National Institutes of Health
Office of Dietary Supplements

Dietary Supplements for Primary Mitochondrial Disorders

Fact Sheet for Health Professionals

Expand All

Introduction

Primary mitochondrial disorders (PMDs) are a heterogeneous group of disorders characterized by impaired mitochondrial structure or function due to mutations in nuclear or mitochondrial DNA [1]. PMDs are the most common inborn errors of metabolism and have a prevalence of approximately 1 in 5,000 individuals [1,2]. Diagnosis, treatment, and day-to- day management of these diseases remain challenging and costly [1].

The metabolic pathway most affected in PMDs is the mitochondrial electron transport chain (ETC), which is the most important pathway for producing energy in the form of adenosine 5'-triphosphate (ATP) [3]. The ETC, found in the inner membrane of the mitochondria, consists of four protein complexes commonly referred to as complexes I, II, III, and IV, along with two mobile electron carriers (ubiquinone or coenzyme Q [CoQ] and cytochrome c) and the ATP synthase complex [4]. ETC dysfunction reduces ATP production, increases anaerobic metabolism (which can lead to elevated lactate concentrations in the blood [lactic acidosis] and/or cerebrospinal fluid [CSF]), and increases free radical production, which can lead to oxidative stress and additional cellular damage and dysfunction.

Tissues that have high energy requirements are the most affected in PMDs. These tissues include the central nervous system, peripheral nerves, eyes, ears, skeletal and cardiac muscles, kidneys, endocrine organs, and gastrointestinal tract. Patients typically present with multisystem or organ-specific disorders [4,5]. The clinical features of PMDs vary and have been reviewed elsewhere [5,6]. Central neurological features include encephalopathy, seizures, stroke-like episodes, dementia, ophthalmoplegia, and hearing deficits. Peripheral neurological features include myopathy (signs include fatigue and exercise intolerance), ataxia, and peripheral neuropathy [5].

To date, these disorders have no cures. However, clinicians use a variety of modalities to treat patients with PMDs, including prescription drugs, specialized diets, and exercise to provide symptomatic relief and slow the progression of clinical symptoms [5,7-10]. Consensus-based recommendations for standardized treatment and preventive health care of patients with PMDs have been published [11]. In addition, clinicians often prescribe one or more dietary supplements for these patients because of their potential beneficial effects on patient symptoms. Dietary supplements are designed to supplement the diet and, by law, may not be marketed to treat, mitigate, or cure diseases [12]. Nevertheless, clinicians

can and do use them for these purposes [10], and patients also frequently manage their disease with these products [13].

Certain dietary supplements may be of value in treating PMDs because, as nutrients and metabolic cofactors, they help increase mitochondrial ATP production, bypass a cellular defect (e.g., a deficiency in the activity of complexes I, II, or III in the ETC), or remove toxic metabolites [9,14].

However, few randomized controlled trials (RCTs) have assessed the effects of dietary supplements in PMDs, and studies have investigated the effects of only a few ingredients in dietary supplements singly or in combination in patients with PMDs [5]. Furthermore, much of the published positive evidence for dietary supplements to manage PMDs comes from studies with designs that do not demonstrate that the intervention studied was responsible for the observed health effects (e.g., case reports as well as retrospective and open-label studies) or from underpowered small clinical trials [10,15,16].

Even when evidence from RCTs (which can demonstrate cause-effect relationships) is available to support the use of one or more dietary supplements to treat a PMD, the use of these products in patient care can be challenging. The reasons include the variability of study designs, dosing regimens, and duration of the interventions tested; differences in clinical and biochemical parameters assessed; small samples; and the clinical, biochemical, and genetic heterogeneity of these disorders [4]. In addition, recruitment of patients to clinical trials has been challenging because of the wide availability and use of certain supplements (e.g., CoQ_{10}) by patients with PMDs before joining the studies. Some patients are reluctant to join a study that might assign them to a placebo group and temporarily stop them from using the supplement, which they believe would jeopardize their clinical status [17,18].

This fact sheet summarizes published scientific trials, other studies, and reports in the English language on the use of dietary supplements to treat PMDs. The PMDs targeted by the studies that are discussed here are:

- Chronic progressive external ophthalmoplegia (CPEO)
- Cytochrome c oxidase (complex IV in the ETC) deficiency
- Kearns-Sayre syndrome (KSS)
- Leber's hereditary optic neuropathy (LHON)
- Leigh syndrome
- Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- Myoclonic epilepsy with ragged-red fibers (MERRF)
- Neurogenic weakness, ataxia, and retinitis pigmentosa (NARP)

Dietary Supplements Commonly Used for Primary Mitochondrial Disorder Therapy

The most commonly used dietary supplement ingredients for PMDs include antioxidants, such as vitamin C, vitamin E, and alpha-lipoic acid; electron donors and acceptors, such as CoQ_{10} and

riboflavin; compounds that can be used as alternative energy sources, such as creatine [14]; and compounds that can conjugate or bind mitochondrial toxins, such as carnitine [10].

Some mitochondrial disorder specialists begin treating PMDs with one ingredient, whereas others use several ingredients together because of their potentially synergistic effects [19]. A combination of three to six compounds is generically referred to as a mitochondrial cocktail [12]. However, there is large variation in the composition of combination products and dosages, and there is no standardization among them [12]; thus, the commonly used term mitochondrial cocktail is nonspecific and nondescriptive. According to one survey, when more than three compounds are recommended to be taken together, most physicians use a compounding pharmacy [19].

Tables 1 and 2 summarize information on the proposed mechanisms of action, efficacy, and safety of the dietary supplement ingredients that are most commonly used for PMDs. These ingredients and combinations are listed in the tables in alphabetical order, and the information on their safety comes from assessments in healthy people, people with PMDs, or people with other conditions. References to support statements in Tables 1 and 2 are provided in the subsequent text.

Table 1. Common Dietary Supplement Ingredients Used in Primary Mitochondrial Disorders

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Evidence of Safety
Alpha-lipoic acid (ALA)*	Cofactor for mitochondrial alpha-keto acid dehydrogenases; also acts as an antioxidant	Case report in a patient with CPEO; no RCTs with ALA alone **Research findings**: Beneficial effect on brain and skeletal muscle energy metabolism	No safety concerns reported for oral administration of 600 mg/day for 6 months to 4 years **Reported adverse effects**: None known
Arginine	Precursor of nitric oxide (NO) that stimulates vasodilation; believed to reduce the severity and frequency of stroke-like episodes in patients with MELAS	Small open-label studies in patients with MELAS given oral or intravenous arginine; no RCTs **Research findings**: Reduced symptoms and frequency of stroke-like episodes; improved cerebral blood flow and endothelial function	No safety concerns reported for oral administration of up to 9 g/day for several weeks **Reported adverse effects**: Diarrhea, nausea, and slightly reduced blood pressure with 9–30 g/day Hyperkalemia, hyponatremia, and death with high doses

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Evidence of Safety
			of intravenous (IV) L-arginine-hydrochloride
Carnitine*	Involved in transfer of long-chain fatty acids into mitochondria for β-oxidation; removal of toxic acetyl coenzyme A metabolites	One RCT in patients with CPEO and mitochondrial myopathy; small open-label study in patients with CPEO, KSS, MELAS, mitochondrial encephalomyopathy, or Leigh's disease **Research findings**: Improved lung function and aerobic exercise performance during intense constant-work exercise test in patients with CPEO; improved muscle strength, exercise tolerance, growth, and cardiac function	No safety concerns with intakes below 2 g/day; safety of long-term supplementation not well studied **Reported adverse effects**: Diarrhea, fishy odor, fatigue, and gastrointestinal upset with approximately 3 g/day
Citrulline	Precursor of arginine, the precursor of NO, which stimulates vasodilation; hypothesized to reduce the severity and frequency of stroke-like episodes in patients with MELAS	Small kinetic studies in patients with MELAS; no RCTs **Research findings**: Increases plasma arginine and NO production more than arginine	No safety concerns reported with 6 g/day for 4 weeks, or 1.35 g/day for 6 weeks **Reported adverse effects**: Gastrointestinal discomfort
Coenzyme Q_{10} (CoQ_{10})*	Transfers electrons from complex I and II to complex III in the ETC; acts as an antioxidant	A few small RCTs in patients with MELAS, CPEO, mitochondrial myopathy, NARP, MERRF, or LHON; open-label studies in patients with CPEO or KSS; case reports in patients with primary CoQ_{10} deficiency and other primary mitochondrial disorders **Research findings**: Few or no beneficial effects in RCTs; other studies suggest that	No safety concerns with up to 900 mg/day for 4 weeks in healthy people and 600 to 3,000 mg/day in patients with Huntington's disease or Parkinson disease **Reported adverse effects**: Hyperactivity, insomnia, rash, mild gastrointestinal symptoms, and nausea

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Evidence of Safety
		CoQ_{10} lowers postexercise lactate levels and increases exercise tolerance and muscle strength	
Creatine*	Regenerates ATP by a reaction involving phosphocreatine breakdown	Small RCTs in patients with MELAS, CPEO, KSS, or mitochondrial myopathy; small open-label studies in patients with KSS, MELAS, or NARP **Research findings**: Conflicting results; two studies suggest improvements in muscle and exercise performance, but two studies found no beneficial effect	No adverse effects reported with 20 g/day for up to 6 weeks **Reported adverse effects**: Weight gain from water retention, muscle cramping, spasm, strains, and gastrointestinal distress
Folinic acid*	Immediate precursor of 5-methyltetrahydrofolate (5-MTHF); increases brain 5-MTHF levels; believed to reduce white matter demyelination in patients with KSS who have comorbid secondary cerebral folate deficiency (CFD) (low cerebrospinal fluid 5-MTHF)	Open-label study and case reports in patients with KSS; no RCTs **Research findings**: Improved brain myelinization and reduced neurological symptoms in some patients	No safety concerns in patients with KSS with 1–8 mg/kg/day for 1 to 8 years **Reported adverse effects**: Rash and pruritus with the prescription form
Niacin*	Increases nicotinamide adenine dinucleotide (NAD) and NAD plus hydrogen (NADH) concentrations, enhancing substrate availability for complex I in the ETC	Case report of a patient with MELAS with complex I deficiency; no RCTs **Research findings**: No evidence of beneficial effects when used alone	No safety concerns reported below its upper limit of 35 mg/day. Some safety concerns with high doses **Reported adverse effects**: Transient flushing with 30 mg to 1 g/day nicotinic acid but not with nicotinamide or inositol hexanicotinate; nausea,

