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The Effect of Photobiomodulation on the Treatment of Hereditary Mitochondrial Diseases

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Abstract

Introduction: Despite a wide variety of clinical presentations in hereditary Mitochondrial Diseases, muscle fatigue is a common theme and impairs a patient's quality of life and ability to function. Current treatments are only supportive and include nutritional supplementation and physical therapy. Photobiomodulation therapy (PBMT) using low-intensity, narrow spectrum light in the red/near infrared (NIR) range, from a low-level laser or light-emitting diode sources, enhances mitochondrial function in preclinical and clinical studies on a range of conditions. However, little research has been done on the effectiveness of photobiomodulation in hereditary mitochondrial disorders.

Methods: We performed a scoping review of the evidence of the beneficial effects of photobiomodulation for treating the muscle-related symptoms of hereditary mitochondrial disease.

Results: No studies regarding photobiomodulation in hereditary mitochondrial disease were identified. However, in other clinical conditions featuring acquired mitochondrial impairment, we identified studies that suggested improved function, although sample sizes were small in number and statistical power.

Conclusion: There is emerging evidence of efficacy for PBMT for diseases involving acquired mitochondrial insufficiency. We identified no published research on PBMT in hereditary mitochondrial disease, but this review confirms a theoretical rationale for a positive effect and suggests further research.

Keywords: Photobiomodulation; Mitochondrial disease; Near-infrared; Cytochrome oxidase; Fatigue; Muscle.

Introduction

Mitochondrial diseases are a group of genetic disorders featuring impaired oxidative phosphorylation and characterised by reduced cellular energy levels, cellular insufficiency, risking progression to cell death, and organ failure.[1] Mitochondria have their own genome, the so-called mitochondrial DNA (mtDNA) which is present in thousands of virtually identical copies in every cell ("homoplasmy"). mtDNA is maternally transmitted because the sperm contributes no mtDNA to the embryo. The number and variety of possible mitochondrial diseases, due to genetic mutations or rearrangements, is large and complex. The mitochondrial structure comprises over 1500 different protein components, largely encoded by nuclear DNA (nDNA) and mtDNA.[2] The 100 proteins involved in oxidative phosphorylation are spread across both genomes, therefore mitochondrial diseases display a range of types of heritability. While healthy individuals' mitochondria are termed "homoplasmic", sufferers from the mitochondrial diseases are frequently "heteroplasmic", harbouring a mix of mutated and normal mitochondria within each cell. The proportion of mutant mtDNA affects overall function and hence the clinical presentation of mitochondrial disease.

Mitochondrial diseases are some of the most common causes of inherited metabolic or neurological diseases and arise from mutations in nuclear and mitochondrial DNA, leading to defective mitochondrial proteins and functional impairment.[3] Organs or tissues with high energy or metabolic requirements are particularly vulnerable to exceeding their mitochondrial functional capacity if the underlying proteins are defective. This can lead to oxidative stress and mitochondrial and cell failure with apoptosis, especially in energetically active brain, retina, and muscle tissue.[4] The spectrum of disease severity is wide, from a progressive course with high mortality to more benign forms in adults.[5]

The clinical presentation of mitochondrial disease is also complicated by the level of heteroplasmy, or proportional mix of mutated and normal mitochondria within each cell, thus affecting overall function.[6] There is currently no definitive treatment to correct the abnormal proteins or restore function. Management comprises supportive therapy with dietary modifications to reduce toxin accumulation and increase fuel substrate availability.[7] Photobiomodulation therapy (PBMT) is a

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form of non-thermal, non-ionizing, light therapy utilising light sources, including low-level lasers, light emitting diodes (LEDs), and broadband light, to promote tissue repair or reduce inflammation. An array of other terms, including photostimulation, low-level laser therapy, and biostimulation, has arisen since the field emerged, with a consensus on PBMT as the term of choice. Specific wavelengths of red or near infrared (NIR) light, within the region of 640 nm to 900 nm, have specific cellular effects and also superior tissue penetration. The electron transport chain (ETC) in the mitochondrial membrane, hosts oxidative phosphorylation. Some of these proteins, known as chromophores, are stimulated by light, which therefore increases metabolic activity and ATP production.[8] PBM therapy is becoming increasingly used in diverse areas of medicine. There is, therefore, a rationale for use in mitochondrial disease where profound fatigue and muscular weakness affect patients, due to deficient oxidative phosphorylation.[9] We first review the basic processes of oxidative phosphorylation and the pathophysiological features of mitochondrial disease and then propose how PBMT can potentially improve some of these features.

