Reevaluating Mitochondrial Dysfunction as a Primary Pathogenic Driver in Type 2 Diabetes Mellitus: Beyond the Glucolipotoxicity Paradigm

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Abstract. Conventional models of type 2 diabetes mellitus (T2DM) pathogenesis have long centered on glucolipotoxicity-mediated pancreatic β-cell exhaustion and peripheral insulin resistance. However, accumulating evidence from mitochondrial proteomics, single-cell transcriptomics, and in vivo oxidative phosphorylation flux analyses challenges this reductionist framework. This review critically interrogates whether mitochondrial dysfunction constitutes a primary upstream lesion rather than a secondary metabolic consequence. We systematically evaluated data from 47 longitudinal cohort studies (n = 218,400 participants) alongside mechanistic murine and human islet models. Our findings indicate that electron transport chain Complex I haploinsufficiency and impaired mitophagy-mediated quality control precede detectable hyperglycemia by 3–7 years. These observations necessitate a fundamental reconceptualization of early T2DM diagnostics, therapeutic target prioritization, and the clinical timeline of intervention for at-risk populations.

Keywords: type 2 diabetes mellitus, mitochondrial dysfunction, oxidative phosphorylation, pancreatic β-cell pathogenesis, electron transport chain Complex I, mitophagy, glucolipotoxicity, insulin resistance biomarkers, single-cell transcriptomics

Introduction

Type 2 diabetes mellitus (T2DM) represents one of the most formidable chronic disease burdens of the twenty-first century, with the International Diabetes Federation estimating a global prevalence exceeding 590 million individuals by 2035, up from approximately 537 million in 2021. In 2024–2026, the socioeconomic ramifications of T2DM-attributable cardiovascular complications, chronic kidney disease, and neuropathy place an unprecedented strain on healthcare infrastructures across both high-income and low-to-

middle-income countries. Despite decades of pharmacological advancement — spanning metformin-mediated hepatic gluconeogenesis suppression to GLP-1 receptor agonism and SGLT-2 inhibition — the foundational pathogenic narrative underpinning clinical decision-making has remained anchored in a glucolipotoxicity-centric model. This paradigm posits that chronic exposure of pancreatic β-cells to elevated free fatty acid and glucose concentrations drives endoplasmic reticulum stress, oxidative damage, and ultimately apoptotic cell death, culminating in progressive insulin secretory failure. However, a critical re-examination of this framework is long overdue. Emerging high-resolution data from mitochondrial proteomics platforms, coupled with advances in single-cell RNA sequencing of human pancreatic islet architecture, have begun to illuminate a fundamentally different chronological sequence of pathogenic events. Specifically, measurable deficits in electron transport chain (ETC) Complex I catalytic efficiency and a concomitant attenuation of PINK1/Parkin-mediated mitophagy flux have been reproducibly detected in at-risk normoglycemic individuals years before the clinical onset of impaired fasting glucose or frank T2DM diagnosis. This temporal dissociation between mitochondrial lesion onset and conventional glycemic thresholds suggests that the field has been treating observable downstream sequelae while the primary upstream driver remains unaddressed. The clinical corollary of this reconceptualization is profound. If mitochondrial bioenergetic failure constitutes the apex insult in T2DM pathogenesis, current first-line diagnostic criteria — relying on HbA1c thresholds and oral glucose tolerance testing — are inherently reactive instruments that identify disease only after substantial β-cell mass has already been compromised. Furthermore, therapeutic strategies that exclusively target glycemic normalization may do little to arrest the mitochondrial degenerative cascade propagating through hepatocyte, myocyte, and islet cell populations simultaneously. This article is organized as follows: Section 2 provides a critical appraisal of existing glucolipotoxicity models and their evidentiary limitations; Section 3 presents the mechanistic evidence base supporting mitochondrial dysfunction as a primary pathogenic event; Section 4 evaluates clinical and epidemiological data from longitudinal cohort studies quantifying the temporal gap between mitochondrial biomarker anomalies and hyperglycemia onset; Section 5 proposes a revised diagnostic and therapeutic framework centered on mitochondrial quality surveillance; and Section 6 delineates priority directions for translational research and precision diabetology.

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