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Evidence of Safety
			vomiting, and liver toxicity with 3 to 9 g/day nicotinamide
Riboflavin*	Major component of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), which serve as electron carriers and cofactors of complexes I and II in the ETC	Case reports in patients with PMDs associated with complex I or complex II deficiency; no RCTs **Research findings**: Improved muscle strength, exercise tolerance, psychomotor development, motor abilities, school performance, and growth; reduced fatigue	No safety concerns with 50–100 mg/day for 46–80 months **Reported adverse effects**: None known
Thiamin*	Coenzyme for pyruvate and alpha-ketoglutarate in the oxidative decarboxylation process; enhances pyruvate aerobic glycolysis	Small open-label study in patients with KSS; no RCTs **Research findings**: Subjective improvements in general well-being and reduced fatigue in some patients	No safety concerns with up to 50 mg/day or more **Reported adverse effects**: None known
Vitamin C*	Cofactor for enzymes involved in biosynthesis of collagen, carnitine, and neurotransmitters; acts as an antioxidant; can donate electrons	Not studied individually	No safety concerns reported below its upper limit of 2,000 mg/day **Reported adverse effects**: Diarrhea, nausea, and abdominal cramps
Vitamin E*	Has antioxidant properties	Not studied individually	Safety concerns reported with high doses **Reported adverse effects**: Increased risk of hemorrhagic effects with more than the upper limit of 1,500

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Evidence of Safety
			International Units (IU)/day of the natural form or 1,100 IU/day of the synthetic form
Vitamin K*	Cofactor for enzymes involved in blood clotting and bone metabolism; acts as an antioxidant; can donate electrons	Not studied individually	No safety concerns for phytonadione (K1) or menaquinone (K2) supplements **Reported adverse effects**: Hepatotoxicity with menadione (vitamin K3), which is no longer available as a dietary supplement in the United States

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*Also studied in combination with other dietary supplements; see Table 2.

Table 2. Combination Therapies in Primary Mitochondrial Disorders used in Published Studies

Ingredients	Proposed Mechanism and Rationale	Evidence of Efficacy	Evidence of Safety
Alpha-lipoic acid, coenzyme Q_{10} (CoQ_{10}), and creatine	Alpha-lipoic acid used as an antioxidant and to enhance creatine uptake; CoQ_{10} used as an antioxidant and to bypass complex I in the ETC; creatine used as an alternative energy source	RCT in patients with MELAS, CPEO, KSS, other mitochondrial diseases, or mitochondrial neurogastrointestinal encephalopathy **Research findings**: Improvements in plasma lactate and oxidative stress with greatest improvements in patients with MELAS; no effects on muscle strength	Safety not reported
Carnitine and riboflavin	Restore activity of complex I in the ETC	Case report of a patient with myopathy associated with complex I deficiency	Safety not reported

Ingredients	Proposed Mechanism and Rationale	Evidence of Efficacy	Evidence of Safety
		Research findings: Improvement in muscle strength	
Carnitine, CoQ_{10}, vitamin C, vitamin K1, and vitamin B complex (biotin, cyanocobalamin, folic acid, niacin, pantothenic acid, pyridoxine, riboflavin, and thiamin)	Increase mitochondrial ATP production and slow progression of clinical symptoms	Open-label trial in patients with LHON, CPEO, MELAS, neurogenic weakness, ataxia, retinitis pigmentosa, or cytochrome c oxidase deficiency **Research findings**: No clinical improvement	No safety concerns reported
Carnitine, CoQ_{10}, vitamin C, vitamin E, vitamin K3*, and riboflavin	Diminish the deleterious effects of abnormal ETC function, reduce toxic agent levels, and correct nutrient deficiencies	Open-label study in patients with CPEO or KSS **Research findings**: Improvement in clinical course in patients with mild clinical forms of diseases but not in patients with more severe clinical forms	Safety not reported
CoQ_{10}, vitamin C, vitamin E, and vitamin K3*	Vitamins C and K3 used as electron transfer mediators to bypass complex III; vitamin C, vitamin E, and CoQ_{10} used as antioxidants	Open-label study in patients with mitochondrial myopathy, KSS, MELAS, or MERRF **Research findings**: No conclusions can be made about the efficacy of this combination therapy based on the study design, data, and reporting of results	No conclusions can be made about the safety of this combination therapy based on the study design, data, and reporting of results
CoQ_{10}, vitamin C, vitamin K3*, niacin, riboflavin, and thiamin	CoQ_{10} used to bypass complex I, vitamins C and K3 to bypass complex III, and other vitamins used as cofactors in the ETC	Open-label trial in patients with KSS, MERRF, myopathy, or a combination of myopathy and demyelinating neuropathy **Research findings**: No beneficial effects on	Temporary adverse effects, including thrombocytopenia and diarrhea, in some patients

Ingredients	Proposed Mechanism and Rationale	Evidence of Efficacy	Evidence of Safety
		oxidative metabolism or clinical symptoms	
Folinic acid and riboflavin	Folinic acid used to increase brain 5-MTHF levels and riboflavin used as a cofactor in the ETC	Case report of a patient with complex I deficiency and cerebrospinal fluid 5-MTHF deficiency **Research findings**: Reduced neurological symptoms and white matter demyelination	Safety not reported
Vitamins C and K3*	Bypass complex III deficiency in the ETC	Case reports in patients with complex III deficiency **Research findings**: Clinical and metabolic improvements	Safety not reported

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*Vitamin K3 (menadione) could be hepatotoxic and is no longer available as a dietary supplement in the United States [20,21].

The sections below discuss each of the ingredients, in alphabetical order, that studies have used as monotherapy to manage PMDs (summarized in Table 1). A subsequent section describes the evidence on combinations of ingredients used to manage PMDs (summarized in Table 2).

To capture all of the research that is pertinent to PMDs, this fact sheet is not limited to studies of dietary supplements that meet the regulatory definition (i.e., a dietary ingredient taken orally). Rather, this fact sheet also includes studies that administered dietary supplement ingredients intravenously or as prescription or nonprescription drugs.

Alpha-Lipoic Acid

ALA, also known as lipoic acid or thioctic acid, is naturally present in the mitochondria. ALA serves as a cofactor for enzymes that participate in intermediary cell metabolism that leads to ATP production. In addition, ALA and its reduced form, dihydrolipoic acid, can act as antioxidants by scavenging reactive oxygen species and helping regenerate other antioxidants, such as vitamin C, vitamin E, and glutathione [22]. Although the body makes sufficient amounts of ALA for basic metabolic functions (e.g., energy metabolism), it can only act as an antioxidant when it is present in greater amounts [22,23].

ALA is endogenously synthesized in mitochondria from octanoic acid [23]. It is also present in small amounts in foods, such as meats, liver, fruits, and vegetables [23], and it is available as dietary supplement. In dietary supplements, ALA is typically a mixture of R-ALA (natural, biologically active form) and S-ALA (manufactured form) enantiomers, but some products contain only R-ALA [24]. Typical amounts in dietary supplements range from 50 to 600 mg ALA [25].

ALA absorption and bioavailability have been studied using the amounts typically present in oral supplements. Pharmacokinetic studies have suggested that only 20% to 40% of an oral dose of a 50/50 mixture of R-ALA and S-ALA is absorbed [26]. Concentrations of R-ALA are 40% to 50% higher than S-ALA levels in plasma after ALA supplementation, suggesting that the R-ALA form is better absorbed and more bioavailable [27].

In patients with PMDs, ALA supplementation is used because of its potential to reduce oxidative stress [9,28] and to improve mitochondrial function [29].

Efficacy

The potential value of ALA in treating PMDs is based on limited evidence [29]. Scientific support comes from one case report of ALA supplementation alone (described below) and one clinical trial of ALA combined with creatine and CoQ_{10} in 18 patients (described in the combination therapies section) [28].

The case report, published in 1995, described the effects of 1 month of oral ALA supplementation (200 mg three times daily) on energy metabolism in the brain and skeletal muscle of a patient with CPEO [29]. After 1 month, energy availability in the brain increased, as shown by a 55% increase in brain phosphocreatine (PCr), 72% increase in brain phosphorylation potential, and decrease in calculated brain adenosine diphosphate (ADP) concentration, suggesting improved mitochondrial function. Further improvement was reported after 7 months of supplementation. Supplementation also had a positive effect on muscle mitochondrial activity during exercise. Moreover, the patient reported general improvement characterized by decreases in pain and discomfort of the eyes and improved muscle strength after supplementation.

In a consensus statement on the diagnosis and management of PMDs, the Mitochondrial Medicine Society (MMS) recommends offering ALA supplementation to patients with PMDs even though no controlled clinical trials have evaluated its use as monotherapy in these patients [1]. The standard doses are 50 to 200 mg/day [30].

Safety

No safety issues were documented in the case report discussed above or the small clinical trial with 600 mg/day ALA [28,29]. Oral supplementation with 600 mg/day ALA for 6 months to 4 years was well tolerated in clinical trials of 233–509 people with diabetic polyneuropathy [31,32]. More studies are needed to address the safety of oral ALA supplementation in patients with PMDs.

Arginine

Arginine is a conditionally essential amino acid involved in many metabolic processes, including protein metabolism, creatine synthesis, and urea detoxification [33]. Arginine is also the precursor of NO, an important neurotransmitter and vasodilator. Arginine can be obtained from dietary protein sources, such as animal-based foods and nuts. It is endogenously synthesized from citrulline via argininosuccinate synthase and argininosuccinate lyase [33,34], and it is available as a dietary supplement [25].

Some patients with PMDs have low concentrations of NO [33]. The causes of NO deficiency include decreased NO synthesis because of impaired endothelial function; sequestration of NO associated with increased activity of cytochrome c oxidase (complex IV in the ETC); decreased levels of the NO precursors arginine and citrulline; and increased asymmetric dimethylarginine (ADMA), an NO synthase inhibitor involved in converting arginine to NO [33]. Because low NO availability might play a role in the pathogenesis of PMDs, arginine supplementation has been used to increase NO concentrations [33].

