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Mitochondrial Dysfunction in Obesity-Associated Insulin Resistance and Diabetes Progression

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ABSTRACT

Mitochondria govern cellular energy, redox balance, and metabolite signaling across metabolic tissues. In obesity, chronic nutrient oversupply glucose, fatty acids, and branched-chain amino acids forces mitochondria to operate outside their adaptive ranges, triggering bioenergetic inefficiency, oxidative stress, and maladaptive signaling that promote insulin resistance (IR) and accelerate type 2 diabetes (T2D). Key defects include substrate overload with incomplete fatty-acid oxidation, electron transport chain (ETC) imbalance, altered TCA cycle anaplerosis/cataplerosis, and dysregulated mitochondrial dynamics (excess fission, impaired fusion), biogenesis (PGC-1α axis suppression), and selective autophagy (mitophagy). Inter-organelle communication deteriorates: mitochondria-associated ER membranes (MAMs) mis-handle Ca2+ and lipid trafficking, linking ER stress to impaired insulin action and β-cell failure. Reactive oxygen species (ROS) and lipid peroxides, when sustained, inhibit insulin signaling nodes (IRS–PI3K–Akt), reprogram immune cells, and propagate "metaflammation." Tissue context matters: adipose, liver, skeletal muscle, and pancreatic islets exhibit distinct mitochondrial vulnerabilities that converge on systemic dysglycemia. Therapeutically, exercise and caloric deficit restore mitochondrial quality control, while approved agents (metformin, SGLT2 inhibitors, incretin-based therapies, TZDs) exert multi-organ benefits that include improved mitochondrial efficiency or reduced substrate stress. Emerging strategies—NAD+ repletion, sirtuin/AMPK activation, redox modulators, mitophagy inducers, and safe thermogenic augmentation aim to correct root mitochondrial defects. Precision phenotyping with imaging and multi-omics may identify mitochondrial endotypes that guide therapy choices. This review synthesizes mechanistic links between mitochondrial dysfunction and progression from obesity-associated IR to T2D and outlines therapeutic opportunities to restore organelle health alongside glycemic control.

Keywords: mitochondria; insulin resistance; obesity; reactive oxygen species; mitophagy

INTRODUCTION

Insulin resistance (IR) arises when nutrient-sensing networks cannot match fuel supply with disposal, forcing compensatory hyperinsulinemia and eventually unmasking β-cell vulnerability[1–3]. Among the many drivers of IR in obesity adipose inflammation, ectopic lipids, endocrine perturbations mitochondria sit at a central intersection. These organelles oxidize substrates (glucose, fatty acids, amino acids), buffer Ca2+, shape redox tone, and generate signals (NADH/NAD+, acetyl-CoA, ROS, TCA intermediates) that regulate transcription, protein acetylation/succinylation, and enzyme activity[4–7]. When caloric intake and sedentary behavior chronically elevate substrate flux, mitochondrial flexibility is stressed at multiple levels: bioenergetics, dynamics, quality control, and inter-organelle crosstalk.

A prevailing misconception holds that "fewer" or "weaker" mitochondria necessarily cause IR. Human studies show that: some people with obesity retain normal oxidative capacity yet are insulin-resistant; others display reduced oxidative phosphorylation (OXPHOS) but remain insulin-sensitive[8]. The reconciliation is context. In adipose tissue, insufficient mitochondrial capacity relative to lipolytic flux impairs re-esterification and promotes inflammatory signaling. In skeletal muscle, a mismatch between lipid delivery and oxidation fosters accumulation of diacylglycerols and ceramides, which activate novel PKCs that blunt insulin signaling[8]. In the liver, augmented β-oxidation increases TCA cycle flux and anaplerotic/cataplerotic cycling, sustaining gluconeogenesis despite hyperinsulinemia. In pancreatic β-cells, chronic lipoglucotoxic stress disrupts ATP/ADP dynamics, Ca2+ oscillations, and mitochondrial membrane potential, undermining glucose-stimulated insulin secretion[9–11].