Mitochondria: Structure and Function

Mitochondria are cell organelles that provide energy in the form of ATP for driving the majority of cell functions. Cells can house hundreds to many thousands of mitochondria depending on the cell type and its energy requirements.[10] Within mitochondria, a convoluted inner mitochondrial membrane (IMM) divides the inner mitochondrial matrix from the outer inter-membranous space. The two compartments enable the ETC to create an electromotive potential difference across the membrane to drive ATP synthesis.[11] Mitochondria take up fuel substrate in the form of 3-carbon pyruvate, formed from glucose. Pyruvate drives the citric acid cycle within the inner matrix to produce reducing agents including NADH. The resulting high energy electrons are fed into a cascade of five protein complexes, the ETC, situated within the IMM. Complex IV, cytochrome C oxidase (COX), facilitates the final transfer of electrons onto oxygen. Oxygen when reduced and coupled with protons, pumped from the matrix, forms water. The resulting proton deficit in the matrix, relative to the intermembranous space, creates a charge difference forming an electrochemical gradient across the IMM.[12] This electromotive force is harnessed to drive the ATP synthase enzyme complex to produce ATP. In practice, the enzyme complex is a molecular motor that is rotated by the flow of protons. The wheel-like rotation generates movements to combine ADP and Phosphate ions, thus catalysing the synthesis of ATP. Previously, COX was held to be a rate-limiting step in the ETC, and therefore, it exerted a regulatory role in ATP synthesis. Within COX, where O_2 molecules are split, excess oxygen radicals not combined into H_2O form unpaired, reactive oxygen species (ROS). ROS is mostly neutralised by superoxide dismutase, but it has important roles in intracellular signalling, REDOX, and inflammatory functions.[13]

Mitochondria can function collectively within a cell and autonomously in isolation, partially due to retaining their own DNA as a historical remnant from when mitochondria evolved from bacteria around 1.5 billion years ago.[14] Mitochondria contain multiple copies of this double stranded circular DNA, the genes of which code for a small proportion of the total ETC proteins. Compared with nDNA, there are limited repair mechanisms for mtDNA, which therefore degrades over time, from oxidative or environmental stresses.[15] In contrast to nDNA, mitochondria undergo continual regenerative processes of mitogenesis, fusion and division, and mitophagy.[16] This enables the orderly disposal of degraded mtDNA and enables the integrity of the mitochondrial population to be maintained. The dynamic process also enables mitochondrial numbers to upregulate to changing cellular requirements and maintain cellular homeostasis.[17]

Mitochondrial Diseases

The number and variety of possible mitochondrial diseases, due to genetic mutations or rearrangements, is large and complex. Combinations of defects across the range of mitochondrial proteins may lead to insignificant or catastrophic changes in function. The 100 proteins involved in oxidative phosphorylation, forming the basis of many mitochondrial diseases, are spread across both nuclear and mitochondrial genomes. Mitochondrial disease due to mutations in nDNA can therefore display autosomal dominant, autosomal recessive, or X-linked inheritance. Mutations in genes in mtDNA will follow strictly maternal inheritance as paternal mtDNA is discarded from the fertilised oocyte during conception.[18]

Although the Mendelian classification of these disorders is complex, in practice the clinical disorders tend to be clustered into syndromes based on the organs affected, with the symptom acronym forming the name. For example, MELAS syndrome is characterized by Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes.[19] Nearly 80% of all cases of MELAS syndrome harbour an m.3243A > G mutation in the MT-TL1 gene.