Efficacy

Arginine supplementation has been used in patients with MELAS because of NO's role in stimulating vasodilation, which is believed to reduce the severity and frequency of stroke-like episodes [35]. However, no RCTs have tested this hypothesis, and evidence of arginine's efficacy in MELAS is based on small open-label studies (with 6 to 15 patients) for 12–24 months [35-39]. Moreover, no studies have assessed the use of arginine supplementation to treat other PMDs. A clinical trial (https://clinicaltrials.gov/ct2/show/NCT02809170) is under way to determine the effects of arginine and citrulline supplementation on endothelial dysfunction in children with PMDs.

The evidence from open-label studies on the use of dietary supplements containing arginine indicates that they have potentially beneficial effects in patients with MELAS. Oral administration of 150 to 300 mg/kg/day arginine for 12–24 months significantly decreased the frequency and severity of stroke-like episodes. Patients did not have major stroke-like attacks, such as hemiconvulsions or hemiparesis (temporary muscle weakness on one side of the body), after arginine supplementation. However, headache and teichopsia (visual sensation of bright shimmering colors) persisted [37-39]. Moreover, oral arginine supplementation for 24 months improved endothelial function, as shown by an increase in flow-mediated vasodilation [38,39].

The evidence from intravenous arginine administration to manage symptoms associated with the acute phase (first few hours) of stroke-like episodes in patients with MELAS, in particular, also appears to be positive. Four studies in 3 to 24 patients showed that intravenous administration of 500 mg/kg arginine within 30 minutes of a stroke resulted in the improvement of all symptoms (e.g., headache, clinical disability, nausea, vomiting, and teichopsia), although teichopsia persisted in three patients [36-39]. In addition, intravenous arginine improved endothelial function, as shown by increased flow-mediated vasodilation 2 hours after arginine infusion [36,38,39].

Further research, including RCTs, is needed to assess the efficacy and safety of this dietary supplement in patients with MELAS. In addition, research on the effects of arginine supplementation in other PMDs is needed.

Safety

Most study results suggest that up to 9 g/day arginine for several days or weeks is safe and well tolerated. At doses of 9–30 g/day, the most commonly reported adverse reactions are gastrointestinal discomfort, such as diarrhea and nausea, and slightly reduced blood pressure [40-42]. The safety of taking high-dose arginine supplements for more than 3 months is not known [42]. No adverse effects were reported from studies that administered arginine intravenously or orally in patients with MELAS [36,37,39]. However, overdoses of intravenous L-arginine-hydrochloride can lead to life-threatening hyperkalemia and hyponatremia [30,43-45].

Carnitine

Carnitine can be synthesized endogenously from the amino acids lysine and methionine in the liver and kidneys. It can also be obtained from the diet; red meat, chicken, fish, and dairy products are the primary sources [9,46]. Carnitine is available as a dietary supplement in the forms of L-carnitine, acetyl-L-carnitine, and propionyl-L-carnitine. It is also available as a prescription drug (Carnitor) that is used to treat primary carnitine-deficiency syndromes (e.g., defective carnitine synthesis) and some secondary ones.

The body maintains carnitine homeostasis by absorption from dietary sources, endogenous synthesis, and reabsorption in the kidneys [46]. Most of the body's carnitine is in skeletal muscle (90%), whereas blood contains 0.5% [9,46]. The carnitine pool comprises free (nonesterified) carnitine and carnitine esters (acylcarnitines).

Carnitine plays an important role in energy metabolism by transferring long-chain fatty acids into mitochondria for β-oxidation. It also facilitates the oxidation of pyruvate and branched-chain amino acids, and it helps remove toxic acetyl coenzyme A metabolites by binding to them for excretion in the urine [9,46,47].

Some patients with mitochondrial myopathies have low levels of carnitine in plasma and skeletal muscle, although carnitine deficiency only occurs in the muscle in some patients [9,47,48].The low carnitine levels in these patients appear to be secondary to impaired mitochondrial function [9,47].

Patients with PMDs use carnitine supplements to increase carnitine levels and support the elimination of toxic acyl compounds [30].

Efficacy

Carnitine is used to manage PMDs, although its efficacy alone or in combination with other dietary supplements has only been investigated in a few small studies [9]. The effects of carnitine in combination with other dietary supplements are described in the combination therapies section.

A small, randomized, double-blind, controlled, crossover study evaluated the effects of 3 g/day oral carnitine supplementation on exercise tolerance in 12 patients with mitochondrial myopathy and CPEO. Patients were studied after 8 weeks of carnitine treatment and 8 weeks of placebo treatment separated by a 4-week washout period [49]. No change was found after carnitine supplementation or

placebo in peripheral muscle strength, which was initially lower compared to values of healthy controls. However, inspiratory capacity (a measure of lung function) and aerobic exercise performance during intense constant-work exercise improved significantly after carnitine supplementation compared with placebo. Because the study did not measure plasma or muscle carnitine concentrations, whether the patients had carnitine deficiency is not known.

An open-label study evaluated the effects of carnitine supplementation (50–200 mg/kg/day in two to four oral doses) for 1–24 months in 21 patients with CPEO, KSS, MELAS, mitochondrial encephalomyopathy, mitochondrial myopathy, or Leigh's disease who had carnitine insufficiency [47]. Carnitine supplementation resulted in the normalization of plasma carnitine levels in all patients after 10 days and in the improvement of symptoms in 20 patients. Muscle tone and strength improved subjectively in 19 of 20 patients with muscle weakness. Growth improved after supplementation in four of eight patients with failure to thrive, and clinical and laboratory evaluation showed improvement in eight patients with cardiomyopathy based on echocardiographic evaluation. Ten percent of patients experienced side effects, mainly nausea and diarrhea.

Additional research is needed to reproduce the findings of these two studies and to clarify the role of carnitine supplementation in patients with other PMDs. The MMS recommends using carnitine supplementation only in patients with PMDs who have a documented carnitine deficiency, and it advises that clinicians monitor blood concentrations during therapy [1]. According to the MMS, the standard doses of carnitine for children are 20 to 100 mg/kg/day divided into two or three doses, and 330 to 990 mg/dose for adults two or three times per day; 3 g/day is the usual maximum [30].

Safety

The authors of a review of evidence on the safety of oral carnitine supplementation concluded, based on clinical studies of the supplement's use for weight loss and energy balance, that carnitine intakes below 2,000 mg/day appear to be safe [50]. However, the evidence is insufficient to ascertain carnitine's long-term safety [50]. A study in patients with organic acidemias indicated that carnitine supplementation (approximately 100 mg/kg) results in significant elevations of plasma trimethylamine N-oxide (TMAO) despite dietary meat restrictions [51]. This compound has been linked to a higher risk of cardiovascular disease [52]. However, the implications of these findings are not well understood and require more research.

At doses of approximately 3 g/day, carnitine supplements can cause nausea, vomiting, abdominal cramps, diarrhea, and a fishy body odor [53,54].

For more information about carnitine as a dietary supplement see the Carnitine (https://ods.od.nih.gov/factsheets/Carnitine-HealthProfessional/) fact sheet from the Office of Dietary Supplements (ODS) of the National Institutes of Health.

Citrulline

Citrulline is a nonessential amino acid that the body produces primarily from glutamine. It can also be obtained from the diet; the best source is watermelon (365 mg citrulline in 1 cup diced seedless

watermelon) [55]. Citrulline is also available as a dietary supplement.

Citrulline serves as an intermediate in the urea cycle and as a precursor for arginine. Approximately 70% of the body's citrulline is converted to arginine in the kidneys, accounting for 5%–15% of arginine produced in the body [33]. Arginine is the precursor of NO, an important neurotransmitter and vasodilator.

Some patients with PMDs have low concentrations of NO [33]. The causes of NO deficiency in these patients can include decreased NO synthesis due to impairment of endothelial function, sequestration of NO associated with increased activity of cytochrome c oxidase (complex IV in the ETC), decreased levels of NO precursors (arginine and citrulline), and increased levels of ADMA (an inhibitor of NO synthase involved in converting arginine to NO) [33].

Low NO availability could play a role in PMD pathogenesis, and citrulline supplementation can increase arginine and NO concentrations. For this reason, some experts have suggested using it as a therapy for PMDs [33,34,56]. NO plays a role in stimulating vasodilation, which is believed to reduce the neurological consequences of stroke-like episodes in patients with MELAS [35].

Efficacy

Citrulline supplementation increased NO production more efficiently than arginine in two small studies in patients with MELAS [33,34,56], but its effects on clinical outcomes in these patients or patients with other PMDs have not been evaluated. A clinical trial (https://clinicaltrials.gov/ct2/show/NCT02809170) is under way to determine the effects of arginine and citrulline supplementation on endothelial dysfunction in children with mitochondrial diseases.

Two studies compared the effects of citrulline and arginine administration on NO production in a total of 10 adults and five children with MELAS [34,56]. Using stable isotope infusion protocols, the authors assessed NO production rate, citrulline and arginine fluxes, and de novo synthesis of arginine before and after citrulline or arginine supplementation. Oral doses were 10 g/m^2 body surface area/day (administered in divided doses every 4 hours for 48 hours) in adults [34], 10 g/m^2 body surface area/day for children weighing 20 kg or more, and 500 mg/kg for those weighing less than 20 kg (administered in divided doses every 4 hours for 48 hours) [56]. Supplementation with citrulline increased plasma arginine levels, fluxes of arginine and citrulline, rates of de novo synthesis of arginine, and production of NO more than arginine supplementation. These studies did not assess any clinical outcomes.

Additional research is needed, including RCTs and studies with larger samples, to determine the efficacy and safety of citrulline supplementation and its effects on clinical outcomes on patients with PMDs.

Safety

The safety of citrulline, particularly when it taken in supplemental form for months at a time, has not been well studied. Stomach discomfort has been reported with 8 g citrulline malate (citrulline

combined with malic acid) [57]. Short-term studies of up to 6 g/day citrulline for 4 weeks and 1.35 g/day for 6 weeks found no adverse effects [58].

