Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 Received 19.07.2026 Accepted 06.08.2026 Online 18.08.2026

THE ROLE OF MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS IN THE DEVELOPMENT OF METABOLIC DISORDERS

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Abstract

Mitochondria play a central role in cellular energy metabolism, fatty-acid oxidation, redox regulation, calcium homeostasis, apoptosis, and metabolic adaptation. Disturbances in mitochondrial function are increasingly recognized as important contributors to obesity, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease. One of the major consequences of mitochondrial dysfunction is excessive production of reactive oxygen species, which can damage lipids, proteins, mitochondrial DNA, and cellular membranes and can also interfere with insulin signaling and inflammatory regulation. The aim of this study was to analyze the biochemical mechanisms linking mitochondrial dysfunction and oxidative stress with the development of metabolic disorders. A qualitative literature-based review was conducted using contemporary studies on oxidative phosphorylation, reactive oxygen species, insulin resistance, mitochondrial dynamics, mitophagy, β-cell dysfunction, hepatic lipid metabolism, and metabolic inflammation. The analysis indicates that chronic nutrient excess increases mitochondrial substrate pressure and promotes electron leakage, oxidative stress, impaired mitochondrial quality control, and metabolic inflexibility. These changes contribute to ectopic lipid accumulation, insulin resistance, pancreatic β-cell dysfunction, hepatic steatosis, and chronic low-grade inflammation. The available evidence suggests that mitochondrial dysfunction and oxidative stress form a self-amplifying pathogenic cycle. Effective prevention and treatment therefore require restoration of metabolic and mitochondrial homeostasis rather than simple nonspecific antioxidant supplementation.

Keywords: mitochondrial dysfunction, oxidative stress, reactive oxygen species, insulin resistance, obesity, type 2 diabetes, metabolic syndrome, MASLD.

Introduction

Metabolic disorders such as obesity, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease are major global health problems. Although these conditions differ clinically, they share several molecular abnormalities, including chronic nutrient excess, altered glucose and lipid metabolism, ectopic fat accumulation, oxidative stress, inflammation, and impaired mitochondrial function.

Mitochondria are traditionally known as the principal sites of cellular ATP production, but their role extends far beyond energy generation. They participate in the tricarboxylic acid cycle,

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fatty-acid β-oxidation, amino-acid metabolism, calcium signaling, redox regulation, thermogenesis, and programmed cell death [1]. Their ability to adapt to changes in nutrient availability is especially important in metabolically active tissues such as skeletal muscle, liver, adipose tissue, and pancreatic β-cells.

Under physiological conditions, electrons derived from NADH and $FADH_2$ pass through the mitochondrial electron transport chain, generating a proton gradient that drives ATP synthesis. A small proportion of electrons may escape and react with molecular oxygen, generating reactive oxygen species. At moderate concentrations, these molecules have important signaling functions. Hydrogen peroxide, for example, participates in reversible redox regulation of proteins and contributes to cellular adaptation [2].

Problems arise when reactive oxygen species are produced excessively or when antioxidant defense is insufficient. This state, generally described as oxidative stress, can damage membrane lipids, mitochondrial proteins, respiratory complexes, and mitochondrial DNA. The resulting mitochondrial damage may further increase electron leakage and reactive oxygen species formation, creating a self-amplifying cycle [3].

Chronic overnutrition is one of the principal drivers of this process. Excess glucose and fatty acids increase substrate delivery to mitochondria. Initially, mitochondria may compensate by increasing oxidation. With persistent metabolic overload, however, oxidative capacity may become insufficient, incomplete oxidation may occur, and lipid-derived intermediates can accumulate. These metabolic changes are strongly associated with insulin resistance [4].

Mitochondrial dysfunction is also linked with abnormal mitochondrial fusion, fission, biogenesis, and mitophagy. These quality-control systems normally maintain a healthy mitochondrial population by allowing damaged organelles to be repaired, separated, or removed. When these mechanisms fail, dysfunctional mitochondria accumulate and contribute to metabolic deterioration [5].

The aim of this study was to analyze the major biochemical pathways through which mitochondrial dysfunction and oxidative stress contribute to the development and progression of metabolic disorders.

Materials and Methods

This study was conducted as a qualitative analytical review of scientific literature related to mitochondrial biology and metabolic disease.

