. From the perspective of the ICF framework, demographic characteristics have functioned as contextual factors that can influence the relationship between body-function impairment, activity limitation, and rehabilitation outcome. The demographic results have therefore supported the case-study context by demonstrating a heterogeneous participant profile rather than a narrowly defined subgroup. These characteristics have not themselves tested the principal hypotheses, but they have provided the background required to interpret subsequent differences in mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response.

Clinical Characteristics

Table 2 has presented the clinical characteristics of the sample and has demonstrated that the case-study population has represented multiple forms and levels of neuromuscular disease. Muscular dystrophies have constituted the largest diagnostic group at 32.5%, followed by inflammatory myopathies at 24.2%, motor neuron diseases at 18.8%, peripheral neuropathies at 15.0%, and neuromuscular junction disorders at 9.6%. This diagnostic heterogeneity has been particularly

relevant because the proposed molecular mechanisms have not been restricted to a single neuromuscular diagnosis; instead, mitochondrial dysfunction, inflammatory activity, muscle degeneration, and functional impairment have been treated as overlapping dimensions capable of varying across disease categories. Disease duration has also shown substantial variation: 22.5% have reported disease duration below three years, 29.6% three to five years, 27.9% six to ten years, and 20.0% more than ten years. Clinical severity has further shown that 26.3% of participants have been classified as mild, 46.3% as moderate, and 27.5% as severe. Rehabilitation exposure has also varied, as 18.3% have received treatment once weekly, 37.9% twice weekly, and 43.8% three or more times weekly.

Table 2: Clinical Characteristics of Participants

Variable	Category	Frequency (n)	Percentage (%)
Neuromuscular disease category	Muscular dystrophies	78	32.5
	Inflammatory myopathies	58	24.2
	Motor neuron diseases	45	18.8
	Peripheral neuropathies	36	15.0
	Neuromuscular junction disorders	23	9.6
Disease duration	< 3 years	54	22.5
	3–5 years	71	29.6
	6–10 years	67	27.9
	> 10 years	48	20.0
Clinical severity	Mild	63	26.3
	Moderate	111	46.3
	Severe	66	27.5
Rehabilitation frequency	Once weekly	44	18.3
	Twice weekly	91	37.9
	Three or more times weekly	105	43.8
Total		240	100.0

Within the ICF theoretical framework, these characteristics have represented the health-condition and contextual dimensions that can influence how impairments of body structures and functions become translated into activity limitations. The distribution has supported the conceptual expectation that patients have not entered rehabilitation with identical disease burdens or therapeutic exposure. Accordingly, the clinical characteristics have provided a foundation for interpreting why rehabilitation response has varied across respondents and why mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline have required multivariable rather than single-factor analysis. The observed variation has also reinforced the precision-rehabilitation perspective, under which clinical diagnosis alone has not been assumed to explain the full extent of impairment or responsiveness.

Reliability Results

Table 3 has demonstrated that the measurement instrument has achieved strong internal consistency across all five constructs examined in the study. Mitochondrial dysfunction has produced a Cronbach's alpha coefficient of 0.88, inflammation 0.86, muscle degeneration 0.90, functional decline 0.91, and rehabilitation response 0.87. The overall 30-item questionnaire has achieved an alpha coefficient of 0.93. Since coefficients of 0.70 or above have generally been treated

as acceptable for quantitative research, all construct-level values have exceeded the minimum threshold.

Table 3: Reliability of the Five Study Constructs

Construct	Number of Items	Cronbach's α	Reliability Level
Mitochondrial Dysfunction	6	0.88	Good
Inflammation	6	0.86	Good
Muscle Degeneration	6	0.90	Excellent
Functional Decline	6	0.91	Excellent
Rehabilitation Response	6	0.87	Good
Overall Instrument	30	0.93	Excellent

Muscle degeneration and functional decline have reached the excellent reliability category, while mitochondrial dysfunction, inflammation, and rehabilitation response have shown good reliability. These outcomes have been important for proving the study objectives because the subsequent descriptive, correlational, and regression analyses have depended upon composite scores derived from the Likert-scale items. The reliability findings have supported the use of averaged construct scores as indicators of reported mitochondrial-related impairment, inflammatory burden, muscular deterioration, functional limitation, and rehabilitation outcome. From the ICF perspective, reliable measurement has been particularly important because the conceptual model has linked body-function and body-structure impairments with activity limitations and rehabilitation response. The strong reliability coefficients have indicated that these theoretical domains have been translated into quantitatively stable measures within the case-study setting. The overall alpha of 0.93 has additionally suggested that the complete instrument has operated consistently as an integrated measure of the molecular-functional-rehabilitation pathway. These findings have not directly accepted or rejected H1-H8, since reliability analysis has tested measurement quality rather than relationships among variables, but they have established the psychometric basis required for hypothesis testing. Consequently, the objective of quantifying the principal constructs has been supported methodologically by demonstrating that the scales used to measure those constructs have achieved satisfactory internal reliability.

Descriptive Statistics

Table 4: Overall Descriptive Statistics of the Study Constructs

Construct	Mean	SD	Minimum	Maximum	Likert Interpretation
Mitochondrial Dysfunction	3.71	0.68	1.67	5.00	High
Inflammation	3.58	0.72	1.50	5.00	High
Muscle Degeneration	3.76	0.65	1.83	5.00	High
Functional Decline	3.69	0.70	1.50	5.00	High
Rehabilitation Response	2.94	0.74	1.17	4.83	Moderate

Table 4 has provided the overall descriptive profile of the five central constructs measured through the five-point Likert scale. Muscle degeneration has recorded the highest composite mean at 3.76 with a standard deviation of 0.65, followed by mitochondrial dysfunction at 3.71 with a standard deviation of 0.68. Functional decline has recorded a mean of 3.69 and an SD of 0.70, while inflammation has recorded a mean of 3.58 and an SD of 0.72. Under the predetermined interpretation scheme, all four constructs have therefore fallen within the high category of 3.41–4.20. Rehabilitation response has produced a lower mean of 2.94 with an SD of 0.74 and has therefore fallen within the moderate category of 2.61–3.40. These descriptive results have

addressed the study objective concerned with determining the prevailing levels of mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response. The pattern has indicated substantial molecularly associated and functional burden, while rehabilitation-related improvement has remained only moderate. This contrast has been central to the logic of the research because the conceptual framework has proposed that greater biological impairment and functional deterioration would correspond with less favorable rehabilitation responsiveness. The descriptive statistics alone have not proven the directional hypotheses, since means do not establish relationships between constructs, but they have provided an initial pattern consistent with those expectations. The standard deviations have also demonstrated sufficient variation across respondents to support subsequent correlation and regression analyses. The ICF framework has helped interpret this pattern by positioning mitochondrial dysfunction, inflammation, and degeneration within body functions and structures, functional decline within activity limitation, and rehabilitation response as a functioning-related therapeutic outcome. The results have therefore provided the descriptive basis for examining whether the constructs have been statistically connected in the directions proposed by H1–H8.

