International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

# Role of Mitochondrial Dysfunction in Neurodegenerative and liver Diseases

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**Abstract**

Mitochondrial dysfunction is a key pathogenic mechanism in liver disease as in neuro degenerative diseases. In parkinsonian disorders (e.g. “Parkinson disease (PD), Alzheimer disease (AD) and ALS”), neuronal-specific energy- homeostasis and synaptic activity is impaired due to malfunctioning oxidative phosphorilation (OXPHOS) and ATP synthesis. The overproduction of “reactive oxygen species (ROS)” initiates oxidative stress, whereas the perturbed dynamics of mitochondria with disproportioned fission and fusion, incomplete trafficking, and reduced mitophagy deteriorate the mitochondrial health even further. Reduced expression of key regulators of “mitochondrial biogenesis” and metabolism, “such as PGC-1α and Tfam”, exacerbates these deficits, contributing to neuronal dysfunction, synaptic loss, and progressive neurodegeneration.

In liver disorders such as “non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH)”, alcohol liver disease, and cirrhosis- the disruption of mitochondrial performance is characterized by poor fatty β-oxidation and OXPHOS, which leads to the shortage of energy and excessive storage of lipids. Elevated mitochondrial ROS generation promotes hepatocyte injury, inflammation, and fibrosis, while defective mitophagy and mitochondrial quality control accelerate disease progression from simple steatosis to advanced liver pathology. Mitochondrial DNA (mtDNA) damage and impaired expression of electron transport chain (ETC) components further worsen mitochondrial performance.

Comparative insights reveal that while both neurons and hepatocytes experience mitochondrial energy failure and oxidative stress, neurons are particularly sensitive to ATP deficits and calcium dysregulation, whereas hepatocytes are more prone to metabolic imbalance and inflammatory signalling.

Understanding these shared and tissue-specific aspects of mitochondrial dysfunction highlights its critical role in disease mechanisms and underscores the therapeutic “potential of targeting mitochondrial pathways to mitigate” neurodegeneration and liver disease progression.

## Introduction

The programs deployed are vested in mitochondria which are obligatory organelles necessary to cellular energy production, redox balance, and the control of programmed cell death. Mitochondria no longer play only the conventional role of acting as the cellular hubs of energy production, but are known to be the critical controllers of cellular homeostasis, in coordinating metabolic, signalling and stress-response pathways. Mitochondrial dysfunction has emerged as a common pathological feature underlying a diverse range of human diseases, prominently including neurodegenerative disorders and liver diseases [1,2].

In reliance on neurodegenerative disorders (Parkinson illness, Alzheimer infection, and amyotrophic lateral sclerosis, ATP ATP has high reliance on oxidative phosphorylation (OXPHOS) in neurodegenerative sicknesses, e.g., Parkinson illness (PD), Alzheimer infection (AD), and Amyotrophic

lateral sclerosis (ALS), to protect ion gradients, neurotransmission, and neuroplasticity [3,4]. Impairment of mitochondrial bioenergetics leads to energy deficits, which, combined with "excessive production of reactive oxygen species (ROS) and increased oxidative stress, contribute to progressive neuronal damage and synaptic loss [5,6]. The impairment of mitochondrial dynamics, including fission, fusion, trafficking, and mitophagy, and low expression of regulators like PGC-1-alpha and Tfam worsen mitochondrial dysfunction and accelerate neurodegeneration". [7,8].

In liver illnesses such NAFLD, NASH, alcoholic liver disease, and cirrhosis, mitochondrial dysfunction is the main cause. [9]. In hepatocytes, impaired β-oxidation and defective OXPHOS result in insufficient energy production and abnormal lipid accumulation, driving steatosis and metabolic stress [10]. Elevated mitochondrial ROS generation induces hepatocyte injury, inflammation, and fibrogenesis, while defective mitophagy and poor mitochondrial quality control promote the progression from benign steatosis to advanced fibrosis and cirrhosis [11]. Furthermore, mitochondrial DNA (mtDNA) damage and impaired expression of electron transport chain (ETC) components compound these metabolic derangements [12].

Comparative insights into neurodegenerative and liver diseases reveal both shared and tissue-specific vulnerabilities [13]. While energy failure and oxidative stress are common denominators, neurons are particularly susceptible to ATP depletion and calcium dysregulation due to their high metabolic demands, whereas hepatocytes are more prone to metabolic imbalance, lipid overload, and inflammatory responses [14].

This article reviews mitochondrial dysfunction as a unifying mechanism of pathogenesis in neurodegenerative disorders and hepatic disorders and how the various overlapping and distinctive pathophysiological mechanisms at the level of impaired bioenergetics, reactive oxygen species production and mitochondrial dynamics and poor-quality control contributes to disease pathogenesis. A further insight into these mechanisms could open an opportunity to develop new techniques of mitochondria-directed therapy intended to restore energy homeostasis in cells and unload damage in tissues. [15].