Coenzyme Q_{10}

CoQ_{10} is a fat-soluble quinone that transfers electrons in the ETC from complex I and II to complex III as part of the ATP production process [59]. CoQ_{10} also acts as an antioxidant in its reduced form, ubiquinol, by inhibiting lipid peroxidation and protecting mitochondria and DNA from oxidative damage [9,60,61].

Humans synthesize CoQ_{10} endogenously. They can also obtain CoQ_{10} from foods, including fish, meats, and whole grains, and from dietary supplements. CoQ_{10} supplements are available in a variety of forms, including powder-filled, hard-shell capsules; oil-based suspensions; and emulsions in soft-gel capsules [9].

CoQ_{10} is insoluble in water, and powder formulations have lower intestinal absorption rates [30,62,63]. Ubiquinol is three to five times more bioavailable than the oxidized form, ubiquinone, making it a preferred form for supplementation [30]. Absorption of CoQ_{10} improves when it is taken with meals or dietary fat [63,64].

CoQ_{10} supplementation is used in patients with PMDs because of its roles as a cofactor in the ETC and as an antioxidant.

Efficacy

The efficacy of CoQ_{10} in PMDs, other than to treat primary CoQ_{10} deficiency, still needs to be determined. In case reports, patients with primary CoQ_{10} deficiency had positive responses to CoQ_{10}, such as increased strength and reduced ataxia [65,66]. However, the evidence of CoQ_{10} efficacy in other PMDs is limited. The efficacy of CoQ_{10} used in combination with other dietary supplements is discussed in the combination therapies section.

Effects of CoQ_{10} supplementation have been explored in various studies that measured functional outcomes (e.g., exercise capacity or muscle strength) and/or biochemical parameters, such as plasma or serum lactate levels in patients at rest and during and after exercise; lactate to pyruvate (L/P) ratio; markers of oxidative stress; mitochondrial enzyme activity; and the PCr/inorganic phosphate [Pi] ratio, a marker of muscular function. However, studies used inconsistent measures, making comparisons of their findings difficult.

Four of five small prospective studies in 8–30 patients with a variety of PMDs showed that doses of 150–1,200 mg or 2 mg/kg/day CoQ_{10} for 2–6 months reduced plasma lactate concentrations [67-69] and the L/P ratio [70] after but not during exercise; supplementation also increased muscle strength [68,69]. The fifth study found no change in serum lactate before and after exercise but did show improvements in muscular function in one patient after supplementation [71].

The first prospective study, a randomized, placebo-controlled, crossover trial, evaluated the effects of CoQ_{10} supplementation in 30 participants with PMDs, including MELAS, CPEO, mitochondrial

myopathy, NARP, ataxia-neuropathy, and LHON [67]. Each patient received 1,200 mg/day CoQ_{10} for 60 days and placebo for 60 days, with a 60-day washout period in between. A more than fivefold increase in plasma CoQ_{10} concentration was reported after supplementation. Supplementation had no effect on biochemical parameters, including resting plasma lactate levels and urinary markers of oxidative stress. However, postexercise plasma lactate concentrations were lower after CoQ_{10} administration. Supplementation with CoQ_{10} did not affect muscle strength.

The second prospective study, a short-term crossover study, administered 160 mg/day CoQ_{10} for 3 months and placebo for 1 month after a 4-week washout period in eight patients with MERRF, MELAS, or CPEO [68]. After 2 months, serum CoQ_{10} concentrations increased significantly, but they did not increase further after another month. Supplementation with CoQ_{10} did not significantly change serum lactate or pyruvate concentrations during exercise. Overall muscle strength increased significantly during CoQ_{10} supplementation, but proximal and distal muscles of the upper and lower limbs showed no changes.

The third prospective study, which had two phases, assessed the effects of CoQ_{10} supplementation in patients with a variety of PMDs [69]. In the first phase, 44 patients with KSS features, KSS, CPEO, mitochondrial myopathy without ophthalmoplegia, or MERRF received 2 mg/kg/day a form of CoQ_{10} known as ubidecarenone in an open- label trial for 6 months [69]. Supplementation with CoQ_{10} significantly decreased mean serum lactate levels after exercise, significantly increased the activity of mitochondrial respiratory chain enzymes (succinate dehydrogenase and succinate cytochrome c reductase) in muscle, reduced citrate synthase levels, and significantly increased muscle strength. Sixteen patients (36%) with at least a 25% decrease in postexercise serum lactate levels participated in the second, double-blinded phase, in which eight patients continued to receive 2 mg/kg/day CoQ_{10} and eight received a placebo. This phase of the study was stopped after 3 months because two patients in the placebo group reported subjective worsening of their condition. Postexercise serum lactate concentrations did not decrease further after the 3 months of supplementation in either group, and there were no significant changes in the other parameters measured.

The fourth prospective study, a small open-label study, assessed clinically valuable metabolic parameters in patients with PMDs. The results showed a decreased L/P ratio after exercise after 150 mg/day CoQ_{10} for 6 months in nine patients with ophthalmoplegia plus syndrome, CPEO, or KSS [70]. Compared with lactate alone, the L/P ratio was more sensitive for detecting metabolic changes in these patients. The authors did not report on clinical outcomes.

The final prospective study, an open-label study, investigated the effects of 150 mg/day CoQ_{10} for 6 months on muscular function in eight patients with CPEO or mitochondrial encephalomyopathy at rest and during and after exercise [71]. The results showed a nonsignificant improvement in muscular function in only one patient, as shown by an increase in the PCr/Pi ratio after 3 months of supplementation, but this value returned to its pretreatment level at 6 months. Accelerated energy repletion was sustained after 6 months. However, the metabolic improvement did not result in a positive effect on exercise performance.

Several case reports on CoQ_{10} supplementation for PMDs were published between 1987 and 1999 [72-77]. Improvements in biochemical parameters (e.g., serum lactate) and reduced muscle weakness after CoQ_{10} supplementation were reported in patients with a variety of PMDs. One case report also described an improvement in neurologic function after 120 mg/day CoQ_{10} supplementation for 1 year in four patients with mitochondrial myopathy and three with KSS [77].

In summary, case reports and small open trials suggest that CoQ_{10} supplementation improves biochemical parameters but provide little or no evidence of improved clinical outcomes in patients with PMDs. In addition, RCTs have found no beneficial effect in these patients. Additional research is needed to clarify the role of CoQ_{10} in managing these disorders.

In its consensus statement on the diagnosis and management of PMDs, the MMS determined that the evidence supporting the use of CoQ_{10} in PMDs is sparse, but it recommends offering CoQ_{10} supplements to most patients with a PMD [1]. According to the MMS, the standard dose is 2–8 mg/kg/day ubiquinol (administered twice a day with meals) [30]. Doses of 5–30 mg/kg/day (administered in two divided doses with meals) are a recommended alternative [30]. The MMS also recommends using ubiquinol and monitoring absorption and adherence to treatment by measuring plasma and/or leukocyte CoQ_{10} levels.

Safety

Clinical studies have shown that CoQ_{10} is safe and well tolerated at up to 900 mg/day for 4 weeks in healthy volunteers [78,79] or at 600–3,000 mg/day in patients with various disorders (e.g., Huntington's disease or Parkinson's disease) [63,80]. Mild side effects include hyperactivity, insomnia, rash, gastrointestinal symptoms, nausea, and stomach upset [63].

For more information about CoQ_{10} dietary supplements, see Coenzyme Q_{10}. (https://ods.od.nih.gov/factsheets/list-all/CoenzymeQ10/)

Creatine

Creatine is naturally produced in the liver and kidneys from the amino acids glycine and arginine. It can also be obtained from the diet (meat and fish are the primary sources [59]) and from dietary supplements, which most commonly contain creatine monohydrate. High concentrations of creatine are present in tissues with high energy demands, including skeletal muscle and brain [30]. In tissue, creatine combines with phosphate to form PCr. PCr breakdown regenerates ATP in a reaction that transfers a phosphate to ADP, a source of energy released during anaerobic metabolism [30].

Patients with mitochondrial myopathies can have low PCr levels in skeletal muscle, and patients with mitochondrial encephalomyopathies might have low creatine levels in the brain [30]. The goal of creatine administration in these patients is to increase creatine concentrations in tissues and the ability of tissues to store PCr, creating a supply of energy in the form of ATP. In healthy individuals, total creatine and PCr levels can increase by 20% in skeletal muscle after daily doses of 10–20 g creatine for 4–6 days [81,82].

Efficacy

The effects of creatine supplementation in patients with PMDs have been investigated in small open-label studies and randomized, double-blind, crossover trials with conflicting results [83-86]. The effects of creatine in combination with other dietary supplements are described in the combination therapies section.

Two prospective studies found that creatine supplements had positive effects on muscular symptoms in patients with PMDs. The first—a randomized, double-blind, crossover study— provided creatine monohydrate for 3 weeks (5 g twice a day for 2 weeks, then 2 g twice a day for 1 week) or placebo for 3 weeks, with a 5-week washout period in between, to seven patients with MELAS or mitochondrial myopathy [84]. Supplementation resulted in a significant increase in ischemic isometric hand grip strength and an overall 11% increase in nonischemic, isometric, dorsiflexion torque compared with placebo. The second, an open-label study, assessed the effects of 0.08 to 0.35 g/kg/day creatine monohydrate supplementation for 9 months to approximately 4 years in five patients (7 to 19 years of age) with KSS, MELAS, or NARP [83]. Skeletal muscle power analyses showed a 12% average increase in maximal muscle performance in all patients. Self-reported muscular symptoms and coordination improved, but cognitive function (i.e., school performance) did not change.

Two randomized, controlled crossover trials found that creatine supplementation (150 mg/kg/day or 20 g/day) or placebo for 4–6 weeks, with a 4-week washout period in between, had no effect on clinical outcomes, such as skeletal muscular function, muscle or hand grip strength, endurance performance, or fatigue in a total of 31 patients with CPEO, KSS, or mitochondrial myopathy [85,86].

In summary, the studies of creatine supplementation in patients with PMDs have had conflicting results. Further research is needed to clarify the role of creatine in managing PMDs.

