Mitochondrial myopathies: developments in treatment

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Purpose of review

Treatment options for mitochondrial myopathies remain limited despite rapid advances in the understanding of the molecular basis of these conditions. Existing therapies continue to be evaluated and novel treatment strategies are starting to appear on the horizon.

Recent findings

Exercise training continues to show promise as a method of improving exercise tolerance and enhancing oxidative capacity. Coenzyme Q10 deficiency appears to be a relatively common finding in mitochondrial disorders and is likely to benefit from exogenous supplementation. Large-scale randomized clinical trials to evaluate these treatment options are now underway and this represents one of the most important developments in recent years. Activation of the peroxisome proliferator-activated receptor/peroxisome proliferator-activated receptor-γ coactivator-1α pathway has been shown to induce mitochondrial biogenesis leading to a delayed onset of myopathy and prolonged lifespan in mouse models. A ketogenic diet has also been found to induce mitochondrial biogenesis in mice with mitochondrial myopathy.

Summary

Therapeutic trials of exercise training and coenzyme Q10 supplementation should continue to be offered to patients with mitochondrial myopathies pending the results of evaluation in randomized clinical trials. Further investigation of peroxisome proliferator-activated receptor/peroxisome proliferator-activated receptor-γ coactivator-1α pathway activation, ketogenic diets and other new strategies is required.

Keywords

coenzyme Q10, exercise training, mitochondrial myopathies, peroxisome proliferator-activated receptor/peroxisome proliferator-activated receptor-γ coactivator-1α pathway, treatment

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Introduction

Mitochondria are intracellular organelles that are responsible for energy production. The mitochondrial respiratory chain (MRC), which consists of five protein complexes, generates adenosine triphosphate (ATP) via a process known as oxidative phosphorylation. The components of the MRC are encoded for by both mitochondrial DNA (mtDNA) and nuclear DNA, and genetic mutations in either can result in mitochondrial disorders due to impaired function of the MRC. Mitochondrial myopathy is a term that encompasses a subclass of clinically heterogeneous conditions in which there is a neuromuscular component. The prevalence of mtDNA disease appears to be higher than previously appreciated and it represents one of the commonest forms of inherited neuromuscular and metabolic disease [1].

Whilst understanding of the molecular basis of mitochondrial disease has developed rapidly over recent years, treatment options have remained limited and mainly rely upon supportive therapies rather than correction of the underlying deficiencies. Anecdotal reports and small-scale nonrandomized trials have demonstrated promising findings for several therapeutic options although these have yet to be substantiated by larger-scale randomized studies. This article will review recent developments in these treatment options and also identify novel therapeutic strategies that are currently under investigation.

Exercise

Exercise training represents a promising therapeutic option for patients with mitochondrial myopathies. Resistance training and endurance training have both been investigated. The proposed modes of action for these two types of training are different, and are discussed in turn below.

The rationale underpinning the use of resistance training relates to a concept known as gene shifting. Each mitochondrion contain multiple copies of mtDNA and in the

presence of a mtDNA mutation there is a mixed population of wild-type mtDNA and mutant mtDNA, which can vary between cells, a situation referred to as heteroplasmy. It is believed that the proportion of mutant mtDNA needs to exceed a threshold in order to exert a pathological effect and it has therefore been suggested that shifting the proportion to below this threshold will have a beneficial effect [2]. Evidence in support of this approach came from two studies in patients with muscle specific mtDNA mutations. These patients had undetectable levels of mutated mtDNA in skeletal muscle satellite cells. The myotoxic agent bupivacaine [3] and resistance training [4] have been shown to activate quiescent satellite cells which fused with the skeletal muscle fibres, increasing the ratio of wild-type DNA to mutant mtDNA and correcting the biochemical defect in some muscle fibres. A recent study [5•] of 12 weeks resistance training in eight patients with mtDNA deletions reported improvements in muscle strength and oxidative capacity and an increase in the proportion of satellite cells, although a significant decrease in the level of mutated DNA was not found with this particular training regime.