**Parkinson's Disease (PD)**

Parkinson disease is a condition which is progressive and is a neurodegenerative disease consisting of loss of dopaminergic nerve cells in the substantia nigra. It is characterised by mitochondrial dysfunction. Certain gene mutations including "PINK1, Parkin and DJ-1 impair mitophagy and mitochondrial quality control" thus causing the build-up of dysfunctional mitochondria [1,2]. Impaired complex I activity reduces ATP synthesis and elevates ROS production, triggering oxidative damage and neuronal apoptosis [3].

**symptoms**: Patients typically present with resting tremors, bradykinesia, muscle rigidity, "postural instability, and, in advanced stages, non-motor symptoms like cognitive decline and mood disorders".

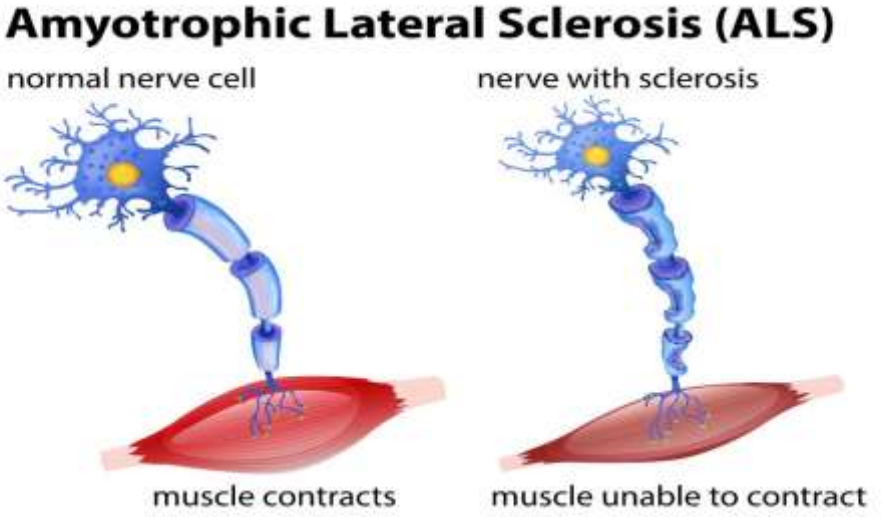
**Alzheimer's Disease (AD)**

The most widespread cause of dementia all over the planet is Alzheimer disease which is characterized by memory impairment and cognitive loss. AD mitochondrial pathology is associated with a direct relationship with the accumulation of amyloid-beta (A-beta) products and hyperphosphorylation of tau proteins that alter the dynamics of mitochondria, inhibit OXPHOS and increase ROS production [4,5]. Reduced "expression of PGC-1α and Tfam diminishes mitochondrial biogenesis", further worsening energy deficits [6,7].


**symptoms**: Patients experience memory impairment, confusion, disorientation, personality changes, and difficulties with speech and problem-solving.

**Amyotrophic Lateral Sclerosis (ALS)**

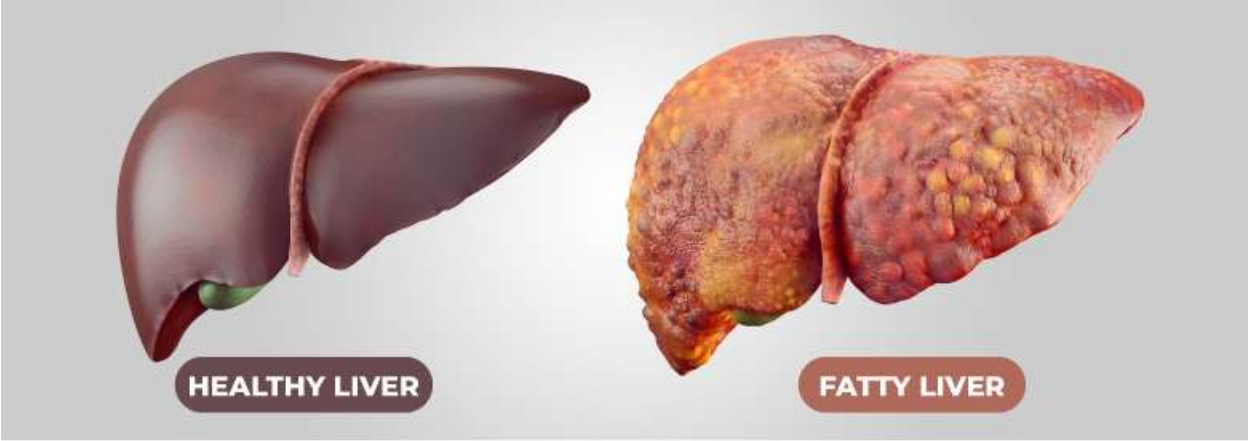
"ALS is a deadly neurodegenerative disorder, which includes degeneration of the upper, and lower motor neurons" resulting in the progressive weakening and paralysis of muscles. Mitochondrial dysfunction in ALS involves impaired OXPHOS, mtDNA mutations, disrupted calcium buffering, and excessive ROS production [8,9]. "Mutations in SOD1, TDP-43, and FUS" genes contribute to mitochondrial pathology and increase motor neuron vulnerability [10,11].



