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Mitochondrial Disease Patients' Perception of Dietary Supplements' Use

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Abstract

Surveys of mitochondrial disease physicians conducted through the Mitochondrial Medicine Society have shown that virtually all providers recommend a variety of dietary supplements as treatments to their patients in an effort to enhance energy production and reduce oxidative stress. In this survey, we asked patients and their parents about their experiences taking these dietary supplements for mitochondrial disease. The survey was disseminated through the North American Mitochondrial Disease Consortium (NAMDC) and the Rare Disease Clinical Research Network (RDCRN) registries and gathered 162 responses. The study ascertaine each patient's mitochondrial disease diagnosis, dietary supplements used, adjunct therapy, and effects of the supplements on symptoms and health.

Regardless of the specific underlying mitochondrial disease, the majority of the survey respondents stated they are or have been on dietary supplements. Most patients take more than four supplements primarily coenzyme Q_{10}, L-carnitine, and riboflavin. The majority of patients taking supplements reported health benefits from the supplements. The onset of perceived benefits was between 2 weeks to 3 months of initiating intake. Supplements seem to be safe, with only 28% of patients experiencing mild side-effects and only 5.6% discontinuing their intake due to intolerance. Only 9% of patients had insurance coverage for their supplements and when paying

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out of pocket, 95% of them spend up to $500/month. Despite the use of concomitant therapies (prescribed medications, physical therapy, diet changes and other), 45.5% of patients think that dietary supplements are the only intervention improving their symptoms. Some limitations of this study include the retrospective collection of data probably associated with substantial recall bias, lack of longitudinal follow up to document pre- and post-supplement clinical status and second hand reports by parents for children which may reflect parents' subjective interpretation of symptoms severity and supplements effect rather than real patients' experience. More extensive prospective studies will help further elucidate this topic.

Keywords

Mitochondrial disease; Dietary supplements; survey

INTRODUCTION

Mitochondrial diseases (MD) are a group of genetically inherited rare diseases that affect approximately 1 in 3,000–5,000 people worldwide [1–4]. They are primarily due to mitochondrial respiratory chain dysfunction impairing adenosine triphosphate (ATP) production. The biochemical defects typically lead to multisystem failure of variable severity affecting all age groups and causing severe morbidity and high mortality and lack specific treatments or cures. Due to the heterogeneity and rarity of the diseases, there has been limited research and few data from randomized trials to guide any symptomatic treatment option[5].

Mitochondrial supportive therapy aims at enhancing mitochondrial function by either (1) increasing ATP production through augmenting substrate availability, respiratory chain enzyme activity, electron transfer or bypassing specific respiratory chain complexes that are known to be deficient; or by (2) reducing toxic metabolites to improve oxidative capacity. The multiplicity of agents explains why only few studies have examined the effects of a single supplement administration in MD [6, 7] and why most therapeutic strategies have focused on combination of supplements targeting diverse processes. None of these therapies has been robust enough to demonstrate efficacy in case reports [8, 9], open-label trials [10–12] retrospective studies [13], or small-scale clinical trials [14]. Furthermore, because most of these therapeutic agents are considered dietary supplements available over the counter rather than pharmaceutical drugs, there have been few financial incentive and resources to study these therapies rigorously[15]. Only one randomized, double-blind, placebo-controlled clinical trial of creatine, coenzyme Q_{10}, and alpha lipoic acid, has shown slight clinical efficacy (mild increase in ankle dorsiflexion strength) in a cohort of 16 patients with heterogeneous mitochondrial diseases [14]. This minor improvement is insufficient to justify widespread use of these supplements in MD patients.

