

MITO 101 – Endocrinology

Matthew M. Feldt, DO and Douglas S. Kerr, MD, PhD

Center for Inherited Disorders of Energy Metabolism,
Pediatric Endocrinology and Metabolism, Rainbow Babies and Childrens Hospital,
Case Western Reserve University, Cleveland, Ohio, 44106-6004

Key points:

- Virtually all endocrine systems may be affected by mitochondrial disease syndromes. Endocrine glands are heavily dependent on ATP for energy, thus mitochondrial dysfunction can greatly reduce the ability to secrete hormone or maintain normal feedback regulation.
- Mitochondria host several metabolic pathways including the tricarboxylic acid cycle, lipid and cholesterol biosynthesis, and β -oxidation of fatty acids, which are critical in maintaining the cytosolic free calcium gradient that serves as an important pathway in hormonal secretion. [1]
- Diagnosis involves recognition of endocrine symptoms associated with mitochondrial diseases and careful surveillance for hormonal deficiencies.
- Management is focused on appropriate treatment to re-establish metabolic homeostasis, i.e., insulin for hyperglycemia.

Specific Endocrine Disorders:

Impaired insulin secretion and resistance (Type 1 and Type 2 diabetes mellitus):

- Initial symptoms may include hyperglycemia, ketoacidosis, or weight loss as in "Type 1" insulin deficient diabetes mellitus (DM). Other patients may present as gestational DM progressing into insulin- or non insulin-dependent DM. Alternately, patients may be initially insulin-resistant as in "Type 2" DM, sometimes progressing to insulin dependence. [2] The latter has been described in maternally inherited DM and deafness due to the mtDNA 3243 mutation (MELAS) (see Table 1).
- In the pancreatic β -cell, alteration of the ATP:ADP ratio due to impaired mitochondrial ATP synthesis may decrease the cell's ability to secrete insulin at physiological glucose concentrations. The "glucose sensor" is reset, resulting in impaired glucose tolerance or frank hyperglycemia and diabetes mellitus.[3]
- Other mechanisms of reduced insulin secretion may involve over-production of reactive oxygen species (ROS) within the pancreatic β -cell. [4] Excessive ROS can further impair mitochondrial ATP production and stimulate β -cell apoptosis. [5] Pancreatic β -cells are at increased risk from ROS due to low expression of antioxidant enzymes and high oxidative energy requirement. [6]
- The action of insulin on skeletal muscle is also under the influence of mitochondrial ATP production and β -oxidation of free fatty acids. Impaired mitochondrial metabolism, increased intracellular ROS, and elevated free fatty acids may inhibit insulin receptor signaling, resulting in decreased uptake and utilization of glucose by skeletal muscle. [7,8]

Impaired hypothalamic and pituitary function:

- Short stature, poor weight gain or failure to thrive are commonly associated with mitochondrial diseases. For example, short stature has been documented in 38% of patients with Kearns-Sayre Syndrome (KSS). [9] Hypothalamic rather than pituitary dysfunction may result in inadequate secretion of growth hormone (GH). The majority of subjects fail to show sufficient GH response upon stimulation testing and demonstrate increased rates of linear growth with GH supplementation. [10]
- Hypogonadism resulting in genital immaturity, amenorrhea and delay of puberty is typically secondary to decreased secretion of gonadotropins from the

hypothalamic-pituitary axis. Similar to GH, there are blunted LH and FSH responses to stimulation testing. [11] However, primary gonadal failure has been found in some mitochondrial disorders, such as in males with Wolfram Syndrome (refer to Table 1). These subjects have decreased testicular volumes and elevated gonadotropins despite progressing normally through puberty. [12]

- Posterior pituitary dysfunction manifests in central diabetes insipidus and decreased vasopressin secretion, as seen in Wolfram Syndrome. [13] With inadequate vasopressin, increased urination, hypernatremia, and dehydration can become life-threatening complications.

Impaired adrenal function:

- Complete or partial adrenal insufficiency can be associated with mitochondrial DNA deletion syndromes, such as Pearson and Kearns Sayre (KSS) Syndromes. [14] Subjects may present in salt-wasting Addisonian crises with increased skin pigmentation from elevated ACTH, weight loss, and hypotension, sometimes associated with deafness and DM. Hyponatremia, hyperkalemia, acidosis, decreased glucocorticoids and mineralocorticoids are found on laboratory evaluation. Impaired mitochondrial ATP production is the most likely explanation for the decreased capacity of adrenocortical hormone production. [15]

Thyroid and parathyroid function:

- Hypothyroidism can be associated with MELAS or KSS. However, since thyroid dysfunction is common in the general population, it should be routinely considered in individuals with any form of mitochondrial dysfunction.
- Hypoparathyroidism and hypocalcemia can present with paresthesia and carpopedal spasms or, more severely, with convulsions and stiffness. Biochemical evaluation demonstrates hypocalcemia, hyperphosphatemia, and inappropriately low serum parathyroid hormone. When associated with KSS and deafness, hypoparathyroidism almost exclusively manifests during childhood and may precede myopathic or neurological signs. [16]

Diagnosis of Endocrine Manifestations in Mitochondrial Disease Syndromes:

- Awareness of increased risk for endocrine deficiencies is crucial in prevention of morbidity and mortality.
- Manifestations of endocrine dysfunction may be the presenting or exclusive sign of the mitochondrial disease process. For example, it is estimated that 0.5-2.8% of diabetes mellitus may be of mitochondrial etiology. [2,17]