The rationale for endurance training is that it may help to overcome the effects of deconditioning that occurs due to inactivity as a result of exercise intolerance, and also to promote increases in mitochondrial biogenesis [6]. Short-term endurance training in patients with heteroplasmic mtDNA disorders has been reported to lead to an increase in oxidative capacity [6–8] as well as improvements in sub-maximal exercise tolerance and quality of life [6]. However, this was not accompanied by a decrease in the proportion of mtDNA [6,8], and one study [7] actually reported an increase in mutational load leading to a call for longer-term studies to evaluate the safety of this type of training. A recent study [9•] looking at long-term training in four patients with mtDNA mutations reported that an increase in oxidative capacity with 3 months of moderate intensity training was sustained by 6–12 months of low-intensity training and did not result in any adverse effects.

A study [10] investigating whether mitochondrial disorders led to a preferential use of fat or carbohydrates during moderate intensity exercise concluded that manipulating the proportion of dietary fat and carbohydrate content would not work as means of improving exercise tolerance. Albuterol, a selective beta-adrenergic agonist, has been used experimentally in combination with aerobic exercise therapy in a few inherited neuromuscular disorders to increase muscle strength and muscle volume. A recent paper reported a significant clinical improvement in a 9-year-old boy with central core disease and mitochondrial dysfunction due to compound heterozygous RYR1 mutations [11].

Studies looking at exercise as a therapeutic option have suffered from small cohorts of patients and a lack of randomization. A recent Cochrane review article [12] on the topic only identified one randomized clinical trial [13] that met its inclusion criteria and concluded from this trial that aerobic exercise and strength training combined appeared to be safe in patients with mitochondrial myopathy and could increase submaximal endurance capacity. Encouragingly, a long-term randomized cross-over clinical trial which aims to recruit 50 patients with mitochondrial myopathy is underway and should provide further information on the use of exercise as a therapeutic option [14].

Coenzyme Q10

Coenzyme Q10 is a lipophilic mobile electron carrier which is located in the inner mitochondrial membrane. It is an important component of the MRC and its absence disrupts the flow of electrons from complexes I and II to complex III. In addition, it may also have a beneficial effect through its role as a scavenger of reactive oxygen species. Primary coenzyme Q10 deficiency occurs as a result of mutations in the genes controlling coenzyme Q10 biosynthesis. Anecdotal evidence appears to support the assertion that patients with primary coenzyme Q10 deficiency are likely to benefit from exogenous coenzyme Q10 administration [15,16]. The benefits of supplementation in other mitochondrial disorders are less well established [17]. However, the lack of any reported adverse side effects and the absence of suitable alternative options has meant that it is often common practice to offer a trial of coenzyme Q10 treatment to patients with mitochondrial disease [18].

A recent multicentre study [19•] was carried out to establish the frequency of coenzyme Q10 deficiency in a cohort of 76 patients with clinically heterogenous mitochondrial myopathies and found coenzyme Q10 deficiency in 36% of patients. A similar previous study [20] reported a reduction in coenzyme Q10 activity in *22%* of patients with clinical suspicion and/or a biochemical–molecular diagnosis of a mitochondrial disorder, although this was most apparent in a subgroup of patients with reduced MRC enzyme activities. An association between coenzyme Q10 deficiency and mtDNA depletion was reported in skeletal muscle of a single patient [21]; however, the clinical implications of this observation need further investigations. These studies appear to suggest that coenzyme Q10 deficiency is a relatively common finding in patients with mitochondrial myopathy.

The above study [19•] also reported a subjective improvement in exercise intolerance, fatigue, cramps and stiffness in seven out of eight patients with coenzyme

Q10 deficiency that received coenzyme Q10 supplementation for at least 12 months. This compared with only 1 patient out of 15 with normal coenzyme Q10 levels reporting a subjective improvement of fatigue with supplementation. Detailed information on this aspect of the study is not provided making interpretation of these findings difficult, but they would appear to support the logical hypothesis that patients with demonstrable coenzyme Q10 deficiency are more likely to benefit from supplementation.

A much needed randomized placebo-controlled, double-blinded trial to assess the safety and efficacy of coenzyme Q10 in patients with mitochondrial disorders is underway [22]. In addition, double-blinded, randomized, placebo-controlled studies assessing the role of idebenone, a synthetic form of coenzyme Q10, in the treatment of both MELAS (mitochondrial enchephalopathy, lactic acidosis and stroke-like episodes) and Leber's heriditary optic neuropathy are also in progress [23,24].