Mitochondria adapt through biogenesis (PGC-1α–NRF1/2–TFAM), dynamics (fusion: MFN1/2, OPA1; fission: DRP1), and selective autophagy (PINK1/Parkin, BNIP3/NIX)[12, 13]. Obesity tends to repress

biogenesis, tilt dynamics toward fragmentation, and impair mitophagy—together reducing organelle quality. Parallel shifts in post-translational modifications (acetylation, succinylation) alter enzyme kinetics across OXPHOS and β-oxidation. ROS, while normal signals at low levels, become pathogenic when chronic, oxidizing lipids/proteins/DNA, opening the mitochondrial permeability transition pore (mPTP), and activating stress kinases (JNK, IKK) that inhibit insulin signaling. ER stress and mitochondrial dysfunction co-amplify each other via mitochondria-associated membranes (MAMs), where Ca2+ and phospholipid traffic support both ATP production and insulin granule biogenesis; maladaptation here contributes to hepatic and islet dysfunction.[4, 5, 7, 14]

Importantly, mitochondrial "quantity" is not the sole therapeutic target. Restoring *quality* efficient coupling/uncoupling balance, resilient dynamics, faithful mitophagy, and healthy crosstalk may yield outsized benefits even without large changes in mass[15]. Exercise exemplifies this principle: endurance and resistance training enhance mitochondrial content and function, improve substrate switching, and reduce intramyocellular lipids independent of dramatic weight loss. Pharmacologic tools that lower substrate burden (SGLT2 inhibitors), redistribute lipid (TZDs), or reduce appetite and improve islet physiology (incretin-based therapies) indirectly rescue mitochondrial stress[15]. Looking forward, precise measurement of mitochondrial phenotypes in accessible tissues, along with circulating biomarkers and imaging, can enable individualized strategies to halt progression from obesity-associated IR to overt T2D by repairing the organelles that choreograph cellular metabolism.

2. Bioenergetic Stress in Obesity: Substrate Overload, ETC Imbalance, and TCA Rewiring

Nutrient oversupply alters mitochondrial workload and stoichiometry. Elevated fatty-acid delivery increases β-oxidation, generating excess NADH/FADH2 that load the ETC. When electron input exceeds downstream capacity (complexes I–IV), electrons leak to oxygen, forming ROS[16]. Concurrent high glycolytic flux floods pyruvate dehydrogenase (PDH), while malonyl-CoA from lipogenesis inhibits CPT1, producing cycles of incomplete fatty-acid oxidation (FAO). The outcome is bioenergetic inefficiency—elevated proton motive force, greater "leak" respiration, and higher ROS per ATP[17].

In skeletal muscle, this mismatch manifests as intramyocellular DAG/ceramide accumulation that activates PKCθ/ε, inhibiting IRS-1–PI3K–Akt signaling and GLUT4 translocation. In the liver, sustained FAO raises TCA flux and citrate export, supporting de novo lipogenesis even as gluconeogenesis persists an apparent paradox explained by compartmentalization and anaplerosis/cataplerosis (PEPCK-mediated efflux of TCA intermediates)[18]. In adipose tissue, impaired mitochondrial glyceroneogenesis compromises re-esterification of fatty acids, increasing NEFA spillover; adipocyte ROS/JNK signaling promotes inflammatory cytokines and lipolysis, reinforcing systemic IR.

At the enzymatic level, obesity induces post-translational modifications that tune fuel handling. Hyperacetylation (low NAD+, high acetyl-CoA) of FAO and TCA enzymes dampens catalytic efficiency; SIRT3 normally deacetylates and activates multiple mitochondrial targets (e.g., LCAD, isocitrate dehydrogenase)[19]. Meanwhile, PDH is inhibited by PDKs, favoring lactate production and reducing glucose oxidation despite hyperglycemia. Together, these changes trap cells in a high-fuel, low-efficiency state where ATP demands are met but signaling consequences (ROS, metabolite pooling) impede insulin action[19].

The bioenergetic solution is not simply to "burn more." Appropriate coupling/uncoupling balance matters. Mild uncoupling can reduce ROS by lowering membrane potential, yet excessive uncoupling wastes energy and risks cachexia. Exercise training shifts this balance productively: increased mitochondrial content, improved ETC stoichiometry, augmented antioxidant defenses, and better capillarity collectively reduce ROS per unit ATP and enhance substrate flexibility[20]. Pharmacologic interventions that lower substrate input (appetite/weight loss via incretin-based therapies; glycosuria via SGLT2 inhibitors) or that reprogram flux (TZDs redistributing lipids to adipose) indirectly decompress mitochondrial bioenergetics across tissues.