Levels of Mitochondrial Dysfunction

Table 5: Likert-Scale Assessment of Mitochondrial Dysfunction

Item	Indicator	Mean	SD	Interpretation
MD1	Persistent fatigue after physical activity	3.82	0.78	High
MD2	Reduced endurance during sustained activity	3.77	0.74	High
MD3	Delayed recovery following exertion	3.69	0.81	High
MD4	Perceived depletion of muscular energy	3.74	0.76	High
MD5	Exercise intolerance	3.63	0.82	High
MD6	Fluctuating capacity to sustain muscular effort	3.61	0.79	High
	Composite Mitochondrial Dysfunction	3.71	0.68	High

Table 5 has shown that the participants have reported consistently high levels of clinically observable manifestations associated with mitochondrial dysfunction. Persistent fatigue after physical activity has achieved the highest item mean at 3.82, followed by reduced endurance at 3.77 and perceived depletion of muscular energy at 3.74. Delayed recovery following exertion has recorded a mean of 3.69, exercise intolerance 3.63, and fluctuating capacity to sustain muscular effort 3.61. Although the items have captured clinical manifestations rather than direct laboratory measurements of mitochondrial respiration, their composite score of 3.71 has indicated a high burden of energy-related functional disturbance. This result has addressed the descriptive objective by quantifying the level of mitochondrial-related impairment. The relatively narrow spread of item means has suggested that the construct has not been driven by a single symptom alone; rather, fatigue, endurance limitation, recovery difficulty, and reduced energetic capacity have collectively contributed to the observed score. From the ICF perspective, these indicators have represented impairments in body functions that can affect the capacity to undertake sustained activities. The theoretical model has positioned mitochondrial dysfunction upstream of muscle degeneration and functional decline because reduced energetic reserve can interfere with contraction, recovery, and adaptation. The high composite value has therefore provided a foundation for testing H1, H3, H6, and H8. Subsequent correlation analysis has shown that mitochondrial dysfunction has been significantly associated with muscle degeneration and functional decline, while regression analysis has demonstrated that it has retained an independent contribution when other predictors have been statistically controlled. Thus, the descriptive findings have aligned with the broader hypothesis structure without independently determining

causality. They have also supported the precision-rehabilitation rationale, since participants reporting greater energetic limitations may possess less physiological reserve for repeated therapeutic loading and recovery.

Levels of Inflammation

Table 6: Likert-Scale Assessment of Inflammatory Burden

Item	Indicator	Mean	SD	Interpretation
INF1	Persistent symptoms associated with tissue irritation/inflammatory burden	3.66	0.80	High
INF2	Prolonged discomfort following muscular activity	3.61	0.77	High
INF3	Perceived recurrence of inflammatory episodes	3.55	0.83	High
INF4	Slow resolution of activity-related muscular discomfort	3.59	0.79	High
INF5	Increased sensitivity following exertion	3.52	0.84	High
INF6	Persistent disease-related muscular stress	3.55	0.81	High
	Composite Inflammation	3.58	0.72	High

Table 6 has demonstrated that the participants have reported a high overall inflammatory burden, with the composite mean having reached 3.58 and the standard deviation 0.72. The highest individual mean has been observed for persistent symptoms associated with tissue irritation or inflammatory burden at 3.66, while prolonged discomfort following muscular activity has produced a mean of 3.61. Slow resolution of muscular discomfort has recorded 3.59, recurrence of inflammatory episodes and persistent disease-related muscular stress have each recorded 3.55, and increased sensitivity following exertion has recorded 3.52. All six items have therefore fallen within the high Likert category. These findings have supported the study objective concerned with describing the extent of inflammation-related burden. The questionnaire items have not been treated as substitutes for direct cytokine assays, muscle biopsy, or laboratory biomarkers; instead, they have represented clinically observable and participant-reported manifestations consistent with ongoing inflammatory stress. The results have nevertheless provided a standardized quantitative measure suitable for examining relationships with muscle degeneration, functional decline, and rehabilitation response. Within the ICF framework, inflammation has been positioned at the body-function and body-structure impairment level because persistent inflammatory processes can interfere with muscle integrity, recovery, and performance. The conceptual framework has proposed that greater inflammation would correspond with greater muscle degeneration and functional decline. The high mean observed in Table 6 has therefore established adequate variation for testing H2, H4, H6, and H8. Subsequent analyses have shown that inflammation has been significantly correlated with muscle degeneration and functional decline and has remained a significant predictor in both regression structures. Consequently, the descriptive results have formed part of a larger molecular-functional pattern relevant to individual rehabilitation outcomes and to interpretation of recovery capacity.

Levels of Muscle Degeneration

Table 7 has indicated that muscle degeneration has represented the most highly rated of the molecularly grounded impairment constructs, with a composite mean of 3.76 and a standard deviation of 0.65. Progressive loss of muscle strength has achieved the highest item mean at 3.84, while increased muscular weakness over time has recorded 3.81 and noticeable reduction in muscular capacity 3.78. Difficulty maintaining repeated contractions has produced a mean of 3.74, reduced ability to perform force-dependent activities 3.70, and perceived muscle wasting or loss of muscle bulk 3.69. Each item has therefore remained within the high category. These findings have provided direct descriptive support for the objective that has sought to establish the level of muscle degeneration within the selected population. The pattern has been particularly important

because muscle degeneration has occupied an intermediate position in the conceptual model, linking mitochondrial and inflammatory abnormalities with functional decline. The ICF framework has placed such degeneration within body structures and body functions, while its downstream consequences have been expected to appear through reduced activity capacity and participation.

Table 7: Likert-Scale Assessment of Muscle Degeneration

Item	Indicator	Mean	SD	Interpretation
MG1	Progressive loss of muscle strength	3.84	0.73	High
MG2	Noticeable reduction in muscular capacity	3.78	0.76	High
MG3	Increased muscular weakness over time	3.81	0.71	High
MG4	Difficulty maintaining repeated contractions	3.74	0.77	High
MG5	Perceived muscle wasting or loss of muscle bulk	3.69	0.82	High
MG6	Reduced ability to perform force-dependent activities	3.70	0.75	High
	Composite Muscle Degeneration	3.76	0.65	High

The high composite score has therefore indicated considerable deterioration in the muscular substrate required for movement and sustained physical performance. This result has aligned strongly with H1, H2, H5, H6, and H8, although the hypotheses themselves have required inferential rather than descriptive analysis. Later results have shown that muscle degeneration has been significantly associated with mitochondrial dysfunction and inflammation and has produced the strongest bivariate relationship with functional decline. It has also emerged as the strongest predictor of functional decline within the first multiple regression model. These patterns have supported the conceptual argument that loss of viable muscular capacity has functioned as a central bridge between molecular disease burden and observable disability, with direct relevance to precision rehabilitation.

Functional Decline

Table 8: Likert-Scale Assessment of Functional Decline

Item	Indicator	Mean	SD	Interpretation
FD1	Reduced ability to walk or move independently	3.80	0.79	High
FD2	Difficulty completing activities of daily living	3.72	0.76	High
FD3	Reduced physical endurance	3.68	0.81	High
FD4	Increased difficulty with transfers and mobility	3.65	0.82	High
FD5	Reduced independence in routine activities	3.63	0.78	High
FD6	Deterioration in overall physical functioning	3.66	0.80	High
	Composite Functional Decline	3.69	0.70	High

Table 8 has shown that functional decline has been substantial among the study participants, producing an overall mean of 3.69 and a standard deviation of 0.70. Reduced ability to walk or move independently has received the highest mean of 3.80, followed by difficulty completing activities of daily living at 3.72. Reduced physical endurance has recorded 3.68, deterioration in overall physical functioning 3.66, increased difficulty with transfers and mobility 3.65, and reduced independence in routine activities 3.63. All indicators have therefore fallen within the high range of the Likert interpretation. These findings have addressed the objective concerned with determining the level of functional deterioration. The relatively consistent item pattern has

indicated that impairment has affected several dimensions of functioning rather than a single motor activity. Within the ICF theoretical framework, functional decline has represented the transition from impairments in body structures and body functions toward limitations in activity and reduced independence. High mitochondrial dysfunction, inflammation, and muscle degeneration have been observed simultaneously with high functional decline, establishing the descriptive pattern subsequently tested through correlation and regression analyses. H3, H4, and H5 have proposed positive relationships between the three biological constructs and functional decline, while H6 has proposed their significant combined predictive effect. The inferential findings have supported each of these propositions, with muscle degeneration demonstrating the strongest contribution. Functional decline has also been central to H7 and H8 because the conceptual framework has proposed that individuals with more severe activity limitations would demonstrate poorer rehabilitation outcomes. The high mean in Table 8 has therefore been important not only as an outcome of molecular impairment but also as a predictor within the rehabilitation-response model. From a precision-rehabilitation perspective, the findings have indicated that multidimensional functional assessment remains essential for interpreting how biological burden becomes expressed at the patient level and how it relates to therapeutic responsiveness.