L-Arginine

L-Arginine has been proposed as a possible treatment option for patients with MELAS. It acts as a donor of nitric oxide, which induces vasodilation and therefore may reduce the impact of stroke-like episodes in this group of patients. Studies have reported that intravenous administration of L-arginine in the acute phase can reduce symptoms of stroke [25], whilst long-term oral administration of L-arginine resulted in a decrease in both the frequency and severity of stroke-like episodes [26]. A recent case report of a 12-year-old child with MELAS reported a rapid disappearance of symptoms with oral administration of L-arginine [27].

An observation that the epileptic status of patients appeared to improve with administration of L-arginine during the acute phase of stroke-like episodes has led to speculation that it may also have an effect on neuronal stability. A study [28] investigating this suggestion indicated that L-arginine may modulate the excitability of neurons by effecting the uptake of glutamate and release of gamma-aminobutyric acid. Although these findings appear promising, concerns have been raised about the safety of L-arginine [29] and a long-term randomized controlled trial to evaluate its role is required.

Cysteine donor supplementation

An increase in oxidative stress biomarkers was detected in blood samples of 27 patients with different types of mitochondrial disease [30]. A double-blind crossover study evaluated whether a 30-day supplementation with a whey-based cysteine donor could modify these markers, reduce lactate concentration during aerobic exercise, or enhance muscular strength and quality of life. Treatment did not modify lactate concentration, clinical scale or quality of life (SF-36), but significantly reduced oxidative stress levels. The significance of these results needs further evaluation.

Removal of toxic metabolites

The disease mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is due to a defect of the enzyme thymidine phosphorylase. This leads to an imbalance of mitochondrial nucleosides with an increase of thymidine levels. A recent study [31] provided an in-vivo model of this in mice with thymidine phosphorylase deficiency. The brains of these mice developed partial depletion of mtDNA, encephalopathy and respiratory chain complex deficiencies. One suggested treatment strategy is the removal of excess thymidine nucleosides. Haemodialysis has been used but the metabolites re-accumulated shortly after the procedure [32].

Enzyme replacement

An alternative approach for MNGIE patients is to attempt to replace thymidine phosphorylase activity. Infusion of platelets [33] and administration of carrier erythrocyte entrapped thymidine phosphorylase [34] both only resulted in a transient reduction in thymidine levels. A possible solution to the problem of the rapid elimination of thymidine phosphorylase is offered through the development of polymeric 'nanoreactors', which are enzymatically active and stable in blood [35], although further investigation of this delivery method is required.

A more promising approach is allogeneic stem cell transplantation [36], however less than 10 patients have been treated with this method thus far. A recent consensus conference on this treatment led to a welcome development in the form of a proposed standardized treatment protocol and approach to patient assessment that should help facilitate evaluation of the efficacy and safety of this treatment [37].

Nucleotide supplementation

Mitochondrial DNA depletion syndrome (MDS) is due to reduced mtDNA copy number in different tissues and results in respiratory chain deficiencies. Mutations in nuclear genes involved in the regulation of mitochondrial nucleotide pools leading to an imbalance in these pools have been identified as contributing to MDS [38] and it has been hypothesized that nucleotide supplementation may be beneficial. A recent study [39] reported a significant increase in mtDNA copy number in myotubes of patients with a mutation in deoxyguanosine kinase

(DGUOK) following in-vitro supplementation with dAMP/dGMP, although this was not seen with mutations in polymerase gamma (POLG). This technique is only in the initial stages of investigation and the authors also acknowledge that an excess of nucleosides could have a detrimental effect.

Activation of peroxisome proliferator-activated receptor/peroxisome proliferator-activated receptor-γ coactivator-1α pathway

A potential therapeutic option which has been the subject of several recent studies is that of manipulating the peroxisome proliferator-activated receptor (PPAR)/PPAR-γ coactivator-1α (PGC-1α) pathway. PPARs are a subfamily of the nuclear receptors responsible for regulating gene expression programmes of metabolic pathways and mitochondrial biogenesis is modulated by PGC-1α, which is a PPAR-γ coactivator. PPAR-γ activation has been found to enhance the ability of cells to maintain their mitochondrial potential [40]. Fibrates have been shown to induce PGC-1α expression in cardiac and skeletal muscle [41]. It has been hypothesized that activation of the PPAR/PGC-1α pathways could play a therapeutic role by increasing mitochondrial biogenesis.