Safety

No adverse effects have been reported in patients with PMDs after oral supplementation with up to 20 g/day creatine monohydrate for up to 6 weeks [84-86]. Creatine is generally considered safe for short-term use (5 days) by healthy adults at up to 20 g/day and up to 3 g/day for maintenance doses [87]. However, the safety of creatine supplementation in children and adolescents is not well established [87]. Creatine supplementation can increase water retention and might stimulate muscle protein synthesis, resulting in weight gain [88]. Anecdotal reports have also associated creatine supplementation with muscle cramping, spasm, strains, and gastrointestinal distress [88].

Folinic Acid

Folate is the generic term for a family of compounds that act as coenzymes in the folate cycle, which plays an important role in DNA and RNA synthesis, creatine synthesis, and homocysteine remethylation. Folate also provides S-adenosylmethionine, the major methyl donor for methylation reactions [89].

Folate is naturally present in a variety of forms and as the fully oxidized synthetic form, folic acid. Folic acid is the most commonly used form in dietary supplements and fortified foods. Other forms of folate

in dietary supplements include L-methylfolate, 5-MTHF, and folinic acid (also known as 5-formyltetrahydrofolate) [25,90]. Prescription drug forms of L-methylfolate (deplin) and folinic acid (leucovorin) are also available.

Folic acid must be reduced by dihydrofolate reductase (DHFR) to tetrahydrofolate and then to the biologically active form 5-MTHF by methylenetetrahydrofolate reductase. In contrast, folinic acid is an immediate precursor of 5-MTHF and does not require these reduction steps to enter the folate cycle. For this reason, folinic acid and 5-MTHF supplements have been proposed as good alternatives to folic acid supplements when folate metabolism is impaired by medications, such as DHFR inhibitors (e.g., methotrexate, aminopterin, pyrimethamine, and trimethoprim), and/or alterations in the DHFR gene [90].

Folinic acid increases brain concentrations of 5-MTHF in patients with primary or secondary CFD. CFD is associated with several PMDs, including KSS, pathogenic POLG variants, NARP, and Leigh syndrome [90,91]. CFD is known as cerebrospinal fluid 5-MTHF deficiency in people with normal peripheral folate status [90].

The exact mechanism of CFD in PMDs is still unclear. It has been suggested that patients with KSS have CFD, possibly because they have inadequate amounts of ATP, which is necessary for the active transport of folate across the blood-brain barrier into the brain [90,92,93]. Low cerebral folate levels can affect the methylation and stability of myelin. Consequently, myelin instability can result in white matter lesions that are common in patients with KSS [90].

Folinic acid is available in dietary supplements alone or in combination with other vitamins, such as calcium folinate, in doses ranging from 400 to 1,000 mcg [25,90].

Efficacy

Limited evidence suggests that folinic acid might reverse white matter abnormalities in patients with KSS [91,94]. For example, a small open-label study assessed the effects of folinic acid supplementation in six patients with KSS who had cerebral 5-MTHF deficiency; follow-up periods ranged from 1 to 8 years [91]. After therapy, cerebral 5-MTHF concentrations normalized in three patients (two receiving 1 mg/kg/day and one receiving 3 mg/kg/day). The patients who received 3 mg/kg/day folinic acid showed improvements in neurological symptoms, such as ataxia (abnormal, uncoordinated movements) and tremor (involuntary, rhythmic, oscillatory movement of a body part), although the disease progressed in all patients. In addition, one of the patients who received 3 mg/kg/day folinic acid also showed improvement in white matter abnormalities, but these abnormalities progressed in the other patients.

In a case report, 2.5 mg/kg/day folinic acid normalized CSF 5-MTHF concentrations and improved white matter myelinization in a patient with a form of KSS, but it had no effect on cerebellar ataxia or areflexia (absence of reflexes) [94].

The effects of folinic acid in combination with other dietary supplements are described in the combination therapies section.

The MMS recommends that clinicians consider folinic acid supplementation for patients with PMDs and central nervous system manifestations and that they routinely administer this supplement to patients with documented CFD or PMDs known to be associated with folate deficiency [1]. According to the MMS, the standard doses of folinic acid are 0.5 to 2.5 mg/kg once or twice a day for children and 2.5 to 25 mg once or twice a day for adults [30].

In summary, folinic acid in patients with cerebral 5-MTHF deficiency appears to be beneficial, but this evidence comes from just two case reports and a small open-label study in patients with KSS. Further research is needed to replicate these findings in larger samples and clarify the role of folinic acid supplementation in patients with PMDs.

Safety

No adverse effects were reported in patients with KSS after supplementation with 1 mg/kg/day or 3 mg/kg/day folinic acid for 1 to 8 years [91]. Hypersensitivity to folinic acid as leucovorin includes anaphylactoid and urticarial reactions [95].

Niacin

Niacin, also known as vitamin B3, is a precursor of the coenzymes NAD and NAD phosphate (NADP), which are involved in many biological redox reactions. NAD and its reduced form NADH play an important role in energy metabolism by transferring electrons from intermediates to complex I in the mitochondrial ETC. NADP serves as a hydrogen donor in fatty acid and steroid synthesis and as a coenzyme for pentose synthesis via the pentose phosphate pathway. Niacin also has antioxidant properties and prevents oxidative stress [96,97].

Niacin is endogenously produced in the body from the amino acid tryptophan and obtained from the diet from such foods as meats, grains, milk, and eggs [97]. Niacin is also available as a dietary supplement in the forms of nicotinic acid, nicotinamide, and inositol hexaniacinate. The amounts in supplements range from 50 to 1,000 mg [25]. Prescription drug forms, such as Niaspan (also available as generic niacin extended release), which contains 500 to 1,000 mg niacin, are also available [98].

The rationale for niacin supplementation in patients with PMDs is to increase NAD and NADH concentrations in cells and thus enhance substrate availability for complex I in the mitochondrial ETC for energy production [9].

Efficacy

The only evidence on the effects of niacin supplementation alone in patients with PMDs comes from a single case report published in 1996. In this report, a patient with MELAS who had decreased complex I activity and the typical m.3243A>G mutation was treated after the first stroke-like episode with 4,000 mg/day nicotinamide in four divided doses for 5 months [99]. Blood NAD concentrations were 24 times higher than pretreatment levels after 6 weeks of supplementation. Blood lactate levels dropped by 40%, and blood pyruvate concentrations declined by 50% on the third day of supplementation; blood lactate levels continued to decline until they approached the normal reference range (1.0–1.8 mmol/l) at 1

month. At 2 weeks, 24-hour urinary lactate levels declined by 50%. However, the patient showed progressive deterioration and died 5 months after treatment began.

The effects of niacin in combination with other dietary supplements are described in the combination therapies section.

In summary, there is insufficient evidence to support the use of niacin supplementation in PMDs. Additional research is needed, including studies with larger samples and RCTs, to determine the efficacy and safety of niacin supplementation in patients with PMDs.

Safety

Flushing is a common side effect in people treated with 30 mg/day or more nicotinic acid by mouth and is characterized by a burning, tingling, and itching sensation primarily on the face, arms, and chest that can be accompanied by pruritus, headaches, and increased intracranial blood flow [97]. Nicotinamide and inositol hexanicotinate do not appear to be associated with flushing [97,100]. The Food and Nutrition Board established a tolerable upper intake level (UL) for niacin of 10 mg for age 1–3 years, 15 mg for age 4–8 years, 20 mg for age 9–13 years, 30 mg for age 14–18 years, and 35 mg for age 19 years and up [97]. These levels, however, apply to the general population and do not apply to individuals receiving niacin under medical supervision. Niacin ULs for infants have not been established.

Some adverse effects have been reported with nicotinamide intakes of 3,000 mg/day, including nausea, vomiting, and signs and symptoms of liver toxicity [97]. In numerous case reports, patients given 3,000–9,000 mg/day niacin for months to years to treat hyperlipidemia developed liver toxicity [97]. Medical supervision should be provided for patients using more than 1,000 mg/day nicotinic acid [100].

For more information about niacin as a dietary supplement, see Niacin (https://ods.od.nih.gov/factsheets/list-all/Niacin/).

Riboflavin

Riboflavin, also known as vitamin B2, is a major component of the flavoproteins flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). These electron carriers serve as cofactors for complexes I and II in the mitochondrial ETC and are involved in fatty acid oxidation and the Krebs cycle [30,96].

Riboflavin is naturally present in such foods as eggs, organ meats, lean meats, and milk. It is also present in fortified foods (e.g., grains and cereals) [96] and dietary supplements. Multivitamin/mineral supplements with riboflavin commonly provide 1.7 mg. Other supplements contain 100 to 400 mg riboflavin [25].

Most riboflavin is absorbed in the proximal small intestine. The body absorbs little additional riboflavin from single doses beyond 27 mg and stores only small amounts of riboflavin in the liver, heart, and

kidneys. Excess amounts are either not absorbed or the small amount that is absorbed is excreted in urine [97].

The rationale for riboflavin supplementation in patients with PMDs is to recover enzyme activity and improve complex I and II of the mitochondrial ETC [9,96]. Doses as high as 150 mg/day riboflavin have been studied in patients with PMDs.

Efficacy

Case reports have shown benefits from riboflavin supplementation in patients with PMDs associated with complex I deficiency [101-103]. For example, 150 mg/day riboflavin for an unspecified period improved muscle strength and reduced plasma lactate and alanine concentrations in a patient with mitochondrial complex I deficiency due to acyl-coenzyme A dehydrogenase 9 (ACAD9) mutations [104]. In five patients with mitochondrial myopathy associated with complex I deficiency, 9 mg/day for patients younger than 12 years and 36 mg/day for older patients for 3–17 months improved muscle strength in two patients and reduced fatigue in one patient. Another patient showed improved psychomotor development and stabilization of clinical symptoms after 9 mg/day riboflavin for 25 months. Riboflavin taken at 36 mg/day for 24 months improved motor coordination, physical condition, school performance, social behavior, and/or motor abilities in one patient, but another patient experienced no benefits from the same dose [101]. In a child with mitochondrial myopathy and complex I deficiency, 20–120 mg/day riboflavin for 16 months normalized serum pyruvate and lactate concentrations and reduced muscle weakness [103]. Finally, 50 mg/day riboflavin for 3 years improved exercise tolerance and muscle tone in a patient with complex I deficiency and skeletal myopathy. Discontinuation of riboflavin for 1 month resulted in significant clinical deterioration that was reversed by resumption of supplementation [102].

