

# The Role of Mitochondrial Biogenesis Dysfunction in Diabetic Cardiomyopathy

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## Abstract

Diabetic cardiomyopathy (DCM) is described as abnormalities of myocardial structure and function in diabetic patients without other well-established cardiovascular factors. Although multiple pathological mechanisms involving in this unique myocardial disorder, mitochondrial dysfunction may play an important role in its development of DCM. Recently, considerable progresses have suggested that mitochondrial biogenesis is a tightly controlled process initiating mitochondrial generation and maintaining mitochondrial function, appears to be associated with DCM. Nonetheless, an outlook on the mechanisms and clinical relevance of dysfunction in mitochondrial biogenesis among patients with DCM is not completely understood. In this review, hence, we will summarize the role of mitochondrial biogenesis dysfunction in the development of DCM, especially the molecular underlying mechanism concerning the signaling pathways beyond the stimulation and inhibition of mitochondrial biogenesis. Additionally, the evaluations and potential therapeutic strategies regarding mitochondrial biogenesis dysfunction in DCM is also presented.

**Key Words:** Mitochondrial biogenesis, Diabetes, Cardiomyopathy, PGC-1 $\alpha$ , Diabetic cardiomyopathy

## INTRODUCTION

Diabetes mellitus (DM) is a global public health concern with an overall prevalence of 9.4% (435 million adults) in 2015. China ranks number one with an estimate of 10.9% (109.6 million) adults with DM (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Notably, it has been well recognized that DM is one of the major risk factors for cardiovascular diseases (CVD). Compared to non-diabetic populations, the risk of heart failure (HF) in diabetes increased 5-fold in women and 2.4-fold in men (Kannel and McGee, 1979), even after adjusting for well-established risk factors such as age, blood pressure, weight, and cholesterol (Kannel *et al.*, 1974; Riehle and Bauersachs, 2018).

Diabetic cardiomyopathy (DCM) is a DM-induced abnormalities in myocardial structure and function without coronary artery disease (CAD), valvular disease, hypertension, or other potential etiologies (Lam, 2015). DCM occurs in almost 12% of diabetic patients and affects approximately 22% of subjects over 64 years old (Lorenzo-Almorós *et al.*, 2017). There are four stages of DCM: being at risk of HF (Stage A), asymp-

tomatic with impaired cardiac diastolic function without systolic dysfunction, a condition termed HF with preserved ejection fraction (HFpEF, EF>50%, Stage B). HF with clinical symptoms (Stage C), and refractory HF (Stage D) with reduced ejection fraction, an end-stage condition without specific therapeutic options (Lam, 2015).

Multiple pathological mechanisms underlying cardiac dysfunction in diabetic patients have been reviewed (Murtaza *et al.*, 2019; Parim *et al.*, 2019; Peterson and Gropler, 2020). They include exposure of the diabetic hearts to both hyperglycemia and high fat levels (Jia *et al.*, 2018b). Hyperglycemia can induce enzymatic O-GlcNAcylation and advanced glycation end-product (AGE) formation, leading to reduced glucose uptake, glycolysis, and glucose oxidation. Besides, exposure to high lipid levels may result in increased free fatty acids (FFAs) release and elevated capacity of myocyte sarcolemma FFA transporters, finally leading to increased FFA uptake and oxidation (Paolillo *et al.*, 2019; Lu *et al.*, 2020). These metabolic remodeling may eventually contribute to cardiomyocyte stiffness, oxidative stress, interstitial fibrosis, cardiomyocyte hypertrophy, inflammation, autonomic neuropathy, microvas-

**Open Access** <https://doi.org/10.4062/biomolther.2021.192>

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Received Dec 26, 2021 Revised Jan 28, 2022 Accepted Feb 22, 2022

Published Online Apr 12, 2022

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cular disorder, and mitochondrial dysfunction (Fig. 1) (Knapp *et al.*, 2019; Paolillo *et al.*, 2019). Considerable progresses have been made concerning mitochondrial dysfunction as a characteristic of the diabetic heart (Liang and Kobayashi, 2016). Thus, how to maintain a pool of healthy mitochondria to support energy demand in diabetic patients may be regarded as novel therapeutics. Of note, mitochondrial homeostasis is maintained through tightly control of mitochondrial biogenesis that generates new mitochondria to replenish the mitochondrial pool (Popov, 2020). Therefore, in this review, we will discuss recent literature shedding light on the functional roles of mitochondrial biogenesis in DCM and explore their potentials for targeted therapeutic manipulations.

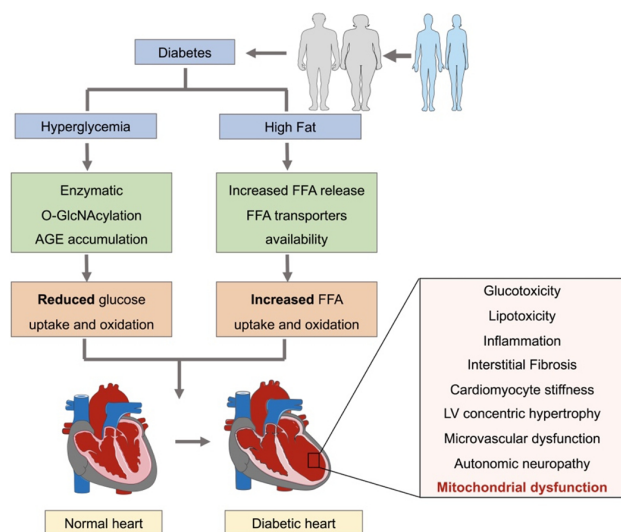
## MITOCHONDRIA AND ITS NORMAL FUNCTION IN MYOCYTES

Mitochondria are double-membrane organelles that construct highly dynamic and multifunctional networks (Balaban, 1990). The predominant physiological function of mitochondria is the generation of adenosine triphosphate (ATP) by oxidative phosphorylation. Additionally, other functions include generation and detoxification of reactive oxygen species (ROS), involvement in cell death and survival, regulation of cytoplasmic and mitochondrial matrix calcium, production and catabolism of metabolites, and transportation of the organelles themselves to suitable locations within the cell. Any abnormalities of these processes can be defined as mitochondrial dysfunction (Golpich *et al.*, 2017). In fact, mitochondria construct a highly dynamic intracellular network modifying their morphology and content in response to external and internal stimuli.

The homeostasis of mitochondria depends on the co-ordination between two opposite processes, including new mitochondrial generation and damaged mitochondrial removal