Despite the lack of sound scientific evidence that dietary supplements are effective for MD, combinations of these compounds, colloquially described as "mito cocktails", are frequently recommended by physicians and have become a "standard of care"[16, 17]. Under pressure from the patients and their advocates and due to the severity of the diseases and lack of other

alternatives, a survey of physicians treating MD in the US revealed that all have adopted this practice [18]. The majority of these providers (69%) did not concur on the form, dose, or measures of efficacy of these cocktails [18]. Lack of reliable biomarkers and generalizable outcome measures for mitochondrial diseases have hindered clinicians from assessing therapeutic efficacy. In spite of the lack of proven efficacy and high cost, patients are paying out-of-pocket for these supplements and health care providers are faced with vexing dilemmas about whether and how those supplements should be used. Physicians must balance the needs of an informed patient base that often demands to be on dietary supplements in part due to influential advertisements which emphasize the benefits of these supplements (more than 50,000 different products on the US market with $36.7 billion spent in 2014 including $14.3 billion for vitamin and mineral containing supplements [19]) with their ethical oath of “do no harm”. This dilemma is even more relevant as more rare genetic conditions with no specific cure are diagnosed for which patients and families will turn to over-the-counter options.

Because perceptions of patients and families regarding the use of dietary supplements is unknown, we conducted this survey study to better understand the landscape of dietary supplement use by MD patients. We assessed the types and doses of supplements used by patients with MD and whether any subjective improvements have been noted. We also gauged the opinions of patients and families regarding dietary supplements therapy in MD.

MATERIAL AND METHODS

A comprehensive questionnaire was designed to capture the patients’ experiences in obtaining and using dietary supplements for their mitochondrial disease. The survey was directed at patients and parents of patients who are or have been on dietary supplements and included 20 questions divided into four parts (Appendix 1). Part 1 queried the primary mitochondrial disease diagnosis and symptoms that impacted patients the most. Part 2 explored the nature of the dietary supplements used, their side-effects, their cost and whether their use had impacted any of the symptoms they described as most bothersome. Part 3 assessed whether other adjunct therapies were used to treat mitochondrial disease and, if so, whether they contributed to symptoms improvement. Lastly, Part 4 evaluated patient satisfaction with dietary supplements use, cost and financial burden incurred if paying out-of-pocket.

The survey was administered electronically through two registries: the self-enrolled patient Contact Registry of the Rare Disease Clinical Research Network (RDCRN) and the North American Mitochondrial Disease Consortium (NAMDC) patient registry, which is a clinician curated registry for individuals with suspected or confirmed mitochondrial diseases. The survey was sent to 1115 subjects who were enrolled in these registries at the time of the survey. They had confirmed biochemical diagnoses of mitochondrial dysfunction, primary mitochondrial diseases, fatty acid oxidation disorders and other metabolic diseases. Responses were obtained from 162 (14.5%). IRB approval for this study was obtained and informed consent was acquired online from each participant prior to administration of the study questionnaire. De-identified survey data was stored and managed

by the RDCRN Data Management and Coordinating Center at the University of South Florida.

Inclusion criteria for patients included mandatory registration through NAMDC Clinical Registry or RDCRN Contact Registry and a diagnosis of a mitochondrial disease confirmed by either electron transport chain abnormalities or molecular genetic testing. Exclusion criteria included patients who did not meet the inclusion criteria or were never on any dietary supplements.

RESULTS

The dietary supplement online survey was completed by 162 respondents: 59% were patients and 41% caregivers of patients with mitochondrial disease (125 completed and 37 incomplete surveys).

PART I: Mitochondrial disease diagnosis

The three most represented diseases were: mitochondrial myopathy (20%), complex I deficiency (10.7%), and chronic progressive ophthalmoplegia [(CPEO/CPEO+); (10.6%)] together comprising more than half of the patients. Mitochondrial DNA disease such as MELAS (5.6%) and MERRF (4.4%) were also well-represented (Table 1). Since the survey did not specifically ask about the genetic mutations for each subject, provided diagnoses are self reported.

The most common symptoms reported by all patients were fatigue (61%) and subjective weakness (50%) followed by: temperature instability (48%), exercise intolerance (42.5%), and myalgia (38%). These likely reflect the majority of the respondents suffering from mitochondrial myopathy. Many of the symptoms involved the neurological and gastrointestinal systems and are summarized in Table 2. When asked about the five most bothersome symptoms, at least 57% of patients described a combination of constitutional, musculoskeletal, neurological, and gastrointestinal complaints.

