Mitochondrial Dysfunction in the Context of Mast Cell Activation, Connective Tissue Disorders, Lipedema, and Postural Orthostatic Tachycardia Syndrome: A Narrative Review

Prepared by Darleen Claire Wodzenski, MS ESE, MA CMHC, PhD, LPC, NCC, ACS

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Introduction

A growing body of literature suggests that mitochondrial dysfunction is not merely a downstream consequence of chronic illness but may function as a shared pathophysiological node connecting several overlapping conditions: mast cell activation syndrome (MCAS) and related mast cell activation disorders (MCADs), hypermobile Ehlers-Danlos syndrome (hEDS) and other connective tissue disorders, lipedema, and postural orthostatic tachycardia syndrome (POTS). These conditions frequently co-occur in the same patients, disproportionately affect women, and share overlapping symptom clusters including fatigue, exercise intolerance, dysautonomia, and impaired recovery from exertion (Gutowski et al., 2023; Kohn & Chang, 2020). Patient history often reveals onset of fatigue during childhood or adolescence. This report, compiled in a joint human-AI collaborative process, synthesizes current evidence documenting mitochondrial involvement across these conditions and outlines proposed shared mechanisms.

Important Notice

- ***Educational Use Only:*** *Content is meant to share general knowledge, not to replace professional medical care.*
- ***Consult Your Team:*** *Bring these details to your personal medical team for review.*
- ***Individual Care:*** *Your providers know your history best and can adjust guidance for your specific body.*

Mitochondrial Dysfunction and Mast Cell Activation

Mast cells are metabolically dynamic immune cells that depend heavily on mitochondrial function to meet the energetic demands of degranulation. Mendoza et al. (2021) described how mast cell activation requires rapid shifts between oxidative phosphorylation and glycolysis, and noted that disruptions to this metabolic flexibility are increasingly implicated in mast cell activation syndrome specifically, not simply mast cell disease broadly.

Mitochondria appear to be mechanistically central to mast cell degranulation itself. A systematic review of anaphylaxis and mast cell degranulation found that mitochondrial respiratory complex integrity and membrane potential are required for degranulation to proceed, and that antigen stimulation increases reactive oxygen species (ROS) production from both NADPH oxidases and mitochondria, which in turn drives further degranulation (Piotin et al., 2024). The same review reported that during anaphylactic shock, cardiac dysfunction has been associated with left ventricular mitochondrial impairment and lipid peroxidation, and that skeletal muscle may experience a near-complete failure of energy production due to impaired oxygen availability during severe mast cell activation events.

There is also evidence for a bidirectional, self-reinforcing relationship between mast cell activity and mitochondrial health. Gorman and Syed (2024) proposed that mast-cell-derived tumor necrosis factor (TNF) may directly contribute to mitochondrial dysfunction, which then exacerbates pro-inflammatory signaling and further upregulates mast cell activity, forming a feedback loop in which impaired mitochondria and dysregulated mast cells sustain one another over time.

Theoharides et al. (2026), in a recent expert review on mast cell activation disorders, emphasized that dysregulated mast cell activation produces hundreds of proinflammatory, neurotoxic, and tissue-disrupting mediators through multiple degranulation mechanisms, and that MCAS overlaps substantially with other neuroinflammatory and dysautonomic conditions. While this review did not focus exclusively on mitochondrial mechanisms, it underscored that MCAS diagnostic criteria and clinical presentation are frequently entangled with comorbid conditions that independently involve mitochondrial and autonomic dysfunction.

Mitochondrial Dysfunction, Ehlers-Danlos Syndrome, and Connective Tissue Disorders

Hypermobile EDS (hEDS) is increasingly understood as a multisystem disease rather than a purely musculoskeletal disorder, with substantial symptom overlap with MCAS and dysautonomia. Gutowski et al. (2023), in a review of mast cell involvement in musculoskeletal disease, noted that up to 25% of patients with hEDS also meet criteria for MCAS, and that both conditions disproportionately affect women and share features including gastrointestinal dysfunction, chronic pain, fatigue, and autonomic dysfunction. The authors highlighted hereditary alpha-tryptasemia as a recently recognized condition linking hEDS and MCAS, and identified tryptase- and histamine-driven effects on fibroblast-to-myofibroblast transition as a plausible mechanistic bridge between mast cell activity and abnormal connective tissue production.