Peer-reviewed research articles, review papers, and authoritative biochemical sources were examined. The literature focused on mitochondrial oxidative phosphorylation, reactive oxygen species, antioxidant defense, insulin signaling, lipid metabolism, mitochondrial biogenesis, fusion and fission, mitophagy, pancreatic β-cell function, hepatic metabolism, and obesity-related inflammation.

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The analysis included evidence from studies involving obesity, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease.

Special attention was given to the relationship between mitochondrial reactive oxygen species production and insulin resistance, as well as to the effects of impaired mitochondrial fatty-acid oxidation, mitochondrial DNA damage, defective mitophagy, and chronic low-grade inflammation.

The findings were interpreted from a biochemical and pathophysiological perspective. Because mitochondrial abnormalities vary between tissues and disease stages, conclusions were based on recurring mechanistic patterns rather than on a single experimental model.

Results

The reviewed evidence shows that mitochondrial dysfunction is closely associated with the major biochemical abnormalities observed in metabolic disorders.

One of the most consistent findings is increased mitochondrial oxidative stress. During chronic nutrient excess, excessive amounts of glucose and fatty acids enter metabolic pathways and increase production of NADH and $FADH_2$. This creates high electron pressure within the mitochondrial electron transport chain. When electron transfer becomes inefficient, electrons can leak from respiratory complexes and react with oxygen, producing superoxide radicals [6].

Superoxide is converted to hydrogen peroxide by mitochondrial superoxide dismutase. Under normal conditions, hydrogen peroxide is subsequently neutralized by glutathione peroxidase, peroxiredoxins, and other antioxidant systems. If production exceeds removal, oxidative stress develops.

Oxidative modification of respiratory-chain proteins can reduce mitochondrial efficiency. Membrane lipid peroxidation can also disrupt the inner mitochondrial membrane and impair the proton gradient required for ATP synthesis. Oxidative damage to mitochondrial DNA may reduce expression of respiratory-chain components, thereby further worsening electron transport [7].

A strong relationship was also found between mitochondrial dysfunction and insulin resistance. In skeletal muscle, excessive fatty-acid delivery may exceed mitochondrial oxidative capacity. This results in accumulation of lipid intermediates such as diacylglycerols, ceramides, and acylcarnitines. These compounds can activate signaling pathways that inhibit insulin receptor signaling and reduce glucose uptake [8].

Mitochondrial reactive oxygen species may also interfere directly with insulin signaling. Experimental studies have shown that increased mitochondrial oxidative stress can induce insulin resistance even when oxidative phosphorylation is not initially severely impaired [9].

In adipose tissue, obesity is associated with abnormal mitochondrial morphology and reduced mitochondrial functional capacity. Recent evidence indicates that obesity can promote mitochondrial fragmentation in white adipocytes, which contributes to impaired metabolism and

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adipose dysfunction [10]. Dysfunctional adipose tissue releases greater amounts of free fatty acids and inflammatory mediators, thereby worsening systemic insulin resistance.

Pancreatic β-cells are especially dependent on normal mitochondrial function. Glucose metabolism increases ATP production in β-cells, leading to closure of ATP-sensitive potassium channels, membrane depolarization, calcium influx, and insulin secretion. Mitochondrial dysfunction therefore directly impairs glucose-stimulated insulin secretion.

Chronic hyperglycemia and elevated fatty acids expose β-cells to glucotoxic and lipotoxic stress. This increases oxidative stress, mitochondrial dysfunction, and endoplasmic-reticulum stress. Because β-cells possess relatively limited antioxidant capacity, prolonged metabolic stress can result in progressive β-cell dysfunction and loss of insulin-secretory capacity [11].

Mitochondrial abnormalities are also prominent in the liver. In early metabolic dysfunction-associated steatotic liver disease, mitochondria may initially increase fatty-acid oxidation as an adaptive response to excess lipid supply. With continued overload, mitochondrial function becomes impaired. Abnormal β-oxidation, increased reactive oxygen species production, mitochondrial DNA damage, and defective mitophagy have all been implicated in disease progression [12].

Oxidative stress contributes to lipid peroxidation in hepatocytes. Reactive aldehydes generated during this process can modify proteins and promote inflammation. As oxidative damage increases, hepatic antioxidant capacity may become insufficient, contributing to progression from simple steatosis toward steatohepatitis and fibrosis [13].