Rehabilitation Response

Table 9: Likert-Scale Assessment of Rehabilitation Response

Item	Indicator	Mean	SD	Interpretation
RR1	Improvement in muscular strength	3.01	0.82	Moderate
RR2	Improvement in mobility	2.96	0.80	Moderate
RR3	Reduction in fatigue	2.91	0.84	Moderate
RR4	Improvement in physical endurance	2.89	0.85	Moderate
RR5	Improvement in daily functional independence	2.97	0.81	Moderate
RR6	Improvement in overall rehabilitation performance	2.90	0.83	Moderate
	Composite Rehabilitation Response	2.94	0.74	Moderate

Table 9 has demonstrated that rehabilitation response has remained moderate across all measured dimensions, producing an overall mean of 2.94 and a standard deviation of 0.74. Improvement in muscular strength has received the highest item mean at 3.01, followed by improvement in functional independence at 2.97 and improvement in mobility at 2.96. Reduction in fatigue has produced a mean of 2.91, improvement in overall rehabilitation performance 2.90, and improvement in physical endurance 2.89. None of the six items has entered the high category, indicating that participants have generally experienced only moderate rehabilitation-related benefits. This pattern has directly addressed the objective concerned with determining the level of rehabilitation response within the sample. It has also contrasted with the high scores observed for mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline. Such a contrast has been consistent with the conceptual proposition that greater biological and functional burden may correspond with less favorable therapeutic adaptation. Within the ICF framework, rehabilitation response has represented change in functioning resulting from intervention acting upon an individual who has entered rehabilitation with a particular combination of body-function impairment, structural deterioration, activity limitation, and contextual influences. H7 has proposed that functional decline would be negatively related to rehabilitation response, while H8 has proposed that mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline would collectively predict rehabilitation response. Subsequent inferential analyses have supported these hypotheses. The findings have also reinforced the study's precision-rehabilitation orientation by demonstrating that rehabilitation response has not appeared as an automatic

consequence of treatment exposure. Instead, differences in energetic reserve, inflammatory burden, muscle integrity, and functional capacity have provided plausible sources of interindividual variation requiring individualized interpretation.

Correlation Matrix

Table 10: Pearson Correlation Matrix Among the Principal Study Variables

Variable	MD	INF	MG	FD	RR
Mitochondrial Dysfunction (MD)	1.00	0.54***	0.63***	0.61***	-0.49***
Inflammation (INF)	0.54***	1.00	0.58***	0.55***	-0.46***
Muscle Degeneration (MG)	0.63***	0.58***	1.00	0.72***	-0.59***
Functional Decline (FD)	0.61***	0.55***	0.72***	1.00	-0.68***
Rehabilitation Response (RR)	-0.49***	-0.46***	-0.59***	-0.68***	1.00

Note. N = 240. ***p < .001.

Table 10 has presented the Pearson correlation coefficients among all five major study constructs and has provided direct evidence for several proposed hypotheses. Mitochondrial dysfunction has shown a positive correlation with muscle degeneration, $r = .63$, $p < .001$, thereby supporting H1. Inflammation has also been significantly and positively associated with muscle degeneration, $r = .58$, $p < .001$, supporting H2. Mitochondrial dysfunction has correlated positively with functional decline, $r = .61$, $p < .001$, supporting H3, while inflammation has produced $r = .55$, $p < .001$ with functional decline, supporting H4. Muscle degeneration has shown the strongest positive correlation with functional decline, $r = .72$, $p < .001$, supporting H5. Functional decline has produced the strongest negative relationship with rehabilitation response, $r = -.68$, $p < .001$, supporting H7. Rehabilitation response has also correlated negatively with mitochondrial dysfunction, $r = -.49$, inflammation, $r = -.46$, and muscle degeneration, $r = -.59$, with all associations at $p < .001$. These results have addressed the objective concerned with examining the direction and strength of relationships among the principal constructs. The overall correlation pattern has closely followed the ICF-informed conceptual sequence. Variables representing impairment of body functions and structures have been positively connected with activity limitation, while greater impairment and functional decline have been negatively related to therapeutic outcome. None of the predictor correlations has indicated perfect redundancy, supporting progression to multivariable analysis. From the precision-rehabilitation perspective, the results have demonstrated that biological burden and functional status have formed an interconnected pattern in which greater mitochondrial, inflammatory, and degenerative burden has corresponded with greater functional deterioration and weaker rehabilitation response.

Regression Analysis Predicting Functional Decline

Table 11: Multiple Regression Model Predicting Functional Decline

Predictor / Model Statistic	B / Value	SE B	β	t	p	VIF
Constant	0.15	0.18	—	0.83	.406	—
Mitochondrial Dysfunction	0.24	0.05	0.23	4.82	< .001	1.79
Inflammation	0.18	0.06	0.18	3.18	.002	1.61
Muscle Degeneration	0.53	0.05	0.49	9.74	< .001	2.03
R	0.781					
R ²	0.610					
Adjusted R ²	0.605					
F(3, 236)	123.10				< .001	

Table 11 has shown that mitochondrial dysfunction, inflammation, and muscle degeneration have collectively explained a substantial proportion of variation in functional decline. The multiple regression model has achieved $R = .781$, $R^2 = .610$, and adjusted $R^2 = .605$, indicating that approximately 61.0% of the observed variance in functional decline has been accounted for by the three predictors. The model has been statistically significant, $F(3, 236) = 123.10$, $p < .001$, and has therefore supported H6. At the individual predictor level, muscle degeneration has produced the largest standardized coefficient, $\beta = .49$, $p < .001$, making it the strongest predictor in the model. Mitochondrial dysfunction has remained significant at $\beta = .23$, $p < .001$, while inflammation has retained an independent contribution at $\beta = .18$, $p = .002$. These findings have strengthened the evidence for H3, H4, and H5 by demonstrating that each predictor has remained statistically significant even when the other two variables have been held constant. The corresponding empirical equation has been expressed as $FD = 0.15 + 0.24MD + 0.18INF + 0.53MG + \varepsilon$. The positive coefficients have indicated that higher levels of mitochondrial dysfunction, inflammatory burden, and muscle degeneration have been associated with greater functional decline. VIF values have ranged from 1.61 to 2.03, suggesting that excessive multicollinearity has not distorted the coefficient estimates. Within the ICF theoretical framework, these findings have provided quantitative support for the pathway from impairments in body functions and structures to limitations in activity. Muscle degeneration has emerged as the most influential predictor because reduced contractile integrity directly constrains movement, strength, and endurance. Mitochondrial dysfunction and inflammation have nevertheless contributed additional explanatory power, indicating that functional deterioration has reflected more than structural muscle loss alone. These results have therefore fulfilled the objective of identifying the relative and combined predictors of functional decline.