Chambers (2023) proposed a more direct biochemical link between connective tissue disorders and cellular energy metabolism, arguing that oxidative stress and overloaded mitochondria are primary determinants of symptom expression across EDS, MCAS, POTS, and related conditions, even though EDS and the MTHFR gene variants discussed are independently genetic. This review reported that intramuscular magnesium supplementation improved pain, emotional state, and energy in patients with EDS, and connected EDS-associated dysautonomia to magnesium-dependent mitochondrial enzyme function, including monoamine oxidase and diamine oxidase, both of which are mitochondrially based and required for catecholamine and histamine clearance.

Kohn and Chang (2020) reviewed the relationship between hEDS, POTS, and MCAS as a commonly co-occurring triad, describing shared connective tissue and autonomic vulnerabilities that may predispose patients to all three conditions simultaneously, though the specific mitochondrial contribution to this triad remains an active area of investigation rather than a settled mechanism.

Mitochondrial Dysfunction in Lipedema

Lipedema, a chronic adipose tissue disorder affecting up to 10% of women and characterized by disproportionate lower-limb fat accumulation, pain, and resistance to conventional weight loss, has recently been linked to intrinsic mitochondrial abnormalities within adipose tissue itself. A 2025 review synthesizing mechanistic and translational evidence described lipedema pathophysiology as involving adipocyte hypertrophy, chronic inflammation, extracellular matrix fibrosis, mitochondrial dysfunction, and sex steroid imbalance operating together, rather than any single mechanism in isolation, and specifically reported that lipedema adipose tissue shows reduced oxidative capacity and downregulation of thermogenic proteins responsible for adaptive energy expenditure (Viana et al., 2025).

A related narrative review by the same research group focused specifically on inflammatory myosteatosis in lipedema, proposing that mitochondrial dysfunction, impaired fatty acid oxidation, chronic inflammation, and extracellular matrix fibrosis act as interrelated pathogenic nodes sustaining metabolic rigidity within lipedema-affected adipose depots and adjacent skeletal muscle. This review described a hypothesized sequence in which ectopic lipid deposition within muscle leads to mitochondrial inflexibility, oxidative stress, and reduced contractile efficiency, potentially explaining reduced muscle strength in advanced lipedema despite preserved or increased limb volume (Viana et al., 2026). Separately, translational research presented through the University of the Pacific Research and Creativity Showcase found that lipedema adipose-derived stem cells show impaired thermogenic activation driven by dysregulated protein expression and mitochondrial dysfunction, limiting the tissue's ability to mobilize stored lipid despite retaining beige adipocyte potential (Scholarly Commons, 2026a, 2026b). Together, this line of evidence positions mitochondrial impairment as a plausible contributor to lipedema's well-documented resistance to standard weight-management interventions, rather than attributing that resistance to behavioral or caloric factors alone.

Mitochondrial Dysfunction in Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is understood as a heterogeneous, multifactorial autonomic disorder, and mitochondrial involvement has been documented both as a downstream consequence of the condition and, in some cases, as a probable upstream contributor. A pediatric POTS review described the condition as arising from a combination of altered central blood volume, abnormal autonomic reflexes, hyperadrenergic activity, impaired skeletal muscle pump function, abnormal vascular tone, mast cell activation, and autoimmune dysfunction, frequently overlapping in the same patient (Chen et al., 2020).