A recent study [42] demonstrated that administration of bezafibrate, a PPAR agonist, resulted in increased activity of complexes I, III and IV enzymes and therefore may be able to correct deficiencies in the respiratory chain. The question of whether activation of this pathway can lead to improve clinical outcomes was investigated in a mouse model of mitochondrial myopathy where mitochondrial biogenesis was induced by either transgenic expression of PGC-1α in skeletal muscle or by administration of bezafibrate [43•]. Both approaches stimulated respiratory capacity in muscle tissue and mitochondrial biogenesis leading to an enhancement of oxidative phosphorylation capacity. The overall outcome was a delayed onset of myopathy and increased life expectancy. It is noteworthy that endurance training in mice with mitochondrial myopathy also resulted in increased PGC-1α in muscle leading to increase mitochondrial biogenesis and again a delay in onset of myopathy and a prolongation of lifespan [44•]. Another recent study [45•] looked at PGC-1α induced expression in cell lines from patients with complex III and IV deficiencies and patients with the MELAS A3243G mutation and reported an increase in respiratory capacity of these cell lines.

Ketogenic diet

Another proposed treatment of interest is the use of a ketogenic diet, consisting of high lipid and low glucose content. The rationale underpinning this approach comes from studies demonstrating that an increase supply of

Table 1 Summary of recently identified human disease genes and some selected clinically significant findings in 2009–2010 in reverse chronological order

	Mitochondrial disease	Significance	Reference
Novel human disease genes			
AIFM1 (X-linked)	Mitochondrial encephalo-myopathy with combined respiratory chain deficiency	Novel pathomechanism: apoptosis inducing factor, mtDNA depletion	Ghezzi *et al.* [51•]
TRMU	Mitochondrial reversible hepatopathy	Age-dependent manifestation and reversibility	Zeharia *et al.* [52]
TACO1	Leigh syndrome and optic atrophy with COX deficiency	Novel pathomechanism: translation activator of the mitochondrial COXI	Weraarpachai *et al.* [53]
SDHAF1	Leukodystrophy with complex II deficiency	Assembly defect of complex II	Ghezzi *et al.* [54]
GFER	Myopathy with cataract and combined respiratory chain deficiency	mtDNA dysintegration and instability	Di Fonzo *et al.* [55]
COQ9	Multisystem mitochondrial disease with coenzyme Q deficiency	Although patient died, possibility of supplementation	Duncan *et al.* [56]
Other findings			
Pronuclear transfer	mtDNA mutations	Prevention of the transmission of mitochondrial disease	Craven *et al.* [57]
m.14674T>C in tRNA-Glu	Infantile reversible COX deficiency myopathy	Easy detection of a severe but reversible infantile disease	Horvath *et al.* [58•]
RRM2B mutations	Autosomal-dominant PEO	In addition to mtDNA depletion, RRM2B may also lead to multiple mtDNA deletions	Tyynismaa *et al.* [59]
Contiguous gene deletion containing *NDUFAF2*	Fatal multisystem disease with complex I deficiency	Chromosomal rearrangements need to be considered in mitochondrial disease	Janssen *et al.* [60]

COX, cytochrome *c* oxidase; PEO, progressive external ophthalmoplegia.

ketone bodies has led to increased mitochondrial biogenesis [46] and a shift in heteroplasmy towards an increase in wild-type mtDNA [47]. It has also been reported that a ketogenic diet reduced the frequency of seizures in patients with epilepsy and respiratory chain complex deficiencies [48]. A recent study [49] also reported a decrease in seizure frequency in a patient with Alpers–Huttenlocher syndrome.

An in-vivo study [50•] of the effects of a ketogenic diet in a mouse model for late-onset mitochondrial myopathy reported a decrease in the number of cytochrome *c* oxidase (COX) negative muscle fibres and increased mitochondrial biogenesis. The overall outcome was a delay in disease progression. In addition the mice with myopathy did not develop the detrimental accumulation of large lipid pools and steatosis-associated inflammation in the liver that was seen in control mice.