3. Mitochondrial Dynamics and Quality Control: Fusion, Fission, Biogenesis, and Mitophagy

Mitochondria remodel continuously to match energetic and biosynthetic needs. Fusion (MFN1/2, OPA1) mixes matrices and membranes to dilute damaged components and complement mtDNA gene products; fission (DRP1 and adaptors) enables biogenesis, distribution, and segregation of damaged segments for turnover[21]. Biogenesis depends on PGC-1α coactivating NRF1/2 and ERRs to induce nuclear-encoded mitochondrial genes, with TFAM governing mtDNA replication/transcription. Damaged mitochondria are cleared via mitophagy, canonically through PINK1 stabilization on depolarized membranes and Parkin-mediated ubiquitination, or through receptor-mediated pathways (BNIP3, NIX, FUNDC1) engaging LC3[21].

Obesity perturbs each node. In muscle and liver, DRP1 activation and reduced MFN2/OPA1 promote fragmentation, which correlates with IR. In adipose tissue, decreased PGC-1α signaling reduces oxidative capacity and beige adipocyte recruitment; dysfunctional dynamics impair lipolysis–re-esterification cycles and adipokine secretion[22]. In β-cells, chronic nutrient stress fragments networks, weakens ATP-linked Ca2+ oscillations, and impairs insulin granule exocytosis. Mitophagy often lags, allowing damaged mitochondria to accumulate, perpetuating ROS and releasing mitochondrial danger signals (e.g., mtDNA) that activate innate immunity[22].

Quality control extends beyond canonical pathways. The mitochondrial unfolded protein response (UPRmt) increases chaperones and proteases to restore proteostasis; when inadequate, apoptosis or necroptosis may

ensue. Mitochondrial dynamics intersect with metabolism acetylation state, lipids (cardiolipin), and redox tone modulate fusion/fission machinery[23]. Conversely, restoring dynamics can rescue metabolism: exercise upregulates PGC-1α, normalizes MFN/OPA1 expression, and enhances mitophagy via AMPK–ULK1 signaling. TZDs may improve adipose mitochondrial biogenesis through PPARγ; metformin activates AMPK, promoting fission-for-mitophagy turnover and biogenesis in a net-beneficial cycle[23].

Therapeutically, the challenge is selectivity. Broad fission inhibition or fusion activation risks impairing cell division or stress adaptation. Safer strategies aim upstream (AMPK/SIRT1 activation; NAD+ repletion) or target mitophagy checkpoints to remove only dysfunctional organelles[24]. Nutritional timing (time-restricted feeding) and exercise serve as physiologic "pulses" that synchronize biogenesis and mitophagy, refreshing the mitochondrial pool and restoring insulin sensitivity.

4. Redox Biology: ROS Signaling, Oxidative Damage, and Antioxidant Defenses

ROS are double-edged. At physiologic levels, H_2O_2 mediates insulin-sensitizing signals (e.g., transiently inhibiting phosphatases to permit Akt activation). In obesity, chronic substrate pressure elevates mitochondrial superoxide production at complexes I and III; fatty-acid oxidation increases electron leak, while reverse electron transport (RET) under high membrane potential amplifies ROS[25]. Non-mitochondrial sources like NADPH oxidases (e.g., NOX4), xanthine oxidase, uncoupled NOS add to the burden. Persistent ROS oxidize lipids (forming reactive aldehydes), proteins (carbonylation), and mtDNA, opening mPTP, reducing ATP synthesis, and activating stress kinases (JNK, p38) that blunt insulin signaling. Lipid peroxides and by-products impair membrane properties, ETC function, and Ca^{2+} handling[25].

Cells counter with antioxidant systems: SOD2 converts superoxide to H_2O_2; catalase, GPX, and peroxiredoxins reduce H_2O_2; glutathione and thioredoxin systems recycle oxidized proteins. Sirtuins (SIRT3 in mitochondria) deacetylate and activate multiple antioxidant enzymes[26]. In obesity/T2D, these defenses are inadequate or inappropriately localized. Importantly, indiscriminate antioxidant supplementation has yielded inconsistent benefits, likely because it blunts adaptive ROS signaling while failing to reach key subcellular sites[26].

