

2. Ariaiev M. L., Kaplina L. Ye., Senkivska L. I., Pavlova V. V. First experience of distance learning in medical universities of Ukraine under COVID-19 quarantine conditions. *Child's Health*. 2020. Vol. 15, No. 3. P. 195-199.
3. https://notebooklm.google.com/notebook/4d8f970f-a83b-4a1d-ab29-cc58828cb36c/artifact/af4cb121-2a61-4d43-9679-82e46ca49e75?utm_source.nlm_web_share&utm_medium=google_oo&utm_campaign=art_share_2&utm_content=&utm_smc.nlm_web_share_google_oo_art_share_2_

THE ROLE OF OXIDATIVE PHOSPHORYLATION IN THE PATHOGENESIS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Abstract. Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as nonalcoholic fatty liver disease, encompasses a continuum of liver disorders characterized by excessive lipid accumulation within hepatocytes in individuals without significant alcohol intake and is associated with metabolic syndrome. Several studies have demonstrated

molecular, biochemical, and biophysical abnormalities in mitochondrial dynamics and function associated with MASLD. However, despite these findings, the mechanisms linking impaired oxidative phosphorylation (OXPHOS) to the initiation and progression of MASLD remain incompletely understood.

Objective: To explore the role of OXPHOS in the initiation and progression of MASLD.

Materials and methods. PubMed, Scopus, and the Cochrane Library databases were searched to identify all reports related to the role of OXPHOS in the initiation and progression of MASLD. The following search terms were included: “metabolic dysfunction-associated steatotic liver disease”, “metabolic dysfunction-associated steatohepatitis”, “mitochondria”, “oxidative phosphorylation”, “electron transport chain”.

Results. OXPHOS is the principal mitochondrial pathway responsible for adenosine triphosphate (ATP) synthesis through the coupling of oxygen reduction to the formation of high-energy phosphate bonds. This process involves a sequence of redox reactions in which electrons derived from reduced nicotinamide adenine dinucleotide (NAD) and reduced flavin adenine dinucleotide are transferred through the mitochondrial electron transport chain (ETC), a network of protein, metal-containing, and lipid-associated complexes, before ultimately reducing molecular oxygen [1].

In the ETC, electrons are transferred through a series of protein complexes with progressively increasing redox potential, resulting in the release of energy used for proton translocation across the inner mitochondrial membrane. The ETC proteins in a general order are Complex I (NAD dehydrogenase), complex II (succinate dehydrogenase), complex III (cytochrome bc1 complex), and complex IV (cytochrome c oxidase). Complex V (ATP synthase) differs functionally from the other ETC complexes, as its primary role is the synthesis of ATP rather than the transfer of electrons [2].

ATP generation depends on the sequential transfer of electrons through the mitochondrial respiratory chain. Oxidation of NAD provides two electrons to complex I, whereas oxidation of succinate to fumarate at complex II contributes electrons to the ETC. Coenzyme Q10 (ubiquinone) mediates electron transport to complex III, which subsequently passes them to cytochrome c. The electrons are then transferred to complex IV, where the final stage of the electron transport process occurs, enabling OXPHOS and ATP synthesis. The high efficiency of

OXPHOS enables the generation of approximately 30-32 ATP molecules from the complete oxidation of a single glucose molecule. Mitochondrial ATP synthesis is a dynamic process that is regulated by multiple factors, including substrate availability, the functional status of the ETC, and mitochondrial morphology [3].

The liver plays a pivotal role in maintaining systemic metabolic homeostasis by regulating carbohydrate, protein, and lipid metabolism. Prolonged exposure to lipid overload impairs mitochondrial bioenergetics through dysfunction of the ETC and diminished ATP generation. Studies involving MASLD patients and animal models have consistently demonstrated that these metabolic alterations are linked to hepatic triglyceride accumulation and disturbances in cellular homeostasis [4]. A consistent reduction in hepatic ATP levels has been observed in both patients with metabolic dysfunction-associated steatohepatitis (MASH) and experimental rodent models, although the magnitude of this decline varies considerably across different studies [5].

In the early stages of MASLD, reduced ATP production may be partially attributed to the uncoupling of OXPHOS mediated by increased expression of uncoupling proteins, particularly uncoupling protein 2. In contrast, during MASH progression, impaired ATP synthesis may result from decreased activity of multiple ETC complexes [6].

In addition, in MASH, impaired mitochondrial function reduces intracellular ATP availability, which may trigger endoplasmic reticulum stress and activate the mt-UPR. Activation of the mt-UPR stimulates *de novo* lipogenesis, thereby enhancing hepatic lipid accumulation and aggravating steatosis. Furthermore, lipid accumulation in hepatocytes induces mitochondrial overload, disrupting OXPHOS and increasing reactive oxygen species production [7].

In addition to lipid overload, patients with MASLD exhibit impaired ATP production associated with reduced activity of mitochondrial ETC complexes, including decreases of 37% in complex I, 42% in complex II, 30% in complex III, 38% in complex IV, and 58% in complex V [8]. These metabolic disturbances contribute not only to the progression of hepatic steatosis but also to the development of inflammation and fibrosis, two defining characteristics of MASLD.

Conclusions. Overall, impaired OXPHOS and progressive dysfunction of the mitochondrial ETC contribute to ATP depletion, increased oxidative stress, and disruption of hepatic metabolic homeostasis, thereby promoting the development and progression of MASLD.

References:

1. Deshpande, O. A., & Mohiuddin, S. S. (2023). Biochemistry, Oxidative Phosphorylation. In *StatPearls*. StatPearls Publishing
2. Ahmad, M., Wolberg, A., & Kahwaji, C. I. (2023). Biochemistry, Electron Transport Chain. In *StatPearls*. StatPearls Publishing
3. Patro, S., Ratna, S., Yamamoto, H. A., Ebenezer, A. T., Ferguson, D. S., Kaur, et al. (2021). ATP Synthase and Mitochondrial Bioenergetics Dysfunction in Alzheimer's Disease. *International journal of molecular sciences*, 22 (20), 11185. <https://doi.org/10.3390/ijms222011185>
4. Li, X., Chen, W., Jia, Z., Xiao, Y., Shi, A., & Ma, X. (2025). Mitochondrial Dysfunction as a Pathogenesis and Therapeutic Strategy for Metabolic-Dysfunction-Associated Steatotic Liver Disease. *International journal of molecular sciences*, 26 (9), 4256. <https://doi.org/10.3390/ijms26094256>
5. Jiang, Y., Zhao, M., & An, W. (2011). Increased hepatic apoptosis in high-fat diet-induced NASH in rats may be associated with downregulation of hepatic stimulator substance. *Journal of molecular medicine (Berlin, Germany)*, 89 (12), 1207-1217. <https://doi.org/10.1007/s00109-011-0790-y>
6. Begriche, K., Massart, J., Robin, M. A., Bonnet, F., & Fromenty, B. (2013). Mitochondrial adaptations and dysfunctions in nonalcoholic fatty liver disease. *Hepatology (Baltimore, Md.)*, 58 (4), 1497-1507. <https://doi.org/10.1002/hep.26226>
7. Tamura, Y., Kawano, S., & Endo, T. (2020). Lipid homeostasis in mitochondria. *Biological chemistry*, 401 (6-7), 821-833. <https://doi.org/10.1515/hsz-2020-0121>
8. Pérez-Carreras, M., Del Hoyo, P., Martín, M. A., Rubio, J. C., Martín, A., Castellano, G., et al. (2003). Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis. *Hepatology (Baltimore, Md.)*, 38 (4), 999-1007. <https://doi.org/10.1053/jhep.2003.50398>