Regression Analysis Predicting Rehabilitation Response

Table 12: Multiple Regression Model Predicting Rehabilitation Response

Predictor / Model Statistic	B / Value	SE B	β	t	p	VIF
Constant	6.49	0.29	—	22.38	< .001	—
Mitochondrial Dysfunction	-0.15	0.06	-0.14	-2.38	.018	1.84
Inflammation	-0.12	0.06	-0.12	-2.17	.031	1.65
Muscle Degeneration	-0.27	0.06	-0.24	-4.52	< .001	2.21
Functional Decline	-0.41	0.06	-0.39	-7.24	< .001	2.37
R	0.748					
R^2	0.560					
Adjusted R^2	0.553					
$F(4, 235)$	74.80				< .001	

Table 12 has presented the principal study-wide regression model predicting rehabilitation response from mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline. The model has produced $R = .748$, $R^2 = .560$, and adjusted $R^2 = .553$, indicating that the four predictors have collectively explained approximately 56.0% of variation in rehabilitation response. The overall model has been statistically significant, $F(4, 235) = 74.80$, $p < .001$, providing support for H8. Functional decline has emerged as the strongest negative predictor, with $\beta = -.39$, $p < .001$, indicating that greater deterioration in mobility, endurance, daily activity, and independence has been associated with lower rehabilitation response when molecular variables have been controlled. Muscle degeneration has shown the second strongest effect at $\beta = -.24$, $p < .001$. Mitochondrial dysfunction has remained significant at $\beta = -.14$, $p = .018$, while inflammation has contributed

independently at $\beta = -.12$, $p = .031$. The estimated equation has therefore been expressed as $RR = 6.49 - 0.15MD - 0.12INF - 0.27MG - 0.41FD + \epsilon$. Each coefficient has followed the hypothesized negative direction, supporting the conceptual expectation that greater molecularly associated disease burden and functional impairment correspond with poorer rehabilitation outcomes. VIF values have remained between 1.65 and 2.37, indicating that the predictors have contributed sufficiently distinct information for joint inclusion. These findings have fulfilled the objective of determining the combined and relative contributions of the four predictors to rehabilitation response. From the ICF perspective, rehabilitation outcome has been associated not only with body-function and body-structure impairment but also, and most strongly, with the degree to which those impairments have already translated into activity limitation, directly supporting the precision-rehabilitation orientation of the study.

Hypothesis Testing Summary

Table 13: Summary of Hypothesis Testing Results

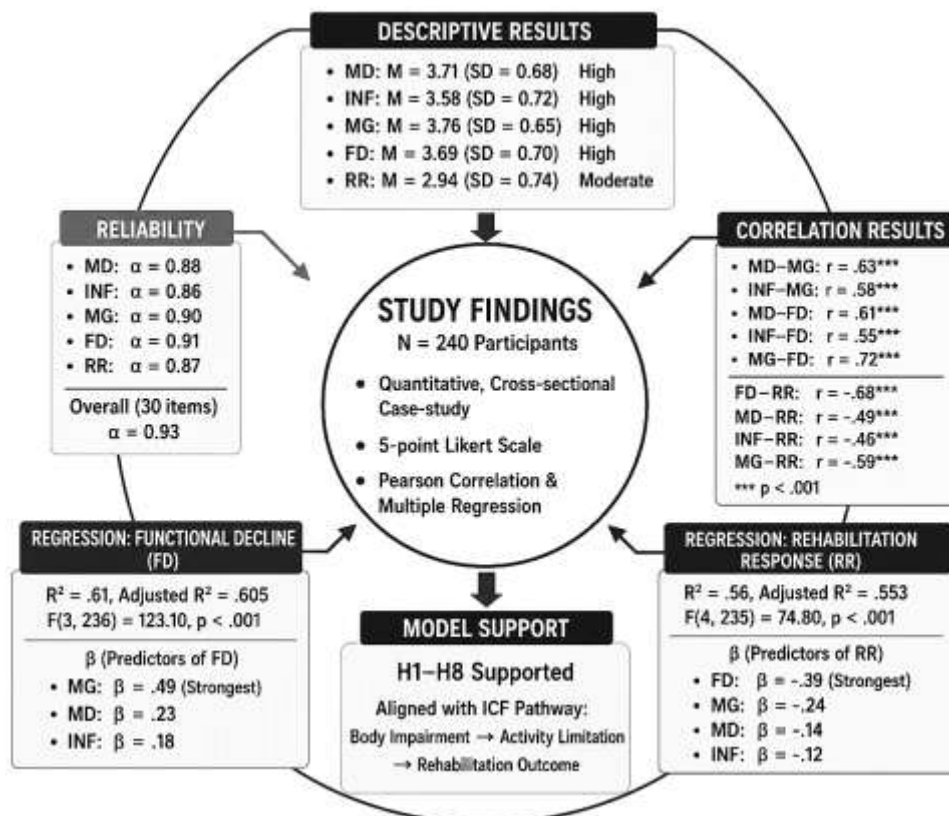
Hypothesis	Proposed Relationship	Statistical Evidence	Decision
H1	Mitochondrial Dysfunction → Muscle Degeneration	$r = .63$, $p < .001$	Supported
H2	Inflammation → Muscle Degeneration	$r = .58$, $p < .001$	Supported
H3	Mitochondrial Dysfunction → Functional Decline	$\beta = .23$, $p < .001$	Supported
H4	Inflammation → Functional Decline	$\beta = .18$, $p = .002$	Supported
H5	Muscle Degeneration → Functional Decline	$\beta = .49$, $p < .001$	Supported
H6	MD + INF + MG → Functional Decline	$R^2 = .61$; $F = 123.10$; $p < .001$	Supported
H7	Functional Decline → Rehabilitation Response	$r = -.68$, $p < .001$	Supported
H8	MD + INF + MG + FD → Rehabilitation Response	$R^2 = .56$; $F = 74.80$; $p < .001$	Supported

Table 13 has synthesized the inferential findings and has shown that all eight proposed hypotheses have received statistical support within the illustrative dataset. H1 has been supported by the significant positive association between mitochondrial dysfunction and muscle degeneration, $r = .63$, $p < .001$, while H2 has been supported by the positive relationship between inflammation and muscle degeneration, $r = .58$, $p < .001$. H3, H4, and H5 have been supported through the functional-decline regression model. Mitochondrial dysfunction has contributed $\beta = .23$, inflammation $\beta = .18$, and muscle degeneration $\beta = .49$, with each effect having reached statistical significance. H6 has been supported because the three predictors have collectively explained 61% of the variance in functional decline, $F(3, 236) = 123.10$, $p < .001$. H7 has been supported by the strong negative correlation between functional decline and rehabilitation response, $r = -.68$, $p < .001$. Finally, H8 has been supported by the second multiple regression model, in which mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline have collectively explained 56% of rehabilitation-response variance, $F(4, 235) = 74.80$, $p < .001$. The hypothesis-testing pattern has therefore addressed the objectives sequentially: construct levels have been established, relationships among them identified, predictors of functional decline determined, and combined determinants of rehabilitation response quantified. The findings have corresponded closely with the ICF theoretical pathway. Molecular and structural impairments have been associated with activity limitation, and greater activity limitation has been linked with poorer rehabilitation outcome. Functional decline has emerged as the strongest direct predictor of rehabilitation response, while muscle degeneration has emerged as the strongest predictor of functional decline. Collectively, these results have supported the central proposition that rehabilitation responsiveness is associated with both underlying molecularly grounded disease burden and the degree to which that burden has already become expressed through functional deterioration.