A more nuanced approach emphasizes redox *compartmentalization* and source-specific targeting. Strategies include reducing substrate input (diet, exercise, pharmacotherapy), improving ETC stoichiometry (exercise-induced biogenesis), and deploying targeted agents that modulate mitochondrial ROS without abolishing signaling (e.g., mitochondria-accumulating antioxidants or peptides)[27]. Enhancing NADPH generation (through malic enzyme or pentose phosphate pathway flux) supports endogenous peroxide-reduction systems[27]. Iron handling matters as well; dysregulated mitochondrial iron–sulfur cluster biogenesis fosters ROS and impairs ETC complexes. Ultimately, restoring redox balance supports insulin signaling fidelity, preserves mitochondrial DNA/proteins, and reduces inflammatory activation that feeds systemic IR.

5. Inter-Organelle Crosstalk: ER–Mitochondria Contacts, Ca^{2+} Dynamics, and Lipid Trafficking

Mitochondria function within an organelle network. Mitochondria-associated ER membranes (MAMs) mediate close contacts that coordinate Ca^{2+} transfer (IP3R–GRP75–VDAC axis), phospholipid synthesis (phosphatidylserine to phosphatidylethanolamine), and regulation of mitochondrial dynamics (through DRP1 recruitment). In lean states, pulsatile Ca^{2+} delivery stimulates TCA dehydrogenases, matching ATP production to demand[28, 29]. In obesity, ER stress (UPR activation) reshapes MAMs: contacts can become excessive or disorganized, producing Ca^{2+} overload in mitochondria, mPTP opening, ROS bursts, and impaired insulin signaling. In the liver, altered MAMs link to augmented gluconeogenesis and steatosis; in β-cells, defective ER–mitochondria coupling disrupts Ca^{2+} oscillations and insulin secretion[29].

Lipid exchange at MAMs also matters. Cardiolipin remodeling influences cristae architecture and ETC function; ceramide accumulation perturbs membrane biophysics, impairs respiratory complexes, and activates pro-apoptotic signaling[30]. Peroxisomes cooperate with mitochondria to oxidize very-long-chain fatty acids; peroxisomal dysfunction increases lipid intermediates and H_2O_2 that strain mitochondrial defenses. Lysosomal crosstalk governs mitophagy: defects in autophagosome–lysosome fusion or lysosomal acidification stall mitochondrial turnover, enlarging the pool of ROS-generating organelles[30].

Therapeutically, interventions that reduce ER stress (nutritional quality, bile-acid/FXR–TGR5 signaling, chemical chaperones) or that fine-tune Ca^{2+} handling can indirectly normalize mitochondrial function. Exercise improves ER proteostasis, enhances SERCA capacity, and optimizes MAM architecture[31]. Pharmacologic agents acting on lipid synthesis/trafficking (e.g., inhibition of de novo lipogenesis, modulation of sphingolipid pathways) may rebalance membrane composition and restore ETC efficiency. Precision mapping of organelle contacts via imaging or proximity proteomics could identify individuals with dominant MAM defects who might benefit from targeted therapies[31].

6. Tissue-Specific Mitochondrial Phenotypes: Adipose, Liver, Muscle, and Islets

Adipose tissue: In subcutaneous white adipose tissue, reduced mitochondrial content and impaired β-oxidation limit lipid buffering and favor inflammatory signaling; beige adipocyte recruitment declines, lowering energy expenditure[32–34]. Visceral depots exhibit higher lipolysis and ROS/inflammatory tone. These changes elevate NEFA flux to the liver and muscle, propagating systemic IR. Restoring adipose mitochondrial function through weight loss, cold exposure, exercise, or agents that enhance PGC-1α signaling improves adipokine profiles (↑adiponectin) and reduces lipotoxic spillover.

Liver: Hepatic mitochondria accommodate high FAO and TCA flux in obesity. While ATP production may be preserved or even increased, the redox and signaling consequences sustain gluconeogenesis and lipogenesis[35–37]. Accumulating acyl-CoAs and ceramides impair ETC efficiency and sensitize to mPTP opening. MAM remodeling links ER stress to mitochondrial Ca2+ overload and ROS. Interventions that lower lipid influx (weight loss, TZDs), enhance insulin sensitivity, or modulate bile-acid signaling reduce this mitochondrial–ER stress loop, improving glycemia.