New gene mutations/disease mechanisms

Understanding of the molecular basis of mitochondrial disease continues to advance rapidly. A summary of clinically relevant, recent discoveries is provided in Table 1 ([51•,52–57,58•,59,60]). Such advances are likely to provide ideas for potential therapeutic strategies. One example is the discovery of a novel X-linked mitochondrial encephalopathy in two male infants caused by mutations in the *AIFM1* gene [51•]. Fibroblasts from both patients showed reduction of respiratory chain complexes III and IV; however, in one patient, supplementation with riboflavin led to correction of respiratory chain defects and improvement in neurological condition.

Another example is the identification of a homoplasmic mutation, which causes infantile reversible COX deficiency myopathy [58•]. In this condition, unlike other childhood onset COX deficiency mitochondrial diseases, which are usually progressive and fatal, the child makes a spontaneous recovery if they survive a critical postnatal period of severe weakness and respiratory failure. Interestingly, some homoplasmic mutation carriers do not develop any signs of myopathy, strongly suggesting the existence of protective disease modifiers. An understanding of the mechanisms behind the improvements seen in these conditions may offer valuable information that can be applied to the development of future treatments.

Conclusion

Treatment options for mitochondrial myopathies remain limited and recent studies have continued to investigate new and existing strategies (see Table 2). Coenzyme Q10 supplementation and exercise training are the therapeutic options that have offered most hope thus far,

Table 2 Summary of recent important studies investigating treatment options for mitochondrial myopathies

Treatment	Reference	Condition	Main findings
Resistance training	Murphy *et al.* [5•]	Single, large-scale mtDNA deletions	Increased strength, increased numbers of satellite cells
Endurance training (long-term)	Jeppesen *et al.* [9•]	mtDNA mutations	Increased oxidative capacity
Dietary fat and carbohydrate content manipulation	Jeppesen *et al.* [10]	mtDNA mutations	Not a feasible therapeutic option
Coenzyme Q10	Sacconi *et al.* [19•]	Clinically heterogenous mitochondrial phenotypes	Coenzyme Q10 deficiency common. Subjective improvement in subgroup of deficient patients with supplementation
Cysteine donor supplementation	Mancuso *et al.* [30]	Various types of mitochondrial disease	Reduced oxidative stress levels
Nucleotide supplementation	Bulst *et al.* [39]	DGUOK and POLG1 mutations	Increase in mtDNA copy number in myotubes of DGUOK mutations
PPAR/PGC-1α pathway activation (transgenic expression and bezafibrate)	Wenz *et al.* [43•]	Mouse model of COX deficiency	Increased mitochondrial biogenesis, delayed onset of myopathy
PPAR/PGC-1α pathway activation (endurance exercise)	Wenz *et al.* [44•]	Mouse model of COX deficiency	Increased mitochondrial biogenesis, delayed onset of myopathy
PGC-1α/β induced expression	Srivastava *et al.* [45•]	Complex III and IV deficiency and MELAS	Increased respiratory function of cell lines
Ketogenic diet	Ahola-Erkkila *et al.* [50•]	Mouse model for late-onset mitochondrial myopathy	Increased mitochondrial biogenesis, slowed disease progression

COX, cytochrome *c* oxidase; DGUOK, deoxyguanosine kinase; MELAS, mitochondrial enchephalopathy, lactic acidosis and stroke-like episodes; POLG1, polymerase gamma-1; PPAR/PGC-1α, peroxisome proliferator-activated receptor/peroxisome proliferator-activated receptor-γ coactivator-1α.

and recent studies have continued to support their use. Given that both of these treatments appear to be safe, there is no reason to discourage the already widespread practice of trialling these treatment modalities in patients with a variety of mitochondrial disorders. The need for randomized clinical trials with large patient cohorts is widely acknowledged [61,62]. Crucially, for exercise training and coenzyme Q10 supplementation at least, such trials are now in progress. This represents an important step forward and the results of these trials will be eagerly awaited.

New approaches to therapy continue to be postulated and investigated. Perhaps the most promising of these involves utilizing activation of the PPAR/PGC-1α pathway to increase mitochondrial biogenesis. Initial findings also suggest that a ketogenic diet may play a beneficial role in mitochondrial disorders. The challenge that lies ahead is the translation of positive laboratory findings for these and other novel strategies into safe and effective therapies for patients. Finally, although not the focus of this article, recent advances in preventing the transmission of mtDNA mutations with spindle transfer [63] and nuclear transfer [57] provide new hope that we will be able to prevent some of these diseases in the future.

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