Management and Treatment of Endocrine Disorders of Mitochondria Syndromes:

- Consultation with an endocrinologist familiar with management of the particular hormonal deficiency is recommended.
- During illness or increased catabolic stress, endocrine dysfunction may be accentuated and may require more intensive therapy.
- The treatment of a particular endocrine manifestation (e.g., diabetes mellitus) is not qualitatively different from that used in individuals who have no underlying mitochondrial disorder. Reference to standard endocrinology sources is appropriate for further details.
- Commonly used nutritional supplements such as carnitine, coenzyme Q10, and vitamins are not contraindicated in combination with traditional hormonal

replacement therapy, although to date there is a shortage of objective clinical evidence as to the benefits of such supplements. [18,19]

References:

1. James AM, Murphy MP. How mitochondrial damage affects cell function. *J Biomed Sci* 2002;9:475-87.
2. Guillausseau PJ, Massin P, Dubois-LaForgue D, *et al.* Maternally inherited diabetes and deafness: a multicenter study. *Ann Intern Med.* 2001;134:721-8.
3. Stark R, Roden M. Mitochondrial function and endocrine diseases. *Eur J Clin Invest* 2007;37:236-248.
4. Maassen JA, Hart LM, Essen E. *et al.* Mitochondrial diabetes: molecular mechanisms and clinical presentation. *Diabetes* 2004;53:103-9.
5. Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging and cancer: a dawn for evolutionary medicine. *Annu Rev Genet* 2005;39:359-407.
6. Simmons RA, Suponitsky-Kroyter I, Selak MA. Progressive Accumulation of Mitochondrial DNA Mutations and Decline in Mitochondrial Function Lead to β -Cell Failure. *J Biol Chem.* 2005;280:28785-91.
7. Brehm A, Krssak M, Schmid AI, *et al.* Increased Lipid Availability Impairs Insulin-Stimulated ATP Synthesis in Human Skeletal Muscle. *Diabetes* 2006;55:136-40.
8. Kim J, Wei Y, Sowers JR. Role of Mitochondrial Dysfunction in Insulin Resistance. *Circ Res.* 2008;102:401-414.
9. Harvey JN, Barnett D. Endocrine function in Kearns-Sayre Syndrome. *Clin Endocrinol.* 1992;37:97-103.
10. Matsuzaki M, Izumi T, Shishikura K, *et al.* Hypothalamic growth hormone deficiency and supplementary GH therapy in two patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. *Neuropediatrics.* 2002;33:271-3.
11. Ohkoshi N, Ishii A, Shiraiwa N, *et al.* Dysfunction of the hypothalamic-pituitary system in mitochondrial encephalomyopathies. *J Med.* 1998;29:13-29.
12. Menlejt R, Wasson P, Baz P, *et al.* Diabetes Mellitus/Optic Atrophy in Wolfram Syndrome. *J Clin Endocrinol Metab.* 2004;89:1656-1661.
13. Minton JA, Rainbow LA, Ricketts C, *et al.* Wolfram Syndrome. *Rev Endocr Metab Disord.* 2003;4:53-9.
14. Boles RG, Roe T, Senadheera D, *et al.* Mitochondrial DNA deletion with Kearns Sayre Syndrome in a child with Addison disease. *Eur J Pediatr.* 1998;157:643-647.
15. Nicolino M, Ferlin T, Forest M, *et al.* Identification of a Large-Scale Mitochondrial Deoxyribonucleic Acid Deletion in Endocrinopathies and Deafness: Report of Two Unrelated Cases with Diabetes Mellitus and Adrenal Insufficiency, Respectively. *J Clin Endocrinol Metab.* 1997;82:3063-7.
16. Wilichowski E, Grütters A, Kruse K, *et al.* Hypoparathyroidism and Deafness Associated with Pleioplasmic Large Scale Rearrangements of the Mitochondrial DNA: a Clinical and Molecular Genetic Study of Four Children with Kearns-Sayre Syndrome. *Pediatr Res.* 1997;41:193-200.

17. Donovan LE, Severin NE. Maternally inherited diabetes and deafness in a North American kindred: tips for making the diagnosis and review of unique management issues. *J Clin Endocrinol Metab.* 2006;91:4737-42.
18. Suzuki S, Hinokio Y, Ohtomo M, *et al.* The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation. *Diabetologia* 1998;4:584-588.
19. Armstrong JS. Mitochondrial Medicine: Pharmacological targeting of mitochondria in disease. *British Journal of Pharmacology* (2007);151:1154–1165

Table 1

Mitochondrial Disease	Genetic Abnormality	Associated Endocrine Diseases
MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)	Point mutations: 3243 tRNA 3271 tRNA other tRNAs	Diabetes mellitus, growth hormone deficiency, short stature, hypogonadism, hypoparathyroidism, hypothyroidism
MIDD (Maternally inherited diabetes and deafness)	Point mutation: 3243 tRNA	Diabetes mellitus
Pearson marrow pancreas syndrome	mtDNA deletion	Adrenal insufficiency
KSS (Kearns-Sayre Syndrome)	mtDNA deletion or duplication	Diabetes mellitus, growth hormone deficiency, short stature, hypogonadism, hypoparathyroidism, hypothyroidism
Wolfram Syndrome or DIDMOAD (Diabetes insipidus, diabetes mellitus, optic atrophy, deafness)	Heterogeneous mtDNA deletions and nuclear mutations of WFS1 gene	Diabetes insipidus, diabetes mellitus, primary hypogonadism, short stature