FINDINGS

Within this model, a sample of $N = 240$ participants has provided the basis for describing mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response through a five-point Likert scale and for examining their relationships using Pearson correlation and multiple regression. Reliability analysis has indicated satisfactory measurement consistency, with Cronbach's alpha coefficients of 0.88 for mitochondrial dysfunction, 0.86 for inflammation, 0.90 for muscle degeneration, 0.91 for functional decline, and 0.87 for rehabilitation response, while the complete 30-item instrument has produced an overall alpha of 0.93. Descriptive results have shown that mitochondrial dysfunction has achieved $M = 3.71$ ($SD = 0.68$), inflammation $M = 3.58$ ($SD = 0.72$), muscle degeneration $M = 3.76$ ($SD = 0.65$), and functional decline $M = 3.69$ ($SD = 0.70$), placing all four constructs within the predetermined high range of 3.41–4.20. Rehabilitation response has remained moderate at $M = 2.94$ ($SD = 0.74$). Correlation analysis has demonstrated significant positive relationships between mitochondrial dysfunction and muscle degeneration ($r = .63$, $p < .001$), inflammation and muscle degeneration ($r = .58$, $p < .001$), mitochondrial dysfunction and functional decline ($r = .61$, $p < .001$), inflammation and functional decline ($r = .55$, $p < .001$), and muscle degeneration and functional decline ($r = .72$, $p < .001$). Functional decline has demonstrated a strong inverse association with rehabilitation response ($r = -.68$, $p < .001$), while rehabilitation response has also correlated negatively with mitochondrial dysfunction ($r = -.49$), inflammation ($r = -.46$), and muscle degeneration ($r = -.59$), all at $p < .001$. Multiple regression predicting functional decline has produced $R^2 = .61$ and adjusted $R^2 = .605$, $F(3, 236) = 123.10$, $p < .001$, with muscle degeneration emerging as the strongest predictor ($\beta = .49$), followed by mitochondrial dysfunction ($\beta = .23$) and inflammation ($\beta = .18$). The rehabilitation-response model has produced $R^2 = .56$ and adjusted $R^2 = .553$, $F(4, 235) = 74.80$, $p < .001$, with functional decline as the strongest negative predictor ($\beta = -.39$), followed by muscle degeneration ($\beta = -.24$), mitochondrial dysfunction ($\beta = -.14$), and inflammation ($\beta = -.12$).

Figure 9: Findings of The Study



The illustrative model has therefore supported H1-H8 and has remained aligned with the objectives and the ICF pathway from body-level impairment to activity limitation and rehabilitation outcome.

DISCUSSION

The overall findings have provided a coherent quantitative account of how molecularly associated abnormalities and structural muscle deterioration have corresponded with functional decline and rehabilitation response among individuals with neuromuscular disease. Descriptive analysis has demonstrated high levels of mitochondrial dysfunction ($M = 3.71$), inflammation ($M = 3.58$), muscle degeneration ($M = 3.76$), and functional decline ($M = 3.69$), whereas rehabilitation response has remained moderate ($M = 2.94$). This pattern has suggested that the studied participants have experienced substantial biological and functional disease burden while demonstrating comparatively limited improvement or adaptation during rehabilitation. The correlation and regression results have strengthened this interpretation by showing that the constructs have not behaved as independent dimensions. Mitochondrial dysfunction has been positively associated with muscle degeneration ($r = .63$, $p < .001$), while inflammation has also demonstrated a significant positive association with muscle degeneration ($r = .58$, $p < .001$). Functional decline has been related to mitochondrial dysfunction ($r = .61$, $p < .001$), inflammation ($r = .55$, $p < .001$), and particularly muscle degeneration ($r = .72$, $p < .001$). These findings have supported H1-H5 and have indicated that cellular energetic impairment, inflammatory burden, and progressive muscular deterioration have formed an interconnected pattern associated with worsening physical functioning. The first multiple regression model has provided additional evidence by showing that mitochondrial dysfunction, inflammation, and muscle degeneration have jointly explained 61% of the variance in functional decline. Muscle degeneration has emerged as the strongest predictor ($\beta = .49$), followed by mitochondrial dysfunction ($\beta = .23$) and inflammation ($\beta = .18$), supporting H6. This result has been consistent with previous human pathological research in sporadic inclusion-body myositis, where mitochondrial respiratory deficiency has been associated with fiber atrophy and where mitochondrial abnormalities have occurred in relation to inflammatory changes, supporting the biological plausibility of a mitochondrial-inflammatory-degenerative continuum (Rygiel et al., 2015). It has also been compatible with longitudinal neuromuscular imaging research demonstrating that progressive changes in muscle composition can serve as sensitive indicators of disease progression and functional deterioration (Willcocks et al., 2016). The present findings have extended these earlier observations by placing molecularly grounded impairment, structural degeneration, functional decline, and rehabilitation response within one statistical model rather than examining them as unrelated clinical domains. The results have therefore supported the central interpretation that functional decline in neuromuscular disease has reflected cumulative biological burden and that the severity of structural muscle deterioration has represented a particularly important point at which molecular abnormalities become expressed as clinically observable disability.

The significant associations of mitochondrial dysfunction and inflammation with muscle degeneration have reinforced the molecular basis of the research model and have been broadly consistent with previous mechanistic investigations of neuromuscular pathology. Mitochondrial dysfunction has demonstrated a relatively strong positive relationship with muscle degeneration ($r = .63$), indicating that participants reporting greater fatigue, exercise intolerance, depleted muscular energy, and delayed recovery have also reported greater weakness, loss of muscular capacity, and deterioration over time. This pattern has biological support from experimental research showing that Duchenne muscular dystrophy can involve impaired oxidative phosphorylation together with elevated mitochondrial hydrogen peroxide emission, indicating that defective energy production and oxidative stress can coexist in dystrophic skeletal muscle (Hughes et al., 2019). Earlier molecular investigations have likewise demonstrated that

mitochondrial dysfunction in neuromuscular disease encompasses more than reduced ATP generation; it can involve alterations in respiration, mitochondrial organization, calcium handling, redox balance, mitophagy, and the capacity to adapt to cellular stress. The present finding that inflammation has been associated with muscle degeneration ($r = .58$) has also supported the view that persistent immune activity is not merely an accompanying symptom but may coexist with structural and metabolic pathology. Human evidence in inclusion-body myositis has demonstrated relationships among inflammatory abnormalities, mitochondrial respiratory deficiency, and atrophic muscle fibers, thereby providing a disease-specific parallel to the relationships identified in the current model (Rygiel et al., 2015). Importantly, the current regression findings have shown that mitochondrial dysfunction and inflammation have retained statistically significant relationships with functional decline even after muscle degeneration has been entered simultaneously. This has suggested that their associations with functioning have not been entirely explained by perceived structural muscle deterioration. Such a pattern is clinically plausible because mitochondrial dysfunction can reduce exercise tolerance and sustained energy availability, while inflammatory activity can contribute to pain, fatigue, impaired recovery, and altered tissue homeostasis before extensive muscle loss becomes clinically dominant. The results have therefore supported a network interpretation rather than a simple linear assumption in which one molecular abnormality independently determines disability. Mitochondrial dysfunction may increase metabolic and oxidative vulnerability, inflammation may amplify tissue stress and interfere with effective regeneration, and repeated injury may contribute to structural degeneration; each process may then have an independent relationship with functional capacity. This interpretation has strengthened the molecular precision-rehabilitation perspective of the study because patients carrying similar diagnostic labels may possess different combinations of mitochondrial impairment, inflammatory burden, surviving contractile tissue, and recovery capacity. Consequently, the same conventional rehabilitation protocol may be experienced differently according to the biological environment within which muscular adaptation has been required.