**symptoms:** Patients present with muscle weakness, fasciculations, spasticity, dysphagia, dysarthria, and ultimately respiratory failure.

**Liver Diseases**

"In non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver disease", and cirrhosis, the dysfunction of mitochondria interferes with hepatocyte metabolism [12]. Impaired β-oxidation and OXPHOS cause energy deficits and lipid accumulation [13]. Excessive mitochondrial ROS drives hepatocyte injury, inflammation, and fibrogenesis [14]. Defective mitophagy and mtDNA damage accelerate progression from steatosis to advanced fibrosis and cirrhosis [15].




**symptoms:** Early stages may be asymptomatic or show fatigue and mild hepatomegaly. Advanced stages present with jaundice, ascites, coagulopathy, hepatic encephalopathy, and increased risk of hepatocellular carcinoma.

**Literature review**

**Mitochondrial Dysfunction in Parkinson's Disease (PD)**

"Mitochondrial dysfunction is well established as a key contributor to the pathogenesis of Parkinson's disease. Schapira et al. [1] first demonstrated a deficiency in complex I activity of the electron transport chain in the substantia nigra of PD patients", linking impaired bioenergetics to dopaminergic neuronal loss. Later, Narendra et al. [2] showed that mutations in the *PINK1* and *Parkin* genes compromise mitophagy, leading to the accumulation of damaged mitochondria and increased oxidative stress. More recently, Exner et al. [3] highlighted the role of mitochondrial dynamics and transport deficits, revealing how impaired trafficking of mitochondria along axons affects synaptic function and neuronal survival. Together, these studies underscore that defective OXPHOS, excessive ROS, and disrupted mitophagy converge to drive neurodegeneration in PD, making mitochondria a promising target for disease-modifying therapies.

**Mitochondrial Dysfunction in Alzheimer's Disease (AD)**

Emerging evidence has solidified the link between mitochondrial dysfunction and Alzheimer's disease pathogenesis. Manczak et al. [4] demonstrated that amyloid-beta (Aβ) accumulates within mitochondria, disrupting complex IV activity and ATP synthesis. Calkins et al. [5] further showed that Aβ impairs mitochondrial dynamics by altering the fission and fusion balance, promoting mitochondrial fragmentation and dysfunction. Sheng and Cai [6] reported that reduced expression of PGC-1α and Tfam

in AD brains leads to compromised mitochondrial biogenesis, exacerbating energy deficits. Moreover, Swerdlow [7] proposed the mitochondrial cascade hypothesis, suggesting that inherited mitochondrial defects initiate Aβ accumulation rather than merely being secondary to it. Collectively, these studies illustrate that mitochondrial bioenergetic failure, oxidative stress, and impaired quality control are central to the synaptic loss and cognitive decline observed in AD.

**Mitochondrial Dysfunction in Amyotrophic Lateral Sclerosis (ALS)**

Research over the past two decades has revealed the significant role of mitochondrial dysfunction in ALS pathogenesis. Wiedemann et al. [8] demonstrated structural abnormalities and respiratory chain defects in mitochondria isolated from ALS motor neurons. Magrane et al. [9] showed that mutant SOD1 proteins localize to mitochondria, causing membrane depolarization, ROS overproduction, and defective calcium handling. Cozzolino et al. [10] reviewed how proteins like TDP-43 and FUS further impair mitochondrial dynamics and bioenergetics, exacerbating motor neuron degeneration. Recent work by Smith et al. [11] highlights that defective mitophagy and mtDNA damage contribute to disease progression. These findings collectively emphasize that bioenergetic failure, oxidative stress, and defective mitochondrial maintenance are integral to the selective vulnerability of motor neurons in ALS.