Case reports also provide some evidence supporting the benefits of riboflavin supplementation in patients with PMDs associated with complex II deficiency. In three children with this deficiency, 50–100 mg/day riboflavin for a mean 4.5 years had beneficial effects (which depended on the child), including moderate improvements in cognitive function, communicative abilities, postural control, and growth. Plasma lactate and pyruvate concentrations declined in one patient whose values were elevated at baseline [105].

The MMS recommends offering riboflavin supplements to patients with PMDs [1], and the standard doses are 50 to 400 mg/day [30].

In summary, evidence from case reports show the potentially beneficial effects of riboflavin supplementation in patients with PMDs associated with complex I and complex II deficiencies. However, further research, including RCTs and studies with larger samples, is needed to fully understand the efficacy and safety of riboflavin supplementation in these patients.

Safety

No adverse events were reported in children with mitochondrial complex II deficiency who received 50–100 mg/day riboflavin for 46–80 months [105]. No adverse effects from high riboflavin intakes from foods or supplements (400 mg/day for at least 3 months) have been reported, and the Food and

Nutrition Board has not established a UL for riboflavin. However, the lack of reported adverse events does not necessarily mean that excessive intakes of riboflavin do not have adverse effects [97,106].

For more information on riboflavin as a dietary supplement, see the Riboflavin (https://ods.od.nih.gov/factsheets/Riboflavin-HealthProfessional/) fact sheet from ODS.

Thiamin

Thiamin, also known as thiamine or vitamin B1, is naturally present in some foods, such as whole grains, meats, and fish. It is also added to some food products (i.e., breads, cereals, and infant formulas) and is available as a dietary supplement [107]. Multivitamin/mineral supplements with thiamin typically provide about 1.5 mg or more, and other supplements contain 50 to 250 mg [25]. The most common forms of thiamin in supplements are thiamin mononitrate and thiamin hydrochloride, which are stable and water soluble. Benfotiamine, a synthetic thiamin derivative used in some dietary supplements (150 to 300 mg), is not water soluble and is converted to thiamin in the body [25,108].

Thiamin plays an important role in energy metabolism. Thiamin pyrophosphate is the main metabolically active form of thiamin, and it serves as a cofactor for enzymes involved in glucose and amino acid metabolism. As glucose is broken down into energy, thiamin is a cofactor for the pyruvate dehydrogenase complex that converts pyruvate to acetyl-coenzyme A in the pyruvate decarboxylation process [109].

The rationale for thiamin supplementation in patients with PMDs is to improve aerobic glycolysis by enhancing pyruvate decarboxylation [9].

Efficacy

Only one small study, published in 1981, has assessed the effects of thiamin supplementation in patients with PMDs. This study found that 900 mg/day (in three divided doses) thiamin hydrochloride in three patients age 18–29 years with KSS normalized plasma lactate in two patients and pyruvate concentrations in one patient with initially abnormal levels after 5 weeks to 3 months [110]. The supplement also improved self-reported general well-being and reduced fatigue in the two patients whose plasma lactate normalized, but it had no effect in the third patient who received thiamin for 4 weeks.

The effects of the combination of thiamin with other dietary supplements are described in the combination therapy section.

To date, the evidence of efficacy of thiamin supplementation to manage PMDs comes from a single, small, open-label study. Further research, including RCTs, is needed to assess the efficacy and safety of this dietary supplement in patients with PMDs.

It is important to note that biotin-thiamin-responsive basal ganglia disease, an autosomal recessive disorder that results in severe neurological impairment, can mimic Leigh syndrome and responds to biotin and thiamin supplementation. Therefore, differential diagnosis is essential [111].

Safety

The body excretes excess amounts of thiamin in the urine [107]. Because of the lack of reports of adverse effects from high thiamin intakes (50 mg/day or more) from food or supplements, the Food and Nutrition Board has not established a UL for thiamin [97]. Thiamin supplementation does not appear to be toxic, possibly because its absorption declines rapidly with intakes greater than 5 mg. However, the lack of reported adverse events does not necessarily mean that excessive intakes of thiamin do not have adverse effects [97,112].

For more information about thiamin as a dietary supplement, see the Thiamin (https://ods.od.nih.gov/factsheets/Thiamin-HealthProfessional/) fact sheet from ODS.

Vitamin C

Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin that is naturally present in some foods. The best food sources are fruits and vegetables. Vitamin C is added to some foods (including fortified breakfast cereals) and is available as a dietary supplement. Unlike most species, humans cannot synthesize vitamin C endogenously, so it is an essential dietary component [113].

Vitamin C is required for the biosynthesis of collagen, L-carnitine, and certain neurotransmitters. Vitamin C is also involved in protein metabolism [113,114], and it is an important physiological antioxidant [115] that can regenerate other antioxidants within the body, including alpha-tocopherol (vitamin E) [116]. In addition to its function as a cofactor and antioxidant, vitamin C facilitates the intestinal absorption of nonheme iron [114].

Approximately 70%–90% of vitamin C is absorbed at moderate intakes of 30–180 mg/day. However, at doses above 1 g/day, the absorption rate drops to less than 50%, and absorbed, unmetabolized ascorbic acid is excreted in the urine [116]. Results from pharmacokinetic studies indicate that oral doses of 1.25 g/day ascorbic acid produce mean peak plasma vitamin C concentrations of 135 micromol/L, which are about twice those produced by consuming 200–300 mg/day ascorbic acid from vitamin C-rich foods [117]. Pharmacokinetic modeling predicts that even doses as high as 3 g ascorbic acid taken every 4 hours would produce peak plasma concentrations of only 220 micromol/L [117].

Supplements typically contain vitamin C in the form of ascorbic acid, which has equivalent bioavailability to that of naturally occurring ascorbic acid in foods, such as orange juice and broccoli [118]. Other forms of vitamin C supplements include sodium ascorbate; calcium ascorbate; other mineral ascorbates; ascorbic acid with bioflavonoids; and combination products [25].

Vitamin C has been used to treat PMDs as an antioxidant [9] and in combination with vitamin K as an electron transfer mediator to bypass complex III deficiency in the ETC [9,119].

Efficacy

No studies have assessed the effect of vitamin C alone in patients with PMDs. Two case reports of patients with mitochondrial myopathy associated with complex III deficiency combined vitamin C with

vitamin K3 (no longer available in dietary supplements because of its hepatotoxicity) [119,120]. These case reports are described in the combination therapy section.

Safety

Vitamin C has low toxicity and is not believed to cause serious adverse effects at high intakes [114]. The most common adverse effects are diarrhea, nausea, abdominal cramps, and other gastrointestinal disturbances because of the osmotic effect of unabsorbed vitamin C in the gastrointestinal tract [114].

High vitamin C intakes also have the potential to increase urinary oxalate and uric acid excretion, which could contribute to the formation of kidney stones, especially in individuals with renal disorders. However, studies evaluating the effects on urinary oxalate excretion of 30 mg to 10 g/day vitamin C have had conflicting results, so it is not clear whether vitamin C plays a role in kidney stone development. The best evidence that vitamin C contributes to kidney stone formation comes from patients with preexisting hyperoxaluria.

The ULs for vitamin C for both food and supplement intakes are 400 mg for age 1–3 years, 650 mg for age 4–8 years, 1,200 mg for age 9–13 years, 1,800 mg for age 14–18 years, and 2,000 mg for age 19 years and up [114]. Vitamin C ULs for infants have not been established. Long-term intakes of vitamin C above the UL could increase the risk of adverse health effects. However, the ULs do not apply to individuals receiving vitamin C for medical treatment, although such individuals should be under the care of a physician [114].

For more information on vitamin C as a dietary supplement, see the Vitamin C (https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/) fact sheet from ODS.

Vitamin E

Vitamin E is naturally present in some foods. The best sources are nuts, seeds, and vegetable oils. Vitamin E is added to other foods, including fortified breakfast cereals, and is available as a dietary supplement.

Vitamin E is the collective name for a group of fat-soluble compounds with distinctive antioxidant activities. Naturally occurring vitamin E has eight chemical forms (alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma, and delta-tocotrienol) that have varying levels of biological activity [121]. Alpha-tocopherol is the only form known to meet human requirements. The main function of alpha-tocopherol is to act as an antioxidant that prevents the propagation of free-radical reactions and protects cell membranes from lipid peroxidation. Regeneration of vitamin E involves other reducing agents, such as vitamin C [114].

Supplements of vitamin E typically provide only alpha-tocopherol, although mixed products containing other tocopherols and even tocotrienols are available. Alpha-tocopherol in dietary supplements and fortified foods is often esterified to prolong its shelf life while protecting its antioxidant properties. The body hydrolyzes and absorbs these esters (alpha-tocopheryl acetate and succinate) as efficiently as alpha-tocopherol [114]. Most vitamin-E–only supplements provide at least 100 IU of the nutrient [25].

Vitamin E is used to manage PMDs because of its antioxidant properties. It is often used in combination with other dietary supplements.

Efficacy

No studies have assessed the effect of vitamin E alone in patients with PMDs. The effects of the combination of vitamin E with other dietary supplements are described in the combination therapies section.

Safety

High doses of alpha-tocopherol supplements can cause hemorrhages and interrupt blood coagulation in animals, and in vitro data suggest that high doses inhibit platelet aggregation. Two clinical trials have found an increased risk of hemorrhagic stroke in participants taking alpha-tocopherol; one trial included Finnish male smokers who consumed 50 mg/day for an average of 6 years [122], and the other involved a large group of male physicians in the United States who consumed 400 IU every other day for 8 years [123]. Because most physicians in the latter study were also taking aspirin, this finding could indicate that vitamin E tends to cause bleeding.

The ULs for vitamin E are based on the potential for hemorrhagic effects. The ULs for all forms of supplemental alpha-tocopherol for children are 200 mg (300 IU) for age 1–3 years, 300 mg (450 IU) for age 4–8 years, 600 mg (900 IU) for age 9–13 years, and 800 mg (1,200 IU) for age 14–18 years. For individuals 19 years and up, the UL is 1,000 mg (1,500 IU) [114]. Vitamin E ULs for infants have not been established.