PART II: Dietary supplements used in mitochondrial disease

When asked “How many dietary supplements have you/your child been taking?” 75% of patients reported taking four or more supplements at once while only 11% of patients reported taking only one supplement. The most commonly used supplements included: coenzyme Q_{10} (42.5% including both ubiquinol and ubiquinone), L-carnitine (36%), riboflavin (26.5%), vitamin D (24%) and vitamin C (15%). In total, 25 different supplements were being used by patients with mitochondrial disease in various combinations that were almost unique to each patient (Table 3). Moreover, 68 out of the 162 respondents reported other over-the-counter products that they were regularly using to treat their symptoms (Table 3).

Despite being on multiple supplements, 72% of respondents reported no side-effects. Among the 36 patients who reported having side-effects attributed to the dietary supplements (too numerous to list), 47% had nausea and upset stomach, 36% unpleasant or increased body odor (8%), and 17% had diarrhea (Table 4). There would be no definitive

method to attribute a side effect to a specific supplement in these cases especially when some patients were not only on supplements but also on other prescribed medications concomitantly. Less than 6% of patients discontinued supplements due to these side effects. Strategies used to minimize side effects included: a decrease in dose (21%), altering timing of supplement intake (11.5%) or intake with food (17%), combining the supplements (10%), or changing brands (8%). Some patients decided to experiment with their supplements on their own using one at a time to pinpoint the major source of the side-effect.

More than half (54%) of patients reported that after initiating supplements, their five most bothersome symptoms were alleviated. Fatigue was the most frequently improved symptom (49%), followed by exercise intolerance, muscle pains, and weakness (26% each). Gastrointestinal dysmotility symptoms and some of the neurological symptoms (headache, seizures, myoclonus, and spasticity) were less responsive to the use of dietary supplements with less than 12% reporting improvement. In addition, patients specifically reported improvement in the ability to concentrate, cognition/memory, focus, gross and fine motor skills, immunity, digestion and sleep. One patient reported less frequent stroke-like episodes, three reported less migraines, and four patients felt that being on the dietary supplements seemed to slow disease progression. There was no correlation between the type of mitochondrial disease and response to supplements intake.

There was no clear timeline between the initiation of the supplements and when the symptomatic improvement started as 29% of respondents thought positive effects started 2 weeks after intake, 15% within 3–4 weeks, 31% within 1–3 months and 25% after 4 full months of treatment.

For the 62 respondents who did not feel any improvement on supplements, 38% noted that there was some unrecognized benefit that became noticeable once off the supplements. Those benefits were mainly related to energy level, muscle weakness, and general symptoms. This same effect was reported by patients who were forced to stop supplements for various reasons (cost 11%, side-effects 5.7%, and other 12%). Interestingly, among patients who reported no subjective benefits from supplements, only 26% of respondents discontinued their use.

Dietary supplements were fully covered by insurance in only 9% of the survey respondents of whom 36% had to resubmit or appeal the insurance decision at least once before obtaining final approval. Insurance coverage was not contingent on the inclusion of the FDA approved drug Carnitor (L-carnitine) to the dietary supplements. For most respondents, monthly out-of-pocket expense ranged from less than $200 a month (69% of patients) to $200–500 range (26%) and more than $500 a month (4.5%) with the highest expense of $800/month. Dietary supplements were compounded by a specialty pharmacy for 24% of respondents and were purchased at a dietary supplement store by 20%, regular pharmacy/ over the counter by 39% or over the internet in 34%.

PART III: Other adjunct therapy

In this survey section, patients were asked if they had started any other therapies concomitant to the initiation of the dietary supplements; 34% answered affirmatively. These

therapies included: increased fluid intake via oral, intravenous or through gastrointestinal tubes (55%), new medications (pain management, thyroid replacement, anti-depressants, anti-seizure and dysautonomia treatments) (45%), dietary changes (e.g. more balanced diet, low fat, high carbohydrae, gluten-free, ketogenic diet, or enteral feeds) (27%) and exercise (e.g. dedicated exercise regimen, walking and physical therapy) (25%). Other interventions included moving from warm states to cooler states, allergy testing with subsequent elimination of specific foods from the diet and cognitive therapy.

Among the patients who reported improvement in clinical symptoms while taking supplements, 45.5% believed that this was the result of dietary supplementation alone while 49% thought it was the effect of combining the dietary supplements to other adjunct therapies. Seventeen patients attributed their improvement to a specific supplement even if they were taking several at once. These supplements were coenzyme Q_{10}, L-carnitine, magnesium, and anti-oxidants. Hormonal therapy for thyroid and adrenal insufficiencies were also noted to improve symptoms.