Even with this pragmatic classification, strict categorization is often impossible as many patients do not easily fit the criteria of syndromes.

Mitochondrial disease can be broadly divided into those of childhood onset, usually under 3 years of age and more severe, and those presenting in early and mid-adulthood, although milder disease can present in even later decades. An individual may present with impairment of single organs such as eyes, although most patients present with multi-organ involvement, with additional organs

becoming affected over time.[20]

For reasons incompletely understood, each gene mutation can develop into different clinical syndromes. This discrepancy between genotype and disease phenotype can further complicate disease classification. Patients with the m.3243A < G mutation may present with chronic progressive external ophthalmoplegia (CPEO), MELAS, or maternally inherited diabetes and deafness (MIDD), or they may remain asymptomatic throughout life as gene carriers. With mutations such as m.3243 A < G, the disease penetrance may be as low as 10%.[21] The level of heteroplasmy present in cells is important in determining disease states, although the roles of epigenetic and environmental influences remain incompletely defined.[22]

In childhood disease, which tends to be more severe, sensorineural hearing loss, retinal disease, cardiomyopathy, and brainstem or cortical degeneration are possible presenting symptoms. Diagnosis and classification of mitochondrial disease presenting in adults is a greater challenge due to the vast range of possible symptoms and severities.

Approximately 10% of all mitochondrial diseases feature a formal myopathy characterised histologically by "ragged red" fibres on histological examination of muscle biopsies.[23] However, less easily definable but almost universal in patients are symptoms of muscular fatigue.[24] Fatigability of the muscles of the eyes and eyelids (ptosis) is well described in mitochondrial disease, but the leg muscles of locomotion are also greatly affected. Fatigue is an increasingly recognised hallmark across all mitochondrial diseases and is variously described by patients as a lack of energy, mental or physical tiredness, diminished endurance, and the need for a prolonged recovery after physical activity.[25] The aetiologies of the forms of fatigue remain poorly understood and involve muscular and central nervous system origins.[26] Despite the difficulties in the terminology of fatigue and quantifiable metrics, in chronic diseases featuring mitochondrial impairment, physical fatigue measures correlate closely with observed changes in mitochondrial density and function in terms of enzyme levels, markers of oxidative stress, ATP production and fatty acid metabolism.[27] In genetic mitochondrial disease, anecdotal evidence suggests a much less clear relationship between symptoms and cellular deficits.

Due to the subjectivity in fatigue symptoms, difficulty in diagnosis and lack of direct treatments, fatigue and physical activity difficulties tend to go underdiagnosed in many chronic conditions, and mitochondrial disease is no exception. This contributes to the overall increased symptom burden and poorer quality of life in these patients.[28] The Newcastle functional scoring questionnaire (NMDAS), as a systematic measure of all mitochondrial symptoms, quantifies Exercise Tolerance between 0 and 5 and has a separate domain for myopathic muscle weakness.[29]

Subjective symptoms can be correlated with objective biomarkers for standardisation. Muscle oxygen consumption as measured by near infrared spectroscopy (NIRS) is a direct marker of *in vivo* cytochrome-c oxidase (Complex IV) and ETC activity, which relates to fatigability.[30] In conditions featuring acquired mitochondrial impairment, fatigue is associated with reduced citrate synthase (oxidative phosphorylation activity), reduced levels of Complexes I –IV, and increased levels of ROS and F2 isoprostane.[27] Abnormal carnitine levels also indicate disturbed fatty acid metabolism within the mitochondrial matrix.[31]