**Mitochondrial Dysfunction in Liver Diseases**

Mitochondrial dysfunction is increasingly recognized as a driver of liver disease progression. Begriche et al. [12] detailed how impaired β-oxidation and defective OXPHOS lead to triglyceride accumulation in hepatocytes, promoting NAFLD development. Fromenty and Pessayre [13] showed that excessive ROS from dysfunctional mitochondria damages hepatocyte membranes, triggering inflammation and fibrogenesis. Sunny et al. [14] demonstrated that defective mitophagy impairs removal of damaged mitochondria, worsening oxidative injury and accelerating progression from simple steatosis to NASH and cirrhosis. Additionally, Gao and Bataller [15] discussed how alcohol-induced mitochondrial damage exacerbates liver injury through mtDNA mutations and impaired ETC component expression. These findings collectively indicate that mitochondrial metabolic failure, ROS-mediated injury, and defective quality control play central roles in liver disease pathology.

**Research gap**

Although extensive research has elucidated the involvement of mitochondrial dysfunction in neurodegenerative and liver diseases, significant gaps remain. Current studies have largely focused on describing isolated aspects such as OXPHOS defects, ROS generation, or mitophagy impairment, but integrated, comparative analyses across tissues are scarce. Moreover, while neurons and hepatocytes both rely heavily on mitochondrial metabolism, tissue-specific vulnerabilities—such as neuronal calcium dysregulation versus hepatic lipid overload—are not fully understood at the mechanistic level. There is also a lack of translational studies bridging basic mitochondrial biology with clinical trials of mitochondria-targeted therapies. Future research should aim to develop unified models explaining how shared mitochondrial pathways diverge to produce distinct tissue pathologies and identify therapeutic interventions that selectively restore mitochondrial function in a tissue-specific manner.

**Discussion**

This paper is a detailed analysis of how mitochondrial dysfunction has become the main mechanism of

pathogenesis of both liver and neuro degenerative assembly. Through integration of existing knowledge, we pointed at the interconnection between "impaired oxidative phosphorylation (OXPHOS), excessive production of reactive oxygen species (ROS), inappropriate dynamics of mitochondria and mitophagy" as well as down-regulated expression of mitochondrial biogenesis regulators, as the manifestations led to cellular dysfunction, tissue pathology and progression to disease.

An overview of a disease perspective of "Parkinson disease, Alzheimer disease and amyotrophic lateral sclerosis (ALS)" showed how each disease has certain unique genetic and molecular triggers to degrade mitochondria culminating in energy deficits, oxidative stress, and death of the neurons. In addition, we studied the "mitochondrial dysfunction in chronic liver diseases, which included non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and cirrhosis" wherein defect in β-oxidation, elevated mitochondrial ROS, defective mitophagy and mitochondrial DNA damage propel injury, inflammation and fibrosis in hepatocytes.

Comparative analysis emphasized the shared pathological threads and tissue-specific vulnerabilities: while neurons are especially sensitive to ATP depletion and calcium imbalance, hepatocytes are more affected by metabolic overload and inflammatory signalling. This understanding underscores that although mitochondria are central players in both conditions, targeted therapeutic approaches must account for the distinct metabolic demands and stress responses of different tissues.

Through this paper, we establish a clear link between mitochondrial bioenergetics failure and progressive tissue degeneration in both the nervous system and liver. The key insight is that restoring mitochondrial function — whether through enhancing OXPHOS, reducing ROS, promoting mitophagy, or boosting biogenesis — holds significant promise for slowing disease progression. However, translating this understanding into effective treatments remains a critical challenge.

This synthesis highlights the need for continued research into mitochondria-focused diagnostics, biomarkers, and targeted interventions that can selectively restore mitochondrial health in affected tissues. By bridging gaps between neurodegenerative and liver disease research, we can identify novel therapeutic strategies with broader clinical impact.

## Conclusion

Mitochondrial dysfunction stands at the crossroads of diverse chronic diseases, profoundly influencing the onset and progression of neurodegenerative and liver pathologies. This review highlights that while impaired oxidative phosphorylation, excessive ROS generation, disrupted mitochondrial dynamics, and defective quality control are shared features, the consequences of mitochondrial failure vary by tissue type. Comparative insights reveal that neurons are particularly sensitive to ATP deficits and calcium dysregulation due to their high metabolic demands and reliance on oxidative metabolism to maintain synaptic function and neuronal signalling. In contrast, hepatocytes, though more metabolically flexible, are especially vulnerable to lipid overload, metabolic imbalance, and inflammation when mitochondrial β-oxidation and respiratory capacity are compromised.

Recognizing these overlapping yet distinct vulnerabilities underscores the importance of developing tissue-specific, mitochondria-targeted therapeutic approaches. Such strategies hold significant promise for restoring cellular energy balance, mitigating oxidative stress, and ultimately slowing or reversing disease progression in both the nervous system and the liver. Continued research into mitochondrial biology, disease-specific mechanisms, and innovative interventions will be essential to translate these insights into effective clinical therapies.

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