PART IV: Dietary supplement(s) evaluation

The last part of the survey assessed the convenience of being on dietary supplements in patients with MD. Most respondents found supplements intake to be convenient (32.5%) or very convenient (36%) whereas less than one-third felt it was somewhat inconvenient (25.5%) to very inconvenient (6%). The main reasons cited for inconvenience were: the overwhelming number and size of the supplements (48%); the frequency of intake that was difficult to follow especially for working patients who had to carry large amounts of bottles and pill holders (26%); dysphagia (18.5%); bad taste of these supplements (5%); and lack of appetite and fatigue (2.5%) that made intake difficult. Apart from logistical issues, a major inconvenience for 53% of respondents was the financial burden caused by the high costs of dietary supplements.

Patients were given the opportunity to comment on any changes that would improve the dietary supplement intake experience. Not surprisingly, the most common requested improvements were cost reduction along with enhanced insurance coverage of the supplements. In addition, a combination pill to reduce volume and frequency of intake was also high on the wish list as were requests for either a liquid form or a capsule formulation that has a better taste and is easier to swallow. A few patients commented on the need for more research to better understand the role of these supplements and to enable more detailed guidelines of supplement choice and dosing for patients.

DISCUSSION

There are no evidence-based efficacious therapies yet for mitochondrial disease. Over the years, physicians have utilized a variety of vitamins and other dietary supplements in attempts to treat mitochondrial patients. The dietary supplements used may increase mitochondrial substrate availability (L-carnitine), increase mitochondrial electron transfer flux (ubiquinol/ubiquinone, riboflavin), serve as co-factors for enzymes (riboflavin, thiamine), provide an energy buffer (creatine), or act as antioxidants (e.g. vitamins C and E, alpha lipoic acid, idebenone, and coenzyme Q_{10}). In addition, compounds such as L-arginine

have been used to increase nitric oxide production, which may ameliorate or prevent mitochondrial strokes attributed to regional vasoconstriction. Few clinical trials have been completed assessing the efficacy of these various compounds [13, 14, 20]. A recent review noted the treatment challenges facing the field of mitochondrial disease in terms of lack of scientific evidence for the appropriate use of dietary supplements** [16] The latest consensus statement from the mitochondrial medicine society only recommends offering coenzyme Q10, riboflavin and alpha lipoic acid to patients with MD. They also add that the use of L-carnitine and folinic acid should be limited to cases with well-documented deficiencies [21].

In this survey, we have observed that the majority of patients with mitochondrial disease are or have been on dietary supplements irrespective of their primary underlying diagnosis and symptoms. The majority of patients take more than 4 supplements at once containing primarily coenzyme Q_{10}, L-carnitine, riboflavin, and vitamin D. These are primarily bought over the counter or on the internet, are not typically covered by insurance, and cause a substantial financial burden on patients and families. More than half the patients reported a health benefit from being on the supplements within 0.5–3 months of initiation. Supplements appear to be safe, with only 28% of patients experiencing side-effects and only 5.6 % of those discontinuing their intake. Despite concomitant other therapies, 45.5% of patients think dietary supplements are the only intervention improving their symptoms. This study has some limitations including the retrospective collection of data probably associated with substantial recall bias. Patients were not followed longitudinally to document their pre- and post-supplement intake status to more accurately assess benefits and side-effects. The multisystemic nature of MD and yearning for a therapy is also likely to influence patients' perception of supplements efficacy and may lead to overestimation of benefit compared to other interventions used. Moreover, a substantial number of responses were obtained from parents on behalf of their children and reflect parents' subjective interpretation of symptoms severity and supplements effect rather than real patients' experience. Lastly, since the survey did not specifically address the molecular diagnosis of each respondent who self reported their mitochondrial disease diagnosis, it is difficult to interpret the effect of the dietary supplements on mitochondrial dysfunction vs. primary mitochondrial disease. It is assumed that all respondents had some degree of mitochondrial biochemical dysfunction which may benefit from dietary supplements to enhance the electron transport chain activity. This survey emphasizes the need for further studies with well defined subject groups having a clearly defined molecular diagnosis of mitochondrial disease vs. a secondary mitochondrial dysfunction to elucidate commonalities and differences in symptom control and side effect profile on dietary supplements within the two groups.