Current Supportive Treatments for Mitochondrial Disease

Despite significant developments in the understanding of the genetics and pathophysiology of mitochondrial disease, there has been little progression in routine treatment, with disappointingly few therapies.[32] For most patients, treatment consists of exercise and dietary supplements of uncertain symptom benefits and no effect on halting disease progression. Multiple vitamins and cofactors are often prescribed in patients with mitochondrial disorders, although these therapies are not yet standardized and lack a strong evidence base of efficacy. Dietary supplements are employed with different objectives, such as increasing respiratory chain flux (Co-enzyme Q10, riboflavin), serving as antioxidants (e.g. Co-enzyme Q10, idebenone, α-lipoic acid, vitamin C and E), acting as cofactors (e.g. riboflavin, thiamine), or functioning as mitochondrial substrates (L-carnitine).[33] In Leber hereditary optic neuropathy: a disorder characterised by painless, subacute visual loss (of the central visual field) in one eye, treatment consists of anti-oxidant supplementation.[34] MELAS, which features stroke-like episodes related to nitric oxide (NO) deficiency, benefits from arginine, which promotes NO synthase.[35]

Mechanisms of Photobiomodulation Therapy

Biological tissues contain a range of chromophores. These are molecules such as water, haemoglobin, cytochromes and flavins, which are capable of absorbing light energy at certain wavelengths, corresponding to intramolecular vibration frequencies. Water molecules significantly absorb light energy at wavelengths greater than 970 nm, whilst wavelengths shorter than 600 nm are absorbed by flavins, haemoglobin, and melanin.[36] Within the intervening window of 600 to 970 nm, representing red and NIR light, lie the absorption peaks of cytochromes, principally Cytochrome c oxidase (COX) of the ETC. COX is the terminal enzyme in the ETC and contains Haem and copper centres responsible for electron transfer from cytochrome C to O_2 molecules, enabling the membrane potential to drive ATP synthase.[37] Specific wavelengths of

light in the red or NIR spectrum excite electrons in the Copper (Cu) centres of COX causing NO dissociation from Cu, increasing binding availability for O_2 and hence ETC activity and ATP synthesis. Conventionally, the wavelengths 670 nm, 740 nm and 850 nm are the light sources most commonly utilised. Increased ETC activity also generates calcium (Ca^{2+}) ions and ROS, leading to the activation of transcription factors, intracellular signals and growth factors including transforming growth factor β, brain-derived neurotrophic factor and platelet-derived growth factor.[38,39] Photobiomodulation, therefore, has downstream cellular and extracellular effects long after light exposure.

By improving the efficiency of the ETC, PBM has a regulatory effect on ROS and NO homeostasis. Increased ROS has the beneficial effects described above, whereas excessive ROS and NO, which cause oxidative and nitrosative stress with organelle damage and apoptosis, are prevented.[40,41]

Although COX stimulation is well described, the precise mechanism of PBM causing excitation of the ETC has not been fully established.

For instance, PMB may also increase the efficiency with which the ETC converts the potential across the IMM into chemical energy. It does this by reducing the viscosity of the nano water layer over the IMM (the "interfacial water layer") and thus enabling the ATP synthase molecular motor to turn more rapidly.[42]

Other theories attribute the increased ETC activity by PBM to light-sensitive calcium channels and NO synthase activation. It is possible that each plays a contributory role.[43]

In addition to increasing mitochondrial ETC activity, PBM exerts effects on key inflammatory mediators including NF-κB, a key inflammatory transcription factor and associated cytokines.[44]

The highly dynamical nature of the ETC system would suggest that the responses to stimulation by light are nonlinear, possibly corresponding to discrete excitation and stability states of the ETC. This is observed in practice where doses below or above optimal stimulation fail to induce ETC activity. The Arndt–Schultz's response curve describes the dose-dependent effects of PBM.[45] It demonstrates that a weak stimulus is sufficient to trigger ETC activity, whilst further stimuli have an inhibitory effect, and with extreme stimulation, the activity is eliminated. The inverted U response is seen with PBM on ETC activity across cell and tissue types and emphasises the importance of tight control and monitoring of the exposure dose. The optimal dose fluency is 1-5 J/cm^2.[46] This accumulated dose is a function of device power and duration. Therefore, in addition to light wavelength specificity, the power of light used (in milliwatts), energy density (fluence) of the beam in J/cm^2, beam area and irradiation times, and frequencies are all variables to be considered when evaluating PBM interventions and comparing them between studies.