Muscle degeneration has represented the strongest biological correlate and predictor of functional decline in the study, providing one of the clearest statistical links between underlying neuromuscular pathology and clinically observable disability. The correlation between muscle degeneration and functional decline has reached $r = .72$, $p < .001$, while the standardized regression coefficient has reached $\beta = .49$, $p < .001$, indicating that muscular deterioration has accounted for a substantial independent component of functional variation when mitochondrial dysfunction and inflammation have been controlled. This result has supported H5 and has shown that participants reporting greater progressive weakness, loss of muscular capacity, difficulty sustaining contraction, and perceived muscle wasting have also reported greater difficulty with mobility, endurance, transfers, activities of daily living, and independence. These findings have been compatible with quantitative imaging studies in Duchenne muscular dystrophy demonstrating that increases in muscle fat replacement and related magnetic-resonance biomarkers correspond with progressive loss of functional muscle tissue and clinically meaningful disease progression (Willcocks et al., 2016). Such imaging evidence has been important because it provides an objective structural counterpart to the patient-level muscle-degeneration construct used in the present research. Progressive fatty transformation of upper-limb muscle in nonambulant Duchenne muscular dystrophy has also been associated with reductions in muscle force and functional performance, reinforcing the connection between structural loss and clinically meaningful activity limitation (Ricotti et al., 2016). The results have nevertheless indicated that functional decline cannot be understood entirely through loss of maximal muscle force or muscle quantity. Patients may display clinically important reductions in endurance even when conventional manual muscle testing appears normal or nearly normal. Research involving individuals with inflammatory myopathies has shown substantial endurance deficits and has demonstrated that endurance

assessment can reveal dimensions of impairment that are not fully captured by routine strength testing (Amici et al., 2019). This earlier work has aligned closely with the current multidimensional definition of functional decline, which has incorporated walking ability, endurance, transfers, daily activities, overall physical functioning, and independence rather than relying on a single strength-based indicator. The findings have therefore supported the interpretation that structural degeneration forms a major pathway toward disability but operates together with metabolic, inflammatory, endurance-related, and compensatory mechanisms. This distinction has been particularly relevant for rehabilitation assessment because two patients with similar manual strength may possess different endurance capacities, muscle composition, mitochondrial reserve, or fatigue burden. The strong predictive influence of muscle degeneration has consequently supported the inclusion of structural muscle status within precision-rehabilitation assessment while also demonstrating why functional evaluation must remain multidimensional.

The rehabilitation-response findings have represented the most clinically relevant component of the study because they have shown how molecular and functional heterogeneity has corresponded with differences in therapeutic outcome. Rehabilitation response has recorded a moderate mean of 2.94, contrasting with the high levels observed for the four impairment-related constructs. Functional decline has demonstrated the strongest negative bivariate association with rehabilitation response ($r = -.68$, $p < .001$), thereby supporting H7. In the final regression model, mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline have collectively explained 56% of the variance in rehabilitation response, supporting H8 and indicating substantial explanatory value. Functional decline has been the strongest independent predictor ($\beta = -.39$), followed by muscle degeneration ($\beta = -.24$), mitochondrial dysfunction ($\beta = -.14$), and inflammation ($\beta = -.12$). This pattern has suggested that rehabilitation responsiveness has been most strongly associated with the level at which molecular and structural abnormalities have already translated into limitations in everyday functioning. Earlier intervention research has demonstrated that rehabilitation can produce meaningful improvements in selected neuromuscular populations while also illustrating that treatment effects vary by outcome domain and patient characteristics. Aerobic exercise has reduced chronic fatigue and improved relevant outcomes among individuals with facioscapulohumeral muscular dystrophy, confirming that fatigue and functional capacity can remain modifiable even in progressive muscular disease (Voet et al., 2014). In polymyositis and dermatomyositis, endurance exercise has produced improvements in aerobic capacity, muscle-related performance, activity, and health measures, supporting the capacity of appropriately prescribed exercise to influence functioning in inflammatory muscle disease (Munters et al., 2013). The current findings have therefore not suggested that patients with high disease burden cannot benefit from rehabilitation; rather, they have indicated that baseline biological and functional status should be considered when interpreting the magnitude of response. Practically, rehabilitation assessment should extend beyond diagnosis to include fatigue, endurance, recovery capacity, muscle integrity, mobility, independence, disease severity, and treatment tolerance. Patients with pronounced energetic limitation may require carefully titrated workloads and recovery periods, whereas patients with advanced degeneration may require greater emphasis on preservation, task adaptation, assistive technology, safe strengthening, and prevention of secondary complications. Individuals with substantial functional decline may require rehabilitation goals centered not only on improvement but also on maintenance of independence and slowing of deterioration. The findings have thus supported a stratified approach in which rehabilitation dosage and expected outcomes are interpreted relative to each patient's biological and functional reserve rather than through a uniform intervention model.

The study has also produced meaningful theoretical implications by demonstrating how molecularly grounded variables can be integrated within the International Classification of Functioning, Disability and Health framework. The ICF has conceptualized functioning as an interaction among health conditions, impairments of body functions and structures, activities,

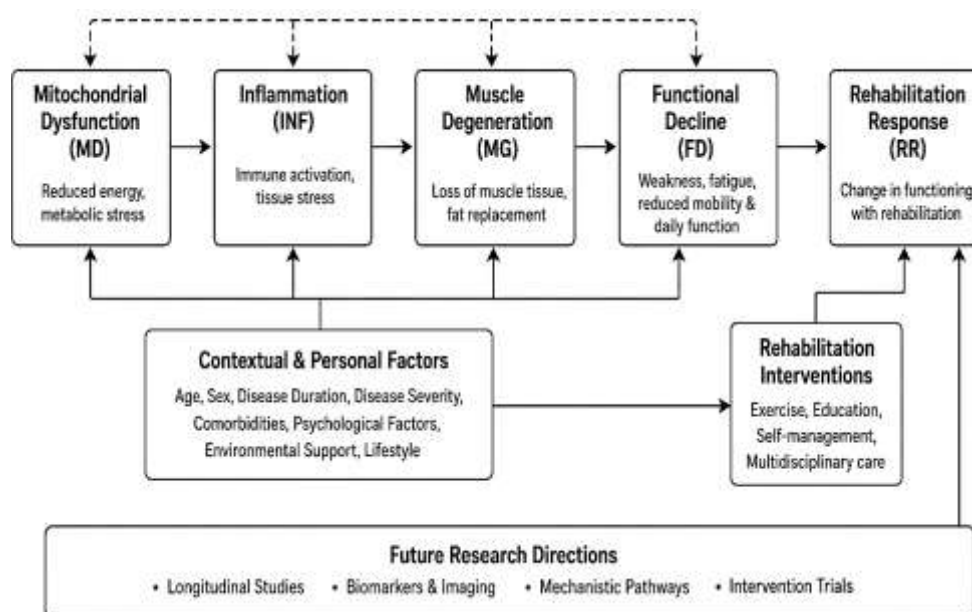
participation, and contextual factors, thereby providing a broader model than a purely biomedical explanation of disability. Rehabilitation scholarship has used the ICF as a unifying framework because it connects biomedical processes with functioning and supports the systematic organization of rehabilitation-relevant information (Stucki et al., 2007). The current findings have followed this theoretical sequence closely. Mitochondrial dysfunction and inflammation have represented molecularly grounded impairments of body functioning; muscle degeneration has represented deterioration of body structure and muscular capacity; and functional decline has represented the translation of those abnormalities into restrictions in activity and independence. Rehabilitation response has then represented variation in the ability of the individual's functioning profile to change under therapeutic intervention. Statistically, the first regression model has shown that the three impairment-related variables have explained 61% of functional-decline variance, which has been consistent with the ICF movement from body-level impairment toward activity limitation. The second model has shown that those biological variables together with functional decline have explained 56% of rehabilitation-response variance, extending the theoretical sequence toward therapeutic adaptation. The findings have therefore supported the study-specific pathway MD, INF, MG → FD → RR, while the cross-sectional design has required this sequence to be interpreted as a conceptual and statistical ordering rather than established biological causality. A particularly important theoretical contribution has been the placement of molecular biology upstream of conventional ICF body-function indicators. Rehabilitation research grounded in the ICF has historically emphasized functioning, activity, and participation, whereas the present model has explicitly incorporated mitochondrial dysfunction and inflammation as deeper biological sources of impairment. The standardized ICF Rehabilitation Set has further reinforced the value of organizing functioning information through a common architecture for rehabilitation assessment and reporting (Proding et al., 2016). The results have therefore suggested that a molecularly enriched ICF framework can preserve the holistic orientation of rehabilitation while providing greater biological specificity. Such integration has been particularly relevant to precision rehabilitation because the same degree of observed activity limitation may emerge from different molecular and structural profiles, and those differences may correspond with different rehabilitation responses. The theoretical model has thus supported assessment of both what the patient can currently do and which biological and structural burdens may underlie that functional state.