CONCLUSION

This survey suggests that the majority of patients with mitochondrial disease take dietary supplements recommended by a physician or on their own and report some level of benefit and with a reassuringly mild side-effect profile. Nevertheless, the use of supplements imposes on patients and their families a large financial burden that is difficult to justify due to the lack of rigorous studies demonstrating significant clinical benefit. More studies are necessary to determine whether a single supplement or a combination of supplements is

acceptably safe and superior in efficacy to placebo. If positive, such studies will establish a much-needed standard of practice for clinicians to optimally treat this vulnerable population with dietary supplements. Conversely, if no overall benefit to the supplements is found, this finding will eliminate unnecessary side-effects and expenses for patients.

In December of 2014, the National Institute of Health Office of Dietary Supplements (ODS) in partnership with the NIH Institutes and other Federal agencies organized the first workshop on “Dietary Interventions in Primary Mitochondrial Disease: Developing and Evidence Base”. All of these issues were addressed by the mitochondrial disease stakeholders, including the Federal partners, NAMDC, mitochondrial advocacy groups, mitochondrial patients, physicians and scientists. Workshop goals included exploring the use of dietary supplements in primary mitochondrial disease; identifying knowledge gaps regarding safety and efficacy of dietary supplements; identifying research opportunities; and forging collaborations[19].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NAMDC	North American Mitochondrial Disease Consortium
RDCRN	Rare Disease Clinical Research Network
MD	Mitochondrial disease
CPEO	Chronic progressive external ophthalmoplegia
MELAS	Mitochondrial encephalomyopathy with lactic acidosis and stroke
MERRF	Myoclonic epilepsy with ragged red fibers

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Highlights

Mitochondrial disease patients highlight their experiences taking dietary supplements.

Most patients take more than four supplements

The majority of patients reported health benefits with mild side-effect profile.

Supplements impose a large financial burden without rigorous proof of health benefit.

Table 1

Mitochondrial disease diagnoses represented in the survey

Mitochondrial disease	Frequency	Percent
Mitochondrial Myopathy	32	20.1
Complex I deficiency	17	10.7
CPEO	12	7.5
MELAS	9	5.7
Kearns-Sayre syndrome	8	5.0
Leigh syndrome	7	4.4
MERRF	7	4.4
Complex III deficiency	6	3.8
Multiple complex deficiencies	6	3.8
Encephalomyopathy	5	3.2
Leber hereditary optic neuropathy (LHON)	5	3.2
Mitochondrial DNA depletion	5	3.2
CPEO "plus"	5	3.2
Coenzyme Q_{10} deficiency	3	1.9
Complex IV deficiency	3	1.9
POLG spectrum (Alpers Syndrome, SANDO)	3	1.9
Carnitine transporter defects	1	0.6
Complex II deficiency	1	0.6
NARP	1	0.6
Pyruvate dehydrogenase deficiency	1	0.6
Other (including: NDUFAF5, CARS2, OPA1, MTCO3, CPT2 mutations; Leigh-like disease*; and ataxia)	23	14.5

*Features of Leigh disease that do not meet all criteria for a clinical diagnosis or remain without a molecular diagnosis.

Table 2

Most frequent patients/parents reported symptoms*.