In clinical practice, PBM therapy involves exposure from an LED or low-level laser, light source, with a typical duration of 1-3 minutes. ETC activity is seen to start increasing from 15-30 minutes post-exposure in vitro and clinical improvements in muscle outcomes 24-96 hours post-exposure. Once stimulated, the mitochondria and surrounding cellular responses persist for up to 5 days.[47] To avoid over-exposure inhibition effects, treatment regimens often comprise short low-dose exposures at set intervals over several days.[48]

Safety Considerations

When evaluating any potential therapy involving light, which is a form of electromagnetic radiation, it is important to consider the safety aspects and possible adverse effects. Although PBM therapy could refer to any wavelength, the term is used to describe wavelengths in the red or near infrared light (600-1000 nm) spectrum as the biological effect of ETC activation only occurs in this region.

PBM therapy is not to be confused with other forms of light treatment such as ultraviolet (UV) therapy from the opposite end of the light spectrum. Short wavelength light such as ultraviolet light (100-400 nm) has an ionising effect on cellular molecules, and treatment doses are designed to have a controlled destructive effect. UV treatment is well established in medical practice in the treatment of psoriasis[49] and other dermatological conditions. Blue light is used to treat neonatal jaundice.[50]

PBM treatment using light in the longer range of wavelengths (600-1000 nm) relies on molecular resonation effects, not ionization. There are no cytotoxic effects of red or NIR light at therapeutic doses. Extensive research in clinical efficacy and specific safety research have reported no adverse effects of PBM.[51]

Clinical Use of PBM

PBM therapy has gained popularity as a mode of treatment in diverse areas of clinical practice. On the premise that red light exposure promotes cell division, tissue repair and remodelling, PBMT has been employed in sports injuries,[52] dental procedures,[53] wound healing in plastic surgery,[54] in spinal cord injury[55] and diabetic peripheral neuropathy.[56]

Emerging research indicates that PBM has demonstrated a beneficial effect on central nervous system (CNS) disorders, such as traumatic brain injury,[57] stroke,[58] and depression,[59] in addition to degenerative CNS diseases such as Parkinson's disease[60] and Alzheimer's disease.[61] This may be due to the high energetic requirements of neurons and their vulnerability to mitochondrial impairment.

In the case of CNS disease, PBM therapy has the added advantage of 600-1000 nm light being able to penetrate

through bone to brain areas usually inaccessible to other treatments.[62] In the CNS, PBM appears to promote neurogenesis which may be a function of light stimulated increase in metabolic activity.[63]

PBM for Muscle Fatigue Symptoms in Hereditary Mitochondrial Disease; Literature Search

We performed a semi-systematic search of PubMed and Google Scholar databases using the terms "*photobiomodulation, low level, low power, laser therapy, red light, photostimulation, biostimulation, and photobiotherapy*", within the domain of muscle-related symptoms for all hereditary mitochondrial diseases.

No published studies were identified with these terms, and therefore, no statistical analysis was possible. Unpublished research by the current authors is suggestive of improved muscle oxygen uptake and reduced exercise recovery time, after exposure to 670 nm light in patients with m.3243 A < G mutation disease.

Although no studies addressing PBMT and hereditary mitochondrial conditions were identified, scoping evidence was identified in acquired and experimentally-induced forms of mitochondrial impairment.

In animal models of mitochondrial dysfunction due to denervation-induced muscle atrophy, PBMT from a laser light source, had both preventative and restorative effects 6 weeks after a single dose.[64] Muscle involvement in mitochondrial disease is characterised by raised blood lactate and creatine kinase as markers of stress and microdamage without excessive exercise.[65] While relatively insensitive, there is some correlation between symptoms of pain and functional scores. In other scenarios of muscle stress, such as excessive exercise in healthy adults and athletes, creatine kinase (CK) and lactate levels are markedly reduced following PBM therapy in the form of low-level laser therapy.[66] Studies suggest that pre- or post-exercise PBM therapy exerts equal effect[67] or that post-exercise exposure is most effective.[68] The dose of light delivered to muscles in trials is measured in multiples of individual diodes or lasers used, and the time of exposure. For example, a 400 mW diode producing a power density of 11 W/cm^2 for 25 seconds produces a total light dose of 10 J. Typical exposures are in the range of 10-50 J.[69]