Another major finding concerns mitochondrial quality control. Mitochondria continuously undergo fusion and fission. Fusion allows exchange of mitochondrial contents and may help compensate for local damage, whereas fission separates damaged regions and facilitates their elimination. Proteins such as mitofusins, OPA1, and dynamin-related protein 1 regulate these processes.

In metabolic disease, this balance is frequently disrupted. Excessive fission and insufficient fusion may produce fragmented mitochondrial networks. Such abnormalities have been observed in obesity and type 2 diabetes and are associated with reduced metabolic efficiency [5].

Mitophagy is also essential for mitochondrial quality control. Damaged mitochondria are selectively removed through autophagic pathways. The PINK1–Parkin pathway is one of the best-characterized mechanisms. When mitochondrial membrane potential is lost, PINK1 accumulates on the outer membrane and promotes recruitment of Parkin, which helps label the damaged mitochondrion for degradation.

Impaired mitophagy allows damaged mitochondria to persist and continue producing excessive reactive oxygen species. Recent studies have linked defective mitochondrial clearance with obesity, diabetes, and related cardiometabolic disorders [14].

The reviewed literature also demonstrates a close relationship between mitochondrial dysfunction and chronic inflammation. Damaged mitochondria may release mitochondrial DNA

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and other danger-associated molecules into the cytoplasm. These signals can activate inflammatory pathways such as the NLRP3 inflammasome.

Inflammatory cytokines can interfere with insulin signaling and worsen metabolic dysfunction. Thus, mitochondrial damage can promote inflammation, while inflammation can further impair mitochondrial function.

Physical activity consistently appears to have beneficial effects on mitochondrial health. Exercise activates signaling pathways involving AMP-activated protein kinase and PGC-1α, promoting mitochondrial biogenesis and oxidative capacity. Exercise also improves insulin sensitivity and can stimulate mitochondrial turnover and mitophagy [15].

Caloric restriction and weight reduction also reduce metabolic pressure on mitochondria. Lower substrate overload reduces ectopic lipid accumulation and improves metabolic flexibility.

The evidence regarding simple antioxidant supplementation is less consistent. Because reactive oxygen species also serve physiological signaling functions, complete suppression of ROS may interfere with beneficial adaptive pathways. In addition, systemic antioxidants may not reach the mitochondrial compartment where oxidative stress is occurring. Therefore, modern therapeutic approaches increasingly focus on restoring mitochondrial function and redox regulation rather than only scavenging free radicals.

Discussion

The findings of this review support the concept that mitochondrial dysfunction and oxidative stress are central components of metabolic disease pathogenesis. However, they should not be interpreted as isolated causes.

Metabolic disorders develop through complex interactions between nutrient excess, genetic susceptibility, hormonal signaling, inflammation, and organ-specific responses. Mitochondrial dysfunction becomes integrated into this network and can both result from and intensify metabolic abnormalities.

One of the clearest mechanisms involves chronic substrate overload. When excessive glucose and fatty acids continuously enter cells, mitochondrial oxidation must increase. During early stages, this response may be compensatory. If overload persists, the mitochondrial system becomes less efficient.

As electron transport becomes disrupted, reactive oxygen species increase. Oxidative stress then damages mitochondrial membranes, enzymes, and DNA. These changes further impair respiration and ATP production.

This creates a pathogenic cycle:

nutrient excess → mitochondrial overload → oxidative stress → mitochondrial damage → metabolic dysfunction → further nutrient overload

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In skeletal muscle, this cycle contributes to impaired insulin signaling and metabolic inflexibility.

Healthy skeletal muscle shifts between fatty-acid oxidation during fasting and glucose oxidation after feeding. In insulin-resistant states, this ability is reduced. Mitochondrial dysfunction contributes to incomplete substrate oxidation and accumulation of lipid intermediates that inhibit insulin signaling [8].

The relationship between mitochondrial dysfunction and diabetes is especially important because mitochondria influence both insulin action and insulin secretion.

Peripheral tissues become resistant to insulin, while pancreatic β-cells must increase insulin secretion to compensate. If mitochondrial stress develops in β-cells, ATP production and insulin secretion decline. Progressive β-cell failure then transforms compensated insulin resistance into persistent hyperglycemia.

