

NIH Office of Dietary Supplements

Nutritional Interventions in Primary Mitochondrial Disorders: Developing an Evidence Base

December 2-3, 2014
Neuroscience Center
6001 Executive Boulevard Rockville, MD

Executive Summary

The Office of Dietary Supplements (ODS), National Institutes of Health (NIH), sponsored a workshop titled “Nutritional Interventions in Primary Mitochondrial Disorders: Developing an Evidence Base” on December 2-3, 2014, at the NIH Neuroscience Center in Rockville, MD. The workshop focused on the use of nutritional interventions, including dietary supplements (e.g., vitamins, minerals, and other dietary ingredients) in primary mitochondrial disorders (PMD). Attendees included researchers, health care providers, government scientists and regulators, and representatives from advocacy organizations and industry who have an interest in research issues pertaining to the use of nutritional interventions in primary mitochondrial disorders.

The goals of the workshop were to:

- Explore the use of nutritional interventions, including dietary supplements, in PMD.
- Identify gaps in knowledge regarding the safety and effectiveness of nutritional interventions.
- Identify research opportunities.
- Develop a research agenda to promote an evidence base for the use of nutritional interventions in PMD.
- Forge collaborations among researchers, clinicians, patient advocacy groups, and Federal partners.

Workshop co-sponsors included NIH’s National Center for Advancing Translational Sciences’ (NCATS) Office of Rare Diseases Research (ORDR) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the Wellcome Trust (London, United Kingdom), and the United Mitochondrial Diseases Foundation (UMDF).

The workshop’s agenda featured sessions and panel discussions on: (1) setting the stage; (2) defining PMD; (3) describing how nutritional interventions are used in PMDs; (4) challenges and barriers to dietary supplement use in PMD; (5) perspectives from patient advocacy groups, industry, and professional organizations; (6) new technologies and -omic approaches to diagnosis, treatment, and understanding mechanisms of action; and (7) research opportunities and resources. After these sessions and panel discussions, workshop attendees participated in a facilitated discussion incorporating the information presented and discussed during the workshop to develop an outline that may be used to help inform a research agenda for PMD in general as well as for the use of nutritional interventions in PMD. The following seven key areas were identified as important issues to incorporate into a research agenda moving forward:

1. Defining the Disease

Defining PMD was a recurrent theme throughout the meeting. The challenges of defining subgroups largely relate to overlapping organ system involvement and extreme heterogeneity in these conditions.

Short-term actions to address these issues/challenges include:

- Using the results of the North American Mitochondrial Disease Consortium (NAMDC) diagnostic criteria review and related efforts in the United Kingdom to inform future work.
- Developing strategies for the sub classification of mitochondrial disorders.
- Establishing a committee or similar body to review and share analyses of select challenging cases.
- Reviewing and refining the definitions of PMD on a regular basis.
- Considering opportunities for genomic nosology.
- Forming a workgroup to focus on issues related to biochemical laboratory testing standards.

Over the long term, the workshop participants agreed on the need for flexible definitions and recognized the importance of precision medicine in this area.

2. Biomarkers/Outcome Measures/Endpoints

A key question facing researchers in the field of PMD is: What biomarkers for monitoring disease exist and are feasible and clinically useful? It would be extremely beneficial if clinical researchers banked samples from current trials so that in the future, if some signal or response is identified, these samples could be mined for quantitative biomarkers that would have clinical utility. Moving forward, a good stress response paradigm for mitochondrial disease is needed, particularly in terms of intermediary metabolism.

One short-term action identified in this area was responding to the public comment period for the National Institute of Neurological Disorders and Stroke Common Data Elements for mitochondrial diseases project. Two long-term actions were also identified: (1) developing measures for metabolic response to stress *in vivo*, dynamic measures, and oligomycin tests; and (2) developing measures of activity.

3. Mechanistic Approaches/Preclinical Studies

Throughout this meeting, the power of systemic, “approach agnostic” efforts was discussed. These include comprehensive transcriptome, proteome, metabolome, etc. approaches that represent the next wave of starting to understand these conditions at an important biochemical/metabolic level. The value of looking at ratios was emphasized, especially those not predicted *a priori* to be valuable. Over the last five years, there has been an explosion in the number of accurate mouse models for mitochondrial disease. Examining the effects of the current agents used in mitochondrial dietary supplement regimens in these models could help inform which genetic subtypes respond to certain therapies. The need for preclinical rigor was also emphasized.