Doses of up to 1,000 mg/day (1,500 IU/day of the natural form or 1,100 IU/day of the synthetic form) in adults appear to be safe, although the data are limited and based on small groups of people taking at least 2,000 IU for a few weeks or months. Long-term intakes above the UL increase the risk of adverse health effects [114].

Two meta-analyses of randomized trials have raised questions about the safety of large doses of vitamin E, including doses lower than the UL. These meta-analyses linked supplementation to small but statistically significant increases in all-cause mortality rates. One analysis found an increased risk of death at doses of 400 IU/day, although the risk began to increase at 150 IU [124]. In the other analysis of studies of antioxidant supplements for disease prevention, the highest-quality trials revealed that vitamin E, whether administered alone (10–5,000 IU/day, mean 569 IU) or in combination with up to four other antioxidants, significantly increased mortality risk [125].

The implications of these analyses for the potential adverse effects of high-dose vitamin E supplements are unclear [126-129]. Participants in the studies included in these analyses were typically middle-age or older and had chronic diseases or related risk factors. These participants often consumed other supplements in addition to vitamin E. Some of the studies analyzed took place in developing countries in which nutritional deficiencies are common. A review of the subset of studies in which vitamin E supplements were given to healthy individuals for the primary prevention of chronic disease found no convincing evidence that the supplements increased mortality rates [130].

However, results from the Selenium and Vitamin E Cancer Prevention Trial show that vitamin E supplements (400 IU/day) might harm adult men in the general population by increasing their risk of prostate cancer [131]. Follow-up studies are assessing whether the cancer risk is associated with baseline blood levels of vitamin E and selenium before supplementation as well as whether changes in one or more genes might increase a man's risk of developing prostate cancer while taking vitamin E.

For more information on vitamin E as a dietary supplement, see the Vitamin E (https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional) fact sheet from ODS.

Vitamin K

Vitamin K, the generic name for a family of compounds with a common chemical structure of 2-methyl-1,4-naphthoquinone, is a fat-soluble vitamin that is naturally present in some foods [132]. These compounds include phylloquinone (vitamin K1), present primarily in green leafy vegetables, that is the main dietary form of vitamin K [21]. The compounds also include a series of menaquinones (MK-4 through MK-13, known as vitamin K2) that are predominantly of bacterial origin and are present in modest amounts in various animal-based and fermented foods [132,133]. Several forms of vitamin K are used in dietary supplements, including vitamin K1 as phylloquinone or phytonadione (a synthetic form of vitamin K1) and vitamin K2 as MK-4 or MK-7 [25]. Few data are available on the bioavailability of the various forms of vitamin K supplements. One study found that both phytonadione and MK-7 supplements are well absorbed, but MK-7 has a longer half-life [134]. Vitamin K3, also known as menadione, is hepatotoxic and is no longer used in dietary supplements [20,21].

Vitamin K is present in most multivitamin/mineral supplements, typically in low amounts. It is also available in dietary supplements containing only vitamin K or vitamin K combined with a few other nutrients, frequently calcium, magnesium, and/or vitamin D. These supplements tend to have a wider range of vitamin K doses than multivitamin/mineral supplements [25].

Vitamin K functions as a coenzyme for vitamin K-dependent carboxylase, an enzyme required for the synthesis of proteins involved in hemostasis (blood clotting) and bone metabolism, and other diverse physiological functions [21]. Vitamin K3 was used in combination with vitamin C as electron transfer mediators to bypass complex III deficiency in the ETC in patients with PMDs [9,119]. Case reports and studies using vitamin K3 are summarized in this fact sheet because of the value of reviewing the available data on the efficacy of this combination of nutrients. Vitamin K1 has also been used to manage PMDs [135].

Efficacy

No studies have assessed the efficacy of vitamin K supplementation alone in patients with PMDs. In two patients with mitochondrial myopathy associated with complex III deficiency, vitamin K3 in combination with vitamin C was used [110-112]. These reports and a trial of vitamin K1 in combination with carnitine, CoQ_{10}, vitamin B complex, and vitamin C are described in the combination therapies section.

Safety

Vitamin K has low potential for toxicity. The Food and Nutrition Board has not established ULs for this nutrient, as no adverse effects have been reported [21].

Vitamin K3 (menadione) was shown to damage hepatic cells in laboratory studies conducted during the 1980s and 1990s, so it is no longer used in dietary supplements or fortified foods [20,21].

For more information on vitamin K as a dietary supplement, see the Vitamin K (https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional) fact sheet from ODS.

Combination Therapies

Combinations of vitamins and other compounds are often used to manage PMDs, even though little evidence supports their safety and efficacy in this setting. A survey on clinical practices for the management of mitochondrial diseases showed that 14 of 32 physicians begin the use of vitamins as combinations rather than one at a time [19]. According to respondents, 69% of physicians recommend unique combinations, 13% use carnitine and CoQ_{10}, and 9% use a combination of creatine, CoQ_{10}, and B-complex vitamins [19].

Only a few published studies and case reports, described below by combination name in alphabetical order, have addressed the effects of specific combinations. Except for case reports, whose findings need to be replicated in RCTs, these studies have found few if any effects of combination supplements in patients with PMDs.

Alpha lipoic acid, Coenzyme Q_{10}, and creatine

A randomized, double-blind, placebo-controlled, crossover study examined the effects of 120 mg CoQ_{10}, 3 g creatine, and 300 mg ALA or placebo twice daily for 2 months, with a 5-week washout period, in 18 patients with MELAS, CPEO, KSS, LHON, MNGIE, or other mitochondrial diseases [28]. The outcome measures included biochemical analyses, strength measures, and pulmonary function. The results showed significant reductions in resting plasma lactate and oxidative stress levels but no effects on pulmonary function (force vital capacity and force expiratory volume) or strength measures (handgrip strength, ankle dorsiflexion fatigue, and knee extension). Patients with MELAS showed the greatest improvement with this supplement combination. The study did not report on safety or adverse events.

Carnitine and riboflavin

A case report found that a combination of 2 g/day L-carnitine and 9 mg/day riboflavin for 7 months improved clinical symptoms and normalized complex I activity in a 6-year-old with myopathy (associated with complex I deficiency) and a pure motor neuropathy [136]. After supplementation, the patient was able to run with mild foot drop and to ride a bike. Hand strength was almost normal, but tendon reflexes could not be elicited. Eighteen months after discharge, the patient had only a slight weakness in the peroneal muscles, and tendon reflexes were normal. The study did not report on safety or adverse events.

Carnitine, Coenzyme Q_{10}, vitamin C, vitamin K1, and vitamin B complex (biotin, cyanocobalamin, folic acid, niacin, pantothenic acid, pyridoxine, riboflavin, and thiamin)

An open-label trial evaluated the effects of a 12-month supplementation regimen that combined 5 mg/kg/day CoQ_{10}; 500 mg/day carnitine; 1,000 mg/day vitamin C; 0.4 mg/kg/day vitamin K1; and a vitamin B complex containing 25 mg/day riboflavin, 25 mg/day thiamin, 25 mg/day niacin, 25 mg/day pyridoxine, 25 mg/day pantothenic acid, 25 mcg/day biotin, 25 µg/day cyanocobalamin, and 1 mg/day folic acid in 12 patients with LHON, CPEO, MELAS, NARP, or cytochrome c oxidase deficiency [135]. Although one patient each with LHON, CPEO, and MELAS reported increased energy levels and improved exercise tolerance, the other nine patients, including some with the same conditions, showed no clinical improvement. Furthermore, one patient with CPEO reported worsening of symptoms. No side effects from the therapy were reported.

Carnitine, Coenzyme Q_{10}, vitamin C, vitamin E, vitamin K3, and riboflavin

A 1998 open-label study evaluated a combination of 100–200 mg/kg/day carnitine, 50–100 mg/kg/day vitamin E, 80–300 mg/kg/day CoQ_{10} as ubiquinone, 50–100 mg/day riboflavin, 80–160 mg/day vitamin K3, and 2 g/day vitamin C for 18 months. The study included 13 pediatric patients with CPEO and ptosis; CPEO with encephalopathy and epilepsy; KSS; or a variety of clinical symptoms, including epilepsy, ataxia, muscle weakness, ptosis, hypotonia, spasticity, neuropathy, and myopathy [137]. Outcomes of therapy differed, and the best responses (e.g., reductions in motor symptoms) were in patients with milder clinical forms of these diseases. The study did not report on safety or adverse events. Vitamin K3 is hepatotoxic and is no longer used in dietary supplements [20,21].

Coenzyme Q_{10}, vitamin C, vitamin E, and vitamin K3

A 1995 open-label study evaluated the effects of a combination therapy in 16 patients with mitochondrial myopathy, KSS, MELAS, or MERRF [138]. The therapy consisted of 30–120 mg/day CoQ_{10}, 20–60 mg/day vitamin K3, 2 g/day vitamin C, 400 IU/day vitamin E as alpha-tocopherol, and 2–16 mg every other day of methylprednisolone (to increase muscle strength and decrease serum lactate). No conclusions can be made about the safety and efficacy of this combination therapy based on the study design, data, and reporting of results. Duration of therapy and follow-up time after the therapy ended are not clear. In addition, the reported data are insufficient to evaluate the supplementation's effects on clinical outcomes. Moreover, some patients died during the study, but the authors did not explain whether these deaths could have been related to the use or discontinuation of the therapy. The study did not report on safety or adverse events. Vitamin K3 is hepatotoxic and is no longer used in dietary supplements [20,21].

Coenzyme Q_{10}, vitamin C, vitamin K3, niacin, riboflavin, and thiamin

A 1993 open-label trial evaluated the effects of a combination of 300 mg/day CoQ_{10}; 60 mg/day vitamin K3; 2 g/day vitamin C; and a supplement containing 25 mg riboflavin, 100 mg thiamin, 200 mg

niacin, and 500 mg vitamin C during two or more 2-month treatment periods in 16 patients with KSS, MERRF, myopathy, or both myopathy and demyelinating neuropathy [139]. The results showed no significant differences in serum lactate levels or urinary lactate-to-creatine ratios after treatment. Similarly, no significant differences were observed in measures of mitochondrial oxidative metabolism or clinical symptoms. Adverse events included temporary thrombocytopenia and diarrhea in some of the patients. Vitamin K3 is hepatotoxic and is no longer used in dietary supplements [20,21].