Constitutional		Musculoskeletal		Neurological		Gastro-Intestinal		Cardiac		Other	
High Frequency symptoms (in >50% of patients)											
Chronic fatigue	61 %			Weakness	50%						
Medium frequency symptoms (in 25–50% of patients)											
Temperature instability Exercise intolerance	48 % 42.5 %	Myalgia	38 %	Ptosis Headaches/Migraines Developmental delay /Intellectual disability	30% 28% 27%	Irritable bowel syndrome Dysphagia	33% 25%			Anxiety	25%
Low frequency symptoms (in <25% of patients)											
Difficulty gaining weight Growth delay Cachexia Lipoma	12 % 6% 5% 3%	Myoglobinuria Rhabdomyolysis	1.5 % 2%	Myoclonus PEO Seizures Ataxia Neuropathy Hypotonia Spasticity Dysarthria Optic Atrophy Dystonia Hearing loss Stroke/TIA Developmental regression Autism Dementia	20 % 17 % 17 % 17 % 17 % 15 % 15 % 15 % 11 % 10 % 9% 7% 5.5 % 8% 3.7 %	Gastroparesis GI dysmotility Nausea/Vomiting Pseudoobstruction Steatosis Pancreatic dysfunction Hepatopathy	23% 14% 12%5 % 4.5% 3% 2%	Arrhythmias SOB Syncope Cardiomyopathy	18 % 11 % 6 % 4 %	Depression Thyroid disease Diabetes Short stature Parathyroid disease Hypogonadism Delayed puberty Renal tubulopathy	19 % 9 % 7 % 7 % 7 % 2 % 3 % 2 %

* patients reported more than one symptom at a time. For most patients a combination of constitutional, musculoskeletal, neurological and gastro-intestinal complaints were reported in combination.

Table 3

Dietary supplement intake reported by patients.

Supplements	Frequency of intake n (%)	Daily Doses
L-Carnitine	58 (36)	330–5000 mg
Ubiquinol	51 (31.5)	30–2000 mg
Vitamin B2 (Ribofalvin)	43 (26.5)	5–400 mg
Vitamin D	39 (24)	400–50,000 IU
Vitamin C (Ascorbic acid)	24 (15)	120–1500 mg
Vitamin B12 (Cobalamin)	22 (13.5)	48–1000 mcg
Alpha Lipoic Acid	22 (13.5)	50–2400 mg
Creatine	22 (13.5)	0.5–12 gram
Vitamin B1 (Thiamin)	21 (13)	5–300 mg
Vitamin E (Tocopherol)	20 (12)	200–2000 IU
Ubiquinone	18 (11)	30–2400 mg
Calcium	16 (10)	200–2000 mg
Vitamin B6 (Pyrodoxin)	14 (8.6)	5–100 mg
Magnesium (Bisglycinate, gluconate, citrate, rotate)	13 (8)	133–1200 mg
Vitamin B3 (Niacin)	13 (8)	25–550 mg
Folic Acid	12 (7)	0.8–800 mg
L-Arginine	10 (6)	0.5–18 gram
Vitamin H (Biotin)	7 (4)	100–1000 mcg
Vitamin K (Phytonadione)	7 (4)	25–3200 mcg
Folinic Acid	7 (4)	0.1–150 mg
N-Acetyl Cysteine (NAC)	7 (4)	100–1000 mg
Citrate (Bi, Tri, Poly)	3 (2)	Variable
Selenium	2 (1)	75–200 mcg
L-Citrulline	2 (1)	100–1500 mg
Phosphorus	1 (0.6)	Unknown
Uridine	0	NA
Succinate	0	NA

Other supplements use reported	
Pro biotics	Blue green algae
MCT oil	Taurine
Multivitamin	Tocotrienols
B complex	Ornithine
Brewers yeast	Alpha-ketoglutarate
Fish oil	Tart cherry juice
Idebenone	Green tea extract
L-Glutathione	Garlic
Methionine	Carotinoids

Supplements	Frequency of intake n (%)	Daily Doses
NADH	Flavinoids	
Coconut oil	Turmeric	
Potassium Gluconate	Ginger	
SAM-e	Sodium pyruvate	
Milk thistle	Spirulina	

Table 4

Reported side effects from dietary supplements intake in 36 patients.

Side effect	Frequency (%)
Nausea	47
Upset stomach	47
Bad smell	36
Other (Shortness of breath, anemia, balance problem, bleeding, deep vein thromboses)	22
Diarrhea	17
Weight gain	14
Sleep disturbances	11
Intolerable taste	11
Vomiting	8
Headaches	8
Increased body odor	8
Rash	5.5
Itching	5.5
Fatigue	5.5
Hives	3
Increased sensitivity to light	3
Anxiety	3
Kidney problems	3
Dizziness	3
Confusion	3
Muscle cramping	3
Loss of appetite	3
Low blood sugar	3