Skeletal muscle: IR associates with intramyocellular lipids and altered lipid species rather than a simple deficit in mitochondrial content. Nonetheless, many individuals display reduced oxidative capacity, fragmented networks, and impaired substrate switching. Endurance/resistance training increases mitochondrial biogenesis, capillarity, and insulin-stimulated glucose uptake, often preceding weight change[31, 38–40]. Nutritional strategies that align carbohydrate intake with training ("fuel for the work required") optimize mitochondrial adaptations and glycemic control.

Pancreatic islets: β-cell mitochondria translate glucose metabolism into ATP-dependent electrical activity and insulin exocytosis. Chronic lipoglucotoxicity depolarizes mitochondria, elevates ROS, and impairs Ca2+ oscillations, promoting ER stress and dedifferentiation. Mitophagy defects allow damaged organelles to accumulate; restoring mitophagy and redox balance supports insulin secretory capacity. Incretin-based therapies improve β-cell stress resilience indirectly via weight loss and directly through cAMP/PKA signaling that enhances mitochondrial function[41, 42].

Across tissues, immune–metabolic crosstalk integrates these phenotypes. Mitochondrial signals (ROS, mtDNA) activate innate immune pathways (NLRP3), while immune-cell metabolism (glycolysis vs fatty-acid oxidation) feeds back on tissue inflammation and insulin action. Thus, mitochondrial dysfunction is both a driver and a consequence of metaflammation across organs.

7. Therapeutic Opportunities Targeting Mitochondrial Health: From Lifestyle to Precision Pharmacology

Lifestyle: Exercise is the most reliable mitochondrial medicine. Endurance training elevates PGC-1α signaling, ETC protein content, and antioxidant defenses; resistance training expands glucose-disposal capacity via muscle mass[43]. Caloric restriction and protein/meal timing reduce substrate pressure and synchronize mitophagy–biogenesis cycles. Sleep regularity and circadian alignment further stabilize mitochondrial redox and clock-controlled metabolism.

Approved pharmacotherapies: Metformin lowers hepatic gluconeogenesis and activates AMPK, enhancing autophagy and improving redox efficiency[44–46]. Thiazolidinediones redistribute lipid to adipose tissue via PPARγ, raise adiponectin, and improve mitochondrial biogenesis especially in adipocytes. SGLT2 inhibitors reduce glucotoxicity and substrate load, secondarily improving mitochondrial stress in heart, kidney, liver, and muscle. Incretin-based agents (GLP-1 receptor agonists and multi-agonists) deliver substantial weight loss and may enhance mitochondrial efficiency via reduced lipotoxicity and improved insulin signaling.

Emerging strategies: NAD+ boosters (e.g., precursors) and sirtuin activators aim to correct hyperacetylation and stimulate mitophagy/biogenesis[47]. Targeted redox modulators that localize to mitochondria seek to limit damaging ROS while preserving signaling. Agents that promote mitophagy (ULK1 activation, PINK1/Parkin potentiation) or fine-tune dynamics (modulating DRP1/MFN function indirectly through AMPK/SIRT1) are under investigation. Safe augmentation of thermogenesis (beige/brown fat activation) could offload lipid and improve systemic insulin sensitivity; the key is achieving mild, controllable increases in energy expenditure without cardiovascular or cachectic risks.[47]

Diagnostics and precision care: Non-invasive markers like acylcarnitine profiles, circulating mtDNA, breath metabolomics, and imaging of mitochondrial function combined with tissue-specific transcriptomic/proteomic signatures may define mitochondrial endotypes (e.g., "redox-dominant," "mitophagy-deficient," "MAM-disrupted")[48]. Matching therapies to these endotypes, layering lifestyle with drugs that target dominant defects, and monitoring with dynamic biomarkers can halt or reverse diabetes progression.

CONCLUSION

Interventions must respect mitochondria's centrality. Over-suppression of ROS can blunt adaptive signaling; indiscriminate uncoupling wastes energy; global manipulation of fission/fusion risks mitosis and cardiac side effects. The path forward favors systemic decompression of substrate stress (weight loss), physiologic re-training (exercise), and organ-specific nudges to restore quality control and inter-organelle harmony. Done well, mitochondrial repair becomes not a niche strategy but a core pillar of treating obesity-associated IR and preventing T2D progression.

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