Folinic acid and riboflavin

In a case report, adding 1.2 mg/kg folinic acid and 0.5–1 mg/kg riboflavin to a folate-free dietary regimen improved neurological symptoms in a patient with mitochondrial complex I deficiency and CSF 5-MTHF deficiency [140]. A combination of 2 mg/kg/day CoQ_{10}, 10 mg/kg vitamin C, and 25 IU/kg vitamin E reduced seizure frequency but had no effect on clinical symptoms. Adding folinic acid and riboflavin to this combination controlled seizures after 1 year and reduced muscle hypotonia (poor muscle tone) and ataxia after 4 years but had no effect on cognitive impairment or lower limb pyramidal deficits. The patient also showed marked recovery from demyelination of the brainstem, thalamus, basal ganglia, and white matter. The study did not report on safety or adverse events.

Vitamin C and vitamin K3

In two case reports published in 1984 and 1995, vitamin K3 was combined with vitamin C in patients with PMDs associated with complex III deficiency.

In the first case report, supplementation with 40 mg/day vitamin K3 and 4 g/day vitamin C in a patient with complex III deficiency improved exercise tolerance and such activities as walking and climbing stairs and decreased fatigue within 2 days of starting supplementation; however, blood lactate levels did not decrease [120]. Phosphorus 31 nuclear magnetic resonance was used to measure the bioenergetic capacity of skeletal muscle. Doubling the dose of vitamin K3 to 80 mg/day did not result in further improvement; however, withdrawal of supplementation resulted in deterioration of clinical symptoms, and this deterioration disappeared in less than 24 hours after vitamin K3 supplementation was resumed. No toxicity was reported with the higher dose of vitamin K3 [141]. In the second report of a patient with complex III deficiency, 40 mg/day vitamin K3 and 4 g/day vitamin C for 9 months improved mitochondrial function in the brain and produced a minor but not significant improvement in skeletal muscle [119]. The supplementation had no effect on lactate levels, but it did mildly reduce ataxia after 3 months. This study did not report on safety or adverse events. Vitamin K3 is hepatotoxic and is no longer used in dietary supplements [20,21].

Interactions with Medications

Dietary supplements can interact with certain medications, and some medications can have an adverse effect on supplement levels. A few examples are provided below. Individuals taking these and other medications on a regular basis should consult their health care providers.

Carnitine

Some medications (e.g., cyclosporine, pivampicillin, and valproate) can decrease carnitine concentrations by forming compounds that are excreted in the urine [46]. In addition, the anticancer drugs etoposide, actinomycin D, and vinblastine; omeprazole for gastroesophageal reflux disease; and the antibiotic levofloxacin impair carnitine transport across the plasma membrane, which can result in secondary carnitine deficiency [46].

Coenzyme Q_{10}

Certain medications decrease the endogenous synthesis of CoQ_{10}. For example, cholesterol-lowering drugs, such as statins, might inhibit 3-hydroxy-3-methylglutaryl-CoA reductase, resulting in a decrease in mevalonic acid, the precursor of cholesterol and CoQ_{10} [63]. A meta-analysis of six randomized clinical trials showed a significant reduction in plasma CoQ_{10} concentrations after statin treatment that was independent of dose and duration [142]. Antihypertensive drugs (e.g., the beta blockers propranolol and metoprolol) and oral hypoglycemic drugs (e.g., glyburide and tolazamide) might inhibit CoQ_{10}-dependent enzymes [63]. Amitriptyline, a commonly prescribed antidepressant, can induce CoQ_{10} deficiency in patients with depressive episodes [143]. CoQ_{10} can also interfere with the effectiveness of warfarin [144,145].

Folinic acid

Folinic acid is used in combination with 5-fluorouracil (5-FU) to enhance 5-FU's effects, but it might also enhance 5-FU's toxicity [95,146]. High-doses of folinic acid might reduce the antiepileptic effects of phenytoin, phenobarbital, and primidone, potentially increasing the number of seizures in pediatric patients [95].

Niacin

Aspirin reduces the flushing associated with niacin supplementation [147-150]. Niacin might elevate plasma glucose concentrations, which could be dangerous for people with diabetes. Monitoring of blood glucose concentrations and adjustments of antidiabetic drugs in patients taking niacin supplements is advisable [149-151].

Vitamin C

Vitamin C in combination with other antioxidants might attenuate the increase in high-density lipoprotein levels that results from combined niacin and simvastatin (Zocor) therapy [152,153]. Whether this interaction occurs with other lipid-altering regimens is not known [149]. Health care providers should monitor lipid levels in individuals taking both statins and antioxidant supplements [149].

Vitamin K

Vitamin K can have a serious and potentially dangerous interaction with anticoagulants. These drugs antagonize the activity of vitamin K, leading to the depletion of vitamin K- dependent clotting factors. People taking warfarin and similar anticoagulants need to maintain a consistent intake of vitamin K from food and supplements because sudden changes in vitamin K intakes can increase or decrease the anticoagulant effect [154].

Thiamin

Although thiamin is not known to interact with any medications, certain medications can have an adverse effect on thiamin levels. Furosemide (Lasix) is a loop diuretic used to treat edema and hypertension by increasing urinary output. Research has linked the use of furosemide to decreases in thiamin concentrations, possibly to deficient levels, as a result of urinary thiamin loss [155-157].

5-FU (Adrucil) is a chemotherapy drug that is commonly used to treat colorectal and other solid tumors. The published literature includes several cases of beriberi or Wernicke's encephalopathy resulting from treatment with this drug, possibly because it might increase thiamin metabolism and block the formation of thiamin diphosphate, the active form of thiamin [158-161].

Vitamin E

Vitamin E can inhibit platelet aggregation and antagonize vitamin K–dependent clotting factors. As a result, taking large doses with anticoagulant or antiplatelet medications, such as warfarin (Coumadin), can increase the risk of bleeding, especially in conjunction with low vitamin K intakes. The amounts of supplemental vitamin E needed to produce clinically significant effects are unknown but probably exceed 400 IU/day [149].

Some people take vitamin E supplements with other antioxidants, such as vitamin C, selenium, and beta-carotene. This collection of antioxidant ingredients can blunt the rise in high-density lipoprotein (HDL) cholesterol levels, especially levels of HDL2, the most cardioprotective HDL component, among people treated with a combination of simvastatin (Zocor) and niacin [152,153].

Weighing the Evidence for Using Dietary Supplements to Manage PMDs

When the scientific literature is assessed for evidence of dietary supplements' effectiveness in supporting patients with PMDs, several general research and clinical challenges emerge.

Translating research results into clinical care decisions, even when higher levels of evidence for causality from RCTs on a particular dietary supplement for PMDs are available, is problematic because of the large variability in study designs and outcome measures used.

In some cases, clinical studies investigate a dietary supplement intervention in multiple PMD conditions and report outcomes without differentiating the level of response between specific PMDs, which may mask indications of effectiveness for only a specific condition. Conversely, indications of

effectiveness in a specific PMD do not necessarily support use of the same intervention in a different condition.

A general lack of consistency in the outcome measures used in studies, which include biochemical, physical, and neurological measures, limits the ability to assess the reproducibility of the research results and identify trends in efficacy. For this reason, mitochondrial specialists participated in a project sponsored by the National Institute of Neurological Disorders and Stroke to identify common data elements for PMDs to assist with future clinical trial designs [162].

Patients' baseline status with respect to specific nutrients and cofactors is not always determined before supplementation begins, making unclear whether the intervention corrected an underlying deficiency. Furthermore, without rigorously validated biomarkers for specific health outcomes, it is difficult to know how reported alterations in biochemical measures, such as blood lactate concentration or PCr/Pi ratio, might or might not translate into a clinically relevant improvement in a patient's health and function [163].

Challenges also abound in relation to the extent to which dietary supplement products used in PMD clinical research are characterized. Dietary supplements are complex products, and their formulations can dramatically affect the bioavailability and bioactivity of their ingredients. The compositions of products manufactured by pharmaceutical companies and biomedical research supply companies might only minimally resemble those of products available to patients and consumers in the marketplace. The studies reviewed in this document of all of these types of interventions offer limited details on the similarities between the products used in the studies and those available commercially. In addition, different supplement products labeled with the same ingredient can be formulated with different isomers, oxidation states, or stabilizing agents. Unfortunately, reporting on these important characteristics in materials and methods sections of research studies is often inadequate for the reader to confidently determine the exact nature of the intervention. In some cases, study reports provide only the common name of the experimental intervention (e.g., simply CoQ_{10}), which makes it nearly impossible to rigorously reproduce or follow up on the results in future studies.

These research design and intervention characterization issues, combined with the wide range of intervention doses and durations reported for certain ingredients (and the general lack of dose-response investigations), make comparison across studies challenging. These weaknesses also create a significant barrier to making definitive conclusions about dietary supplement effectiveness for managing PMDs.

Regulation and Quality of Dietary Supplements

The U.S. Food and Drug Administration (FDA) regulations for dietary supplements are different from those for prescription or over-the-counter drugs. Unlike drugs, which must be approved by FDA before they can be marketed, dietary supplements do not require premarket approval by FDA. The supplement company is responsible for having evidence that their products are safe and the label claims are truthful and not misleading. However, if a dietary supplement contains a new ingredient, manufacturers

must notify FDA about that ingredient prior to marketing. The notification will be reviewed by FDA, but only for safety, not effectiveness.

FDA has issued Good Manufacturing Practices (GMPs) for dietary supplements, a set of requirements and expectations by which dietary supplements must be manufactured, prepared, and stored to ensure quality. In addition, several nongovernmental organizations conduct product testing and GMP auditing programs. Dietary supplement products that display the seals from these independent certification programs give consumers more assurance that the product contains the ingredients and amounts listed on the label and that it does not contain harmful contaminants or adulterants. Importantly, the GMPs for dietary supplements and the certification programs do not guarantee that a product is safe or effective.

For more information on dietary supplements, see the ODS health information (https://ods.od.nih.gov/HealthInformation/makingdecisions.sec.aspx) page.

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