This explains why mitochondrial pathology may contribute to both major components of type 2 diabetes.

The liver demonstrates a similar stage-dependent response. During early lipid excess, increased mitochondrial fatty-acid oxidation may help prevent excessive triglyceride accumulation. Over time, however, persistent substrate pressure increases oxidative stress and damages mitochondrial structure.

When mitochondrial quality control becomes impaired, dysfunctional organelles accumulate and hepatic metabolism deteriorates. This contributes to progression of metabolic dysfunction-associated steatotic liver disease [12].

The role of mitochondrial dynamics also deserves attention.

Mitochondrial fusion, fission, biogenesis, and mitophagy are not independent processes. They operate together to maintain mitochondrial quality. Fission separates damaged mitochondrial segments, mitophagy removes them, fusion allows exchange of functional components, and biogenesis produces new mitochondria.

If one component of this system becomes abnormal, the entire mitochondrial network can deteriorate.

This has important therapeutic implications. Simply increasing mitochondrial number may not be beneficial if quality-control mechanisms remain defective.

Similarly, aggressively stimulating mitophagy could be harmful if mitochondrial replacement is insufficient.

The therapeutic objective should therefore be restoration of balance.

Exercise is one of the best physiological examples of balanced mitochondrial adaptation. It can transiently increase reactive oxygen species, but this moderate stress activates endogenous

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antioxidant and mitochondrial biogenesis pathways. This phenomenon demonstrates that reactive oxygen species are not universally harmful.

The concept of oxidative stress has consequently evolved.

Rather than defining oxidative stress as the mere presence of free radicals, modern redox biology emphasizes disruption of regulated redox signaling [2].

This helps explain why many nonspecific antioxidant trials have produced inconsistent clinical results.

Removing reactive oxygen species without correcting mitochondrial dysfunction, chronic overnutrition, or insulin resistance may not solve the underlying metabolic problem.

More targeted approaches may therefore be necessary.

Potential future strategies include mitochondria-targeted antioxidants, modulators of AMPK and PGC-1α, regulators of fusion and fission, stimulators of mitophagy, and compounds affecting NAD^+ metabolism.

However, such interventions require careful evaluation because mitochondrial functions differ among tissues.

For example, increasing fatty-acid oxidation may be beneficial in skeletal muscle but may have different consequences in another organ or disease stage.

The most reliable current approaches remain lifestyle and metabolic interventions.

Regular exercise improves mitochondrial biogenesis and insulin sensitivity.

Weight reduction decreases lipid overload.

Improved glycemic control reduces glucotoxicity.

Reduction of ectopic fat decreases lipotoxicity.

These strategies improve the metabolic environment in which mitochondria function.

Thus, mitochondrial health is not determined solely by the organelle itself but also by whole-body energy balance.

Conclusion

Mitochondrial dysfunction and oxidative stress play major roles in the pathogenesis of metabolic disorders, including obesity, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease.

Chronic nutrient excess increases mitochondrial substrate pressure and can disturb electron transport, promote reactive oxygen species production, and impair ATP generation.

Persistent oxidative stress damages mitochondrial proteins, membranes, and DNA and can further reduce respiratory efficiency.

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At the cellular level, these processes contribute to insulin resistance, ectopic lipid accumulation, pancreatic β-cell dysfunction, hepatic steatosis, and inflammatory activation.

Abnormalities in mitochondrial fusion, fission, biogenesis, and mitophagy further amplify metabolic dysfunction by allowing damaged mitochondria to accumulate.

The relationship is bidirectional: metabolic disorders damage mitochondria, while damaged mitochondria worsen metabolic regulation.

Therefore, mitochondrial dysfunction should be understood as part of a self-reinforcing biochemical network rather than as a single isolated defect.

Current evidence supports strategies that restore overall metabolic and mitochondrial homeostasis. Regular physical activity, reduction of chronic caloric excess, improvement of insulin sensitivity, and control of hyperglycemia remain particularly important.

Future therapies may target mitochondrial quality control, redox regulation, biogenesis, and mitophagy more specifically.

Overall, a deeper understanding of mitochondrial metabolism and oxidative stress provides an important biochemical foundation for developing more precise approaches to the prevention and treatment of metabolic disease.

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