A direct connection between primary mitochondrial disease and POTS has also been documented clinically. In a single-center study of patients with confirmed mitochondrial cytopathy, four of six patients demonstrated a postural orthostatic tachycardia response on tilt-table testing, presenting with the classic POTS symptom cluster of fatigue, palpitations, near-syncope, and syncope (as summarized in Oracle Health Sciences, 2025, drawing on primary clinical literature). This suggests that autonomic dysfunction consistent with POTS may be a recognized, if underappreciated, manifestation of underlying mitochondrial myopathy rather than a coincidental comorbidity.

More recent interventional research has demonstrated that mitochondrial function in POTS patients is measurable and modifiable. A pilot study evaluating time-restricted eating in POTS patients found that the intervention improved not only quality of life and heart rate metrics but also mitochondrial-derived ATP production over a 12-week period, with heart rate increase upon standing reduced by an average of 11 beats per minute. The authors specifically noted that circadian rhythm disruption is increasingly recognized as a shared feature of POTS and myalgic encephalomyelitis/chronic fatigue syndrome, contributing to mitochondrial dysfunction, impaired immune response, and autonomic dysregulation (Dzotsi et al., 2025).

Shared Mechanistic Threads: Methylation, Magnesium, and Oxidative Stress

Chambers (2023) proposed a unifying biochemical framework connecting Long COVID, chronic fatigue syndrome, POTS, MCAS, small intestine bacterial overgrowth, and EDS through abnormalities in the methylenetetrahydrofolate reductase (MTHFR) gene and its downstream effects on methylation, oxidative stress, and mitochondrial cofactor availability. This review argued that MTHFR variants, present in a majority of the general population, create either a hypomethylated or hypermethylated state depending on genotype and available cofactors (riboflavin, B6, folate, B12, and magnesium), and that this methylation imbalance directly affects mitochondrially based enzymes responsible for clearing catecholamines and histamine, including monoamine oxidase (MAO), diamine oxidase (DAO), and catechol-O-methyltransferase (COMT).

Under this framework, hypomethylation is proposed to favor high-flow POTS (via impaired histamine clearance and vasodilation) and to activate genes associated with EDS, MCAS, and small intestine bacterial overgrowth, while more severe methylation disruption may favor a hyperadrenergic, low-flow POTS presentation instead (Chambers, 2023). The review further noted that magnesium deficiency independently increases histamine release and mast cell numbers, and that magnesium, vitamin D, and B-vitamin insufficiency are each individually documented in POTS, EDS, and MCAS populations, suggesting a shared nutritional and biochemical vulnerability across all three conditions rather than three unrelated disease processes.

Oxidative stress emerges as a recurring theme across every condition reviewed here: excess reactive oxygen species generated during mast cell degranulation, adipose tissue dysfunction in lipedema, and autonomic dysregulation in POTS all converge on impaired mitochondrial oxidative phosphorylation, reduced ATP availability, and a cellular shift toward glycolysis and fermentation as a protective but less efficient alternative energy pathway (Chambers, 2023; Evrard et al., 2024; Mendoza et al., 2021).

Summary

Current literature does not yet establish mitochondrial dysfunction as a single unifying cause of MCAS, hEDS/connective tissue disorders, lipedema, and POTS. However, **converging evidence across independent lines of research supports mitochondrial involvement as a consistent and mechanistically plausible feature of each condition individually, and several proposed frameworks (methylation status, magnesium-dependent enzyme function, oxidative stress, and mast-cell-mitochondria feedback loops) offer testable explanations for why these conditions cluster together clinically, particularly in female patients with multisystem symptom presentations**. Further prospective and mechanistic research is needed to clarify causal direction and to identify which mitochondrial biomarkers may be clinically actionable in this patient population. Meanwhile, patients affected by co-occurring disorders as discussed herein who also deal with fatigue or malaise can bring this information to discuss with medical professionals to explore possible ameliorating strategies that address mitochondrial optimization.

This educational handout provides general information on nutrition and mitochondrial health only. It is not medical advice, diagnosis, or treatment. Always share and discuss this information with your primary care provider, doctor, pharmacist, registered dietitian, or other qualified healthcare professional before making any changes to your health plan.

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