Short-term actions identified in this area include: (1) evaluating mouse models for response to mitochondrial dietary supplements, and (2) the development of a consortium (similar to NCI’s Mouse Models Consortium) to allow comparison of data across laboratories.

4. Clinical Trial Design

Examples of well-designed clinical trials that have been incorporated in the mitochondrial field were discussed throughout the workshop, but these types of trials may not always be feasible (particularly in patients already on regimens that include multiple dietary supplements). Workshop participants emphasized the need to consider the rigorous evaluation of any intervention with particular care given to the inclusion criteria/stratification of subjects, dose and duration of treatment, and study endpoints.

The value of crossover designs (allowing patients to serve as their own control) was noted, as was the need for creative strategies to address studies with very small enrollments.

Identified short-term actions in this area include:

- Developing a prioritization scheme of interventions for limited patients.
- Reaching agreement on therapeutic priorities.
- Holding annual meetings to prioritize PMD therapies
- Developing a central repository of comparative data related to molecules and supplements used to treat primary mitochondrial disorders (possibly using MSeqDR) and developing a standard template to collect data.
- Utilization of centralized institutional review boards.

5. Challenges of Nutritional Interventions for Primary Mitochondrial Disorders

There is a lack of consistency in the content of mitochondrial dietary supplement regimens and a lack of evidence regarding their effectiveness when used in PMD. Translating cell-based assays of dietary supplements to use in patients is challenging, and there is limited understanding of the benefits and risks associated with long-term dietary supplement use. Issues related to the access to dietary supplements include insurance coverage and the high costs to patients and families. One common theme throughout the workshop was again emphasized: the mitochondrial disease community should strongly encourage every potential patient to enroll in a community registry.

Identified short-term actions in this area include:

- All clinicians who see mitochondrial patients who are taking supplements can encourage them to choose products that have some standardized label (e.g., with symbols from the U. S. Pharmacopeia, Natural Products Association, or Consumer Labs) to demonstrate that the content is as listed on the dietary supplement facts label.
- Development of a “toolkit” for patients, providers, and hospitals to provide helpful information about use of dietary supplements in mitochondrial diseases.
- Exploring additional opportunities for partnership with foundations.
- Encouraging all patients to be part of registry.
- Bench-to-bedside collaborations between NIH intramural and extramural investigators.
- Utilizing NIH’s Therapeutics for Rare and Neglected Diseases services for drug development.
- Meeting with the FDA to discuss how to move a dietary supplement into the drug regulatory process and to seek help with clinical trial design for testing and comparing supplements.

An identified long-term action was the development of a central pharmacy source of dietary supplements for clinical use.

6. Standards of Clinical Care for Patients with Primary Mitochondrial Disorders

A number of important issues were identified that have not been rigorously studied. For example, within the context of standards of clinical care for patients with PMD, it has been well recognized that the baseline status of these patients is poorly understood. This understanding is needed in order to optimize their nutrition. Some clinicians are using the ketogenic diet, yet little is known about its use for those with refractory epilepsy, and there are questions regarding its safety. The development of clinical guidelines for patients with mitochondrial disorders is an important need; groups such as the American College of Medical Genetics can provide assistance in this regard. A comprehensive guideline for all mitochondrial diseases is not feasible; however, it may be possible to develop guidelines in certain areas of focus (e.g., a particular genotype or phenotype).

Short-term actions related to standards of clinical care for patients with PMD include:

- Identifying a phenotype for an initial venture for practice guidelines
- Using clinical care guidelines developed by the Newcastle group in the United Kingdom to inform the development of guidelines in the United States.

One long-term action was identified: potentially accrediting mitochondrial disease “Centers of Excellence.”

7. Collaboration Issues

Collaboration issues are cross-cutting. Mitochondrial disorders are rare diseases and the number of patients is small. There is a need to pool resources and coordinate efforts and registries; this needs to be an international effort. Partners in this endeavor include researchers, clinicians, foundations and patient advocacy groups, international partners, regulatory bodies, patients and families, and industry.