Discussion

This is the first paper to suggest PBM as a potential treatment for fatigue and reduced exercise capacity in hereditary mitochondrial disease. Although we identified no current direct studies, further research is supported by both theoretical and clinical rationale and indirect evidence from acquired mitochondrial disease. Muscle tissue contains high densities of mitochondria, which struggle to maintain normal levels of oxidative phosphorylation in mitochondrial disease. In mitochondrial disease, clinical symptoms of fatigue correlate with biochemical markers of muscle stress (CK, lactate), oxidative stress (superoxide dismutase), and reduced ETC activity (citrate synthase). Numerous systematic reviews have demonstrated the effect of narrow wavelength, red or NIR light on improving these blood levels of muscle stress in animals[70] and in healthy individuals[71-75] (See Table 1).

We hypothesise that PBM will have a similarly beneficial effect on hereditary mitochondrial disease. Although the precise target sites of PBM therapy are still disputed, all of the prevailing theories agree on the net outcome of increased ETC activity and ATP and ROS production. Other extracellular effects of PBMT such as vasodilatation from endothelial NO release would also tend to improve, rather than exacerbate, mitochondrial disease symptoms.[76] One effect of PBMT is the "abscopal effect" whereby light exposure in one area of the body has distant beneficial effects elsewhere. These remote effects of PBMT have been described in other treatments, such as radiotherapy, and relates to signalling peptides such as cytokines in the circulation.[77] In a mouse model of Parkinson's disease, BPMT at a distant site exerted a neuroprotective effect on the brain. Mitochondrial disease is a systemic condition with multisystem involvement. It is plausible that single-site PBMT in these patients exerts multi-site effects.[78]

Similar to other patient groups, there are no obvious contraindications of PBMT to patients with mitochondrial disease or significant risk of adverse effects.

Conclusion

Knowledge of mitochondrial diseases in recent years has clarified the central role of ETC dysfunction in the aetiology of mitochondrial disease symptoms. Clinical, in vitro and animal studies have shown the benefits of narrow spectrum low-level red or NIR light exposure (PBMT) on functionally impaired muscle tissue by stimulating ETC activity. Despite short exposure treatment, benefits can

Table 1. Reviews of Clinical Studies Assessing PBMT on Muscle Performance and Recovery

First Author	Review	Studies	Muscle Recovery and Pain Metrics	Muscle Performance
Ferraresi[71]	Narrative	46	Reduced recovery time and inflammation	Enhanced muscle mass and performance
Fisher[72]	Critical	5	Reduced muscle recovery time	Enhanced performance
Felito [73]	Meta-analysis	4	Reduced recovery time & soreness but inflammation unaffected	Enhanced muscle strength
Clijsen[74]	Meta-analysis	18	Reduced non-exercise muscle pain	Not assessed
Vanin[75]	Meta-analysis	39	Not assessed	Improved muscle strength and time to exhaustion

persist for days or weeks and appear to be cumulative with additional exposures. There are currently no clinical studies of PBMT in reducing muscle symptoms in patients with Mitochondrial Disease, although initial studies are ongoing. The authors conclude that PBMT, which has a low cost and high safety profile, warrants further research for the muscular and fatigue symptoms in mitochondrial disease, for which there is currently no effective treatment.

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Conceptualization: Richard Baskerville, Nykle Krijgsveld, Patrick Esser, Glen Jeffery, Joanna Poulton.
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Project administration: Richard Baskerville.
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Writing–review & editing: Richard Baskerville, Joanna Poulton, Patrick Esser, Nykle Krijgsveld, Glen Jeffery.

Competing Interests
The authors declare that they have no conflicts of interest.

Ethical Approval
Not applicable.

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