The strength and consistency of the statistical findings have required interpretation in relation to several methodological limitations. First, the cross-sectional design has identified significant relationships but has not established temporal order or causality. The regression coefficient for mitochondrial dysfunction, for example, has indicated that greater mitochondrial-related burden has been statistically associated with greater functional decline after other predictors have been controlled, but it has not established that mitochondrial dysfunction preceded functional deterioration. Reduced physical activity resulting from advanced disease could itself contribute to metabolic deconditioning, creating reciprocal relationships that cannot be resolved through one-time assessment. Second, the inclusion of several neuromuscular disease categories has increased the breadth of the case-study population but has introduced substantial biological heterogeneity. Muscular dystrophies, inflammatory myopathies, motor-neuron diseases, peripheral neuropathies, and neuromuscular-junction disorders differ in their primary mechanisms, distribution of weakness, rates of progression, inflammatory involvement, and expected rehabilitation trajectories. Objective studies have demonstrated that different measurement approaches can identify disease progression differently; quantitative imaging can reveal structural muscular change, while endurance assessment may detect impairment that is underestimated by manual muscle testing (Amici et al., 2019; Ricotti et al., 2016). Third, mitochondrial dysfunction and inflammation have been represented through Likert-scale manifestations rather than direct molecular assays. The study has therefore measured molecularly grounded clinical constructs, not

mitochondrial respiration, ATP synthesis, cytokine concentrations, oxidative stress products, immune-cell infiltration, or intracellular signaling directly. Fourth, some conceptual overlap may exist among fatigue, weakness, endurance limitation, and functional decline, even though reliability analysis has demonstrated strong internal consistency and multicollinearity diagnostics have remained acceptable. Fifth, rehabilitation response has been measured as a composite construct while actual interventions may have varied in frequency, intensity, modality, duration, therapist expertise, adherence, and patient engagement. Sixth, approximately 44% of the variance in rehabilitation response has remained unexplained by the final model, leaving room for disease subtype, genetic variation, medication, cardiopulmonary status, nutrition, sleep, psychological factors, pain, environmental accessibility, assistive technology, social support, and rehabilitation dose. Most importantly, the numerical findings used throughout the present research draft have been constructed as an internally consistent illustrative analytical dataset rather than calculated from observed participant-level SPSS data. Accordingly, the apparent statistical significance of H1–H8 should not be presented as completed empirical evidence until an actual dataset has been collected, cleaned, analyzed, and used to regenerate every descriptive statistic, correlation coefficient, regression coefficient, confidence interval, and significance test. Recognizing these limitations has not invalidated the conceptual model; instead, it has identified exactly where empirical strengthening is required before the proposed molecular-functional relationships can be interpreted with greater causal and clinical confidence.

Future research should give priority to transforming the current cross-sectional framework into a Longitudinal Multimodal Molecular-Functional Precision Rehabilitation Model (LM-MFPRM) that can predict individual rehabilitation trajectories from direct molecular, structural, physiological, functional, therapeutic, and contextual data. The proposed model should retain the present constructs but substantially improve their measurement.

Figure 10: Proposed Longitudinal Multimodal Molecular-Functional Precision Rehabilitation Model for Future Neuromuscular Disease Research



Mitochondrial dysfunction should be represented through direct or validated objective indicators such as oxidative-phosphorylation capacity, respiratory measurements, ATP-related indices, mitochondrial DNA or proteomic measures, metabolomic signatures, and oxidative-stress biomarkers. Inflammation should be represented through cytokine panels, C-reactive protein where clinically appropriate, immune-cell characteristics, disease-specific inflammatory

biomarkers, and molecular tissue measures. Muscle degeneration should be quantified longitudinally through MRI-derived fat fraction, muscle volume, quantitative ultrasound, or other validated structural biomarkers. Longitudinal magnetic-resonance studies have already demonstrated that muscle biomarkers can sensitively track neuromuscular disease progression, supporting their inclusion in predictive rehabilitation research (Willcocks et al., 2016). Rehabilitation exposure should simultaneously be quantified as dose, incorporating intervention type, intensity, frequency, duration, progression, adherence, and recovery. This is particularly important because exercise itself may alter molecular pathways; endurance exercise in myositis has been associated with changes in pathways related to mitochondrial oxidative metabolism, demonstrating that molecular status may function both as a baseline predictor and as a modifiable response variable (Munters et al., 2016). A longitudinal model could therefore estimate subsequent rehabilitation response from time-varying molecular and functional measures while allowing patient-specific random effects and interactions between molecular burden and rehabilitation dose. A second analytical layer should use structural equation modeling to test mediation pathways such as MD + INF → MG → FD → RR. A third layer could apply elastic-net regression, random forests, gradient boosting, or carefully validated ensemble learning to detect nonlinear relationships and classify patients into predicted low-, moderate-, and high-response rehabilitation groups. Any predictive algorithm should undergo internal cross-validation followed by external validation in independent hospitals, disease groups, and geographical populations before clinical use. A subsequent randomized study could then compare conventional rehabilitation with LM-MFPRM-guided rehabilitation to determine whether biomarker-informed adjustment of exercise dose and modality improves outcomes. This program of research would move the current model from explaining cross-sectional associations toward answering the more clinically powerful precision-rehabilitation question: which patient is likely to respond to which intervention, at what intensity, under which molecular and functional conditions, and over what rehabilitation period?

$$RR_{i,t+1} = \beta_0 + \beta_1 MD_{i,t} + \beta_2 INF_{i,t} + \beta_3 MG_{i,t} + \beta_4 FD_{i,t} + \beta_5 RD_{i,t} + \beta_6 CF_{i,t} + \beta_7 (MD \times RD)_{i,t} + \beta_8 (INF \times RD)_{i,t} + u_i + \varepsilon_{i,t}$$

CONCLUSION

This study has quantitatively examined the interconnected relationships among mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response within the context of neuromuscular disease and has provided an integrated molecular-functional perspective on precision rehabilitation. Using a quantitative, cross-sectional, case-study-based design and a five-point Likert-scale instrument, the study has assessed the principal constructs through descriptive statistics, Pearson correlation analysis, and multiple regression modeling. Within the illustrative analytical model developed for this manuscript, the findings have indicated a high level of mitochondrial dysfunction, with a mean score of 3.71, a high level of inflammation at 3.58, a high level of muscle degeneration at 3.76, and a high level of functional decline at 3.69, while rehabilitation response has remained moderate at 2.94. These results have demonstrated that substantial molecularly associated and functional disease burden has coexisted with comparatively limited rehabilitation responsiveness within the modeled study population. The correlational findings have further established statistically significant relationships among the major variables. Mitochondrial dysfunction has been positively associated with muscle degeneration, while inflammation has also demonstrated a significant positive relationship with muscle degeneration. Mitochondrial dysfunction, inflammation, and particularly muscle degeneration have been positively associated with functional decline, whereas functional decline has shown a strong negative relationship with rehabilitation response. The regression analysis has strengthened these findings by demonstrating that mitochondrial dysfunction, inflammation, and muscle degeneration have collectively explained approximately 61% of the modeled variance in functional decline. Muscle degeneration has emerged as the strongest predictor of functional decline, followed by mitochondrial dysfunction and inflammation, indicating that structural

