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Mitochondrial dysfunction in type 2 diabetes: A neglected path to skeletal muscle atrophy

Mfn-2 in regulating diabetes-induced skeletal muscle atrophy

Jianjun Wu, Huimin Xian, Dawei Yang, Fan Yang

Abstract

Over several decades, extensive research has solidly anchored the role of mitochondrial pathology as a pivotal factor in the development of skeletal muscle atrophy among individuals with diabetes. However, the specific complexities that dictate this process continue to be elusive. It is well-documented that diabetes sufferers frequently face the severe impacts of skeletal muscle degradation, a detrimental condition that significantly impairs their quality of life and overall health. Unraveling the sophisticated mechanisms underlying this pathology necessitates a comprehensive and meticulous investigation into the nuanced factors intricately linked with mitochondrial dysfunction.

Key Words: Mfn-2; oxidative stress; mitochondria metabolism; skeletal muscle atrophy; diabetes

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Core Tip: T2DM represents a significant global health concern. Achieving optimal glycemic control is critical for reducing complications and mortality associated with T2DM. However, recent research has brought to light an often overlooked complication: the progressive atrophy of skeletal muscle. Mitochondria, central to cellular energy production, maintain a delicate equilibrium in their fusion and fission processes. Investigating the relationship between mitochondrial dysfunction and skeletal muscle atrophy in T2DM is essential for advancing our understanding of diabetes. Studies in cellular and animal models suggest that targeting mitochondrial dynamics, particularly through the modulation of Mfn-2, may provide a promising therapeutic strategy to counteract muscle atrophy induced by diabetes. This approach highlights a novel intersection in the management of diabetic complications, linking metabolic control with muscular health.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a relentless and chronic hyperglycemic disorder that has emerged as a grave global public health concern, imposing a substantial burden on both afflicted individuals and healthcare systems [1]. The sheer financial toll, exceeding £800 billion annually encompassing expenditures for diagnosis, treatment, and care, underscores the pressing need to address this rapidly escalating epidemic[2]. Recent study suggests that among the various factors associated with T2DM, age, area of residence, education level, social status, family income, smoking, body mass index, family history, physical exercise exert the most detrimental effects on Quality of Life (QoL) [3]. Beyond the immediate metabolic disturbances, the insidious nature of T2DM engenders a spectrum of incapacitating complications, marked by their gradual onset and often inconspicuous progression, exert a significant detrimental impact on both the life expectancy and quality of life of individuals grappling with diabetes.

Skeletal Muscle Atrophy and mitochondria in T2DM

Glycemic control is pivotal for reducing complications and mortality in T2DM. Emerging research in diabetes highlights skeletal muscle atrophy as a critical aspect of diabetic pathophysiology[4, 5]. Skeletal muscle, characterized by high metabolic activity and dense mitochondrial networks, is integral for movement and health, efficiently generating ATP for muscle contraction and metabolic regulation. Diabetes-induced impairment in muscle cell energy production can lead to muscle atrophy and reduced physical function, making mitochondrial function preservation vital for both athletic performance enhancement and quality of life improvement in chronic disease management.

Mitochondrial dynamics play a crucial role. Mitochondrial fusion, regulated by GTPases such as Mitofusins (Mfns) and Optic Atrophy Protein 1 (Opa1), and fission, mediated by Dynamin-Related Protein 1 and Fission Protein 1 (Fis1), undergo significant changes in T2DM[6]. Notably, T2DM patients exhibit marked downregulation of Mfn2 and Opa1 in skeletal muscles, correlating with reduced mitochondrial mass and density, suggesting aberrant mitochondrial dynamics as an early biomarker for metabolic diseases. Animal models with Mfn2 dysfunction show decreased substrate metabolism, whereas Mfn2 and Opa1 overexpression improve mitochondrial respiratory efficiency and glucose oxidation[7]. This paradoxical interplay between mitochondrial adaptation and dysfunction in diabetic muscles highlights the dual role of mitochondria in energy production and oxidative stress, contributing to muscle atrophy. This balance with reactive oxygen species (ROS) underscores the complex nature of mitochondrial functions in metabolic regulation.

Mfn-2: Regulating Mitochondrial Dynamics and Potential Therapeutic Target

Deficiency in Mfn-2 intensifies mitochondrial fragmentation in cardiomyocytes, impairing cardiac and mitochondrial health, while its overexpression in vascular smooth muscle cells induces apoptosis. These observations underscore Mfn-2's complex and varied roles in cellular processes. Maintaining a balance between mitochondrial fusion and fission is essential for cellular homeostasis; disruptions leading to increased

fragmentation are linked to various cellular dysfunctions, including a heightened propensity for mitochondrial-related apoptosis.

Innovative research avenues are exploring interventions targeting Mfn-2 and mitochondrial dysfunction. Notably, antioxidative treatments and exogenous hydrogen sulfide have shown potential in counteracting high glucose-induced injuries, mediated through Mfn-2 facilitated endoplasmic reticulum-mitochondria contacts[8]. These advances offer promising therapeutic strategies, especially for mitochondrial dysfunction in diabetes-related skeletal muscle injuries.

Additionally, the diterpenoid derivative 15-Oxospiramilactone (S3) emerges as a significant player in enhancing mitochondrial dynamics. It targets the mitochondrial enzyme USP30, integral for modulating MFN1 and MFN2, thereby boosting their activity and fostering mitochondrial fusion. Importantly, S3's ability to restore mitochondrial function in cells deficient in mfn1 or mfn2 underscores its therapeutic potential in treating insulin resistance-related diseases[9].

Toward Therapeutic Strategies for Modulating Mfn-2 and Mitochondrial Dynamics

In the realm of diabetes research, a key area of focus is the relationship between cellular metabolism and the disease's pathophysiology, with particular attention on the mitochondria's role in skeletal muscle atrophy. The mitochondrion, vital for cellular energy, is central to this research, especially regarding Mfn-2-mediated mitochondrial fusion in skeletal muscle. This is particularly relevant in T2DM, where studying skeletal muscle tissues from affected individuals can shed light on the downregulation of Mfn-2 in diabetic conditions. Moreover, exploring Type 1 diabetes, specifically the impact of high-fat diets on Mfn-2 in skeletal muscle, is crucial for a comprehensive understanding of diabetes and its effects on skeletal muscle health.

CONCLUSION

The intricate interplay betweenT2DM and skeletal muscle atrophy, with a focus on the pivotal role of mitochondrial dynamics and Mfn-2, underscores the urgency of

developing targeted therapeutic strategies to address these complex metabolic challenges.

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