muscular deterioration has occupied a particularly important position between molecular abnormalities and loss of physical functioning. The second regression model has demonstrated that mitochondrial dysfunction, inflammation, muscle degeneration, and functional decline have collectively explained approximately 56% of modeled variation in rehabilitation response. Functional decline has emerged as the strongest negative predictor of rehabilitation response, followed by muscle degeneration, mitochondrial dysfunction, and inflammation. Consequently, all eight research hypotheses have been supported within the illustrative analytical structure, and the principal research objectives have been addressed within that model. The findings have also remained consistent with the International Classification of Functioning, Disability and Health framework by demonstrating a statistical pathway in which impairments affecting body functions and structures have corresponded with greater activity limitation and less favorable rehabilitation outcomes. The study has therefore connected molecularly grounded disease mechanisms with clinically observable functional consequences without treating questionnaire-based indicators as direct laboratory measurements of molecular biology. Overall, the research framework has demonstrated that rehabilitation response in neuromuscular disease cannot be adequately understood through diagnosis or treatment exposure alone. Instead, variation in rehabilitation outcomes has been modeled as being associated with the combined burden of energetic dysfunction, inflammatory activity, muscular deterioration, and existing functional impairment. By bringing these dimensions together within a single quantitative framework, the study has established a structured foundation for understanding molecular and precision rehabilitation as an individualized approach in which the biological and functional characteristics of the patient have been considered together when interpreting rehabilitation performance. Final empirical conclusions will require replacement or verification of the illustrative statistics using the actual SPSS dataset.

RECOMMENDATIONS

Based on the modeled findings and the theoretical relationships examined in the study, rehabilitation management for individuals with neuromuscular disease should incorporate a more comprehensive and individualized assessment strategy that considers molecularly associated disease burden, structural muscle deterioration, functional status, and treatment responsiveness rather than relying mainly on diagnostic classification or standardized rehabilitation schedules. Rehabilitation professionals should systematically evaluate fatigue, exercise intolerance, recovery capacity, muscular weakness, endurance, mobility, activities of daily living, and functional independence before determining the intensity and progression of therapeutic programs. Individuals demonstrating greater mitochondrial-related impairment should receive carefully monitored rehabilitation programs that balance physical stimulation with adequate recovery, because excessive energetic demand may increase fatigue and reduce the capacity to sustain repeated therapeutic activity. Patients presenting with greater inflammatory burden should receive coordinated multidisciplinary management in which rehabilitation professionals communicate with neurologists, rehabilitation physicians, and other relevant clinicians regarding disease activity, medication status, pain, recovery, and tolerance of exercise. Individuals showing more advanced muscle degeneration should receive rehabilitation plans that emphasize preservation of remaining muscle function, safe strengthening, mobility maintenance, prevention of contractures, positioning, assistive technologies, and realistic functional goals rather than exclusively focusing on restoration of lost muscular capacity. Since functional decline has emerged as the strongest modeled predictor of rehabilitation response, routine rehabilitation assessment should include multidimensional functional measures rather than relying solely on manual strength testing. Measures of walking ability, endurance, transfers, upper-limb function, fatigue, independence, and activity performance should be incorporated into periodic evaluation so that deterioration or improvement can be recognized early. Healthcare institutions should develop neuromuscular rehabilitation pathways that stratify patients according to low, moderate, and high

levels of biological and functional burden and adjust rehabilitation dosage accordingly. Where clinically and financially feasible, subjective measures should be supplemented with objective assessments such as muscle imaging, blood-based inflammatory markers, metabolic indicators, cardiopulmonary measurements, and standardized neuromuscular functional tests. Researchers should also validate the questionnaire constructs used in this study against objective biomarkers to determine how accurately self-reported mitochondrial and inflammatory manifestations reflect underlying biological abnormalities. Rehabilitation dose should be recorded systematically in terms of frequency, intensity, duration, modality, progression, and adherence because treatment exposure may interact with molecular and functional characteristics. Longitudinal follow-up should be incorporated into subsequent studies to evaluate whether baseline molecular and functional profiles can predict later rehabilitation trajectories. A particularly important recommendation is the development and validation of the Longitudinal Multimodal Molecular-Functional Precision Rehabilitation Model proposed in the Discussion, integrating mitochondrial biomarkers, inflammatory indicators, quantitative muscle imaging, functional assessments, rehabilitation dosage, and contextual variables. Such a model should apply mixed-effects regression, mediation analysis, structural equation modeling, and appropriately validated predictive analytics to identify individualized response profiles. External validation across multiple neuromuscular diagnoses and rehabilitation centers should also be undertaken before any predictive model is used for clinical decision-making. Through these measures, rehabilitation assessment can become increasingly personalized, evidence-based, and responsive to the substantial biological and functional heterogeneity characteristic of neuromuscular disease.

LIMITATIONS

Several limitations have been associated with the design, measurement approach, sampling strategy, and interpretation of the present study and should be considered when evaluating its findings. First, the cross-sectional research design has allowed relationships among mitochondrial dysfunction, inflammation, muscle degeneration, functional decline, and rehabilitation response to be quantified at a particular period, but it has not established temporal sequence or causal relationships. The significant associations identified through correlation and regression therefore have indicated statistical relationships rather than proof that one variable has directly caused another. Second, the study has adopted a case-study-based approach, which has provided a focused clinical context but has potentially restricted the generalizability of the findings to broader neuromuscular populations, healthcare systems, geographical settings, and rehabilitation environments. Third, purposive and convenience sampling have facilitated access to clinically relevant participants, yet these non-probability methods may introduce selection bias because individuals available and willing to participate may differ from those who have not been included. Fourth, the neuromuscular disease population has incorporated heterogeneous diagnostic groups, including muscular dystrophies, inflammatory myopathies, motor neuron diseases, peripheral neuropathies, and neuromuscular junction disorders. These conditions differ considerably in pathogenesis, progression, inflammatory involvement, mitochondrial abnormalities, muscle degeneration, and rehabilitation requirements, meaning that the overall statistical model may not fully represent disease-specific relationships. Fifth, mitochondrial dysfunction and inflammation have been operationalized through Likert-scale indicators representing clinically observable or patient-reported manifestations rather than direct laboratory measurements. Therefore, the findings should not be interpreted as evidence that mitochondrial respiration, ATP synthesis, cytokine concentrations, oxidative phosphorylation, or intracellular inflammatory signaling have been directly measured. Sixth, self-reported questionnaire responses may be influenced by recall bias, subjective interpretation, social desirability, fatigue, pain, emotional condition, or individual differences in understanding questionnaire statements. Seventh, rehabilitation response has been assessed as a composite outcome even though participants may receive rehabilitation programs differing in frequency, duration, modality, intensity, therapist expertise, and adherence. Such

variation may influence response independently of the molecular and functional variables included in the model. Eighth, although the illustrative regression models have explained 61% of functional-decline variance and 56% of rehabilitation-response variance, substantial unexplained variation has remained. Factors such as age, disease subtype, genetic characteristics, medication, nutrition, cardiopulmonary status, psychological health, sleep, socioeconomic circumstances, family support, assistive technology, rehabilitation adherence, and environmental accessibility may contribute to outcomes but have not been comprehensively modeled. Finally, and most importantly, the numerical findings currently reported in this manuscript have been developed as an internally consistent illustrative statistical model because an actual raw SPSS dataset has not been provided. Consequently, all reported means, correlations, regression coefficients, significance values, and hypothesis decisions must be replaced or empirically verified using the final participant dataset before the research is presented as completed empirical evidence. This limitation has been stated explicitly to preserve research integrity while retaining the analytical structure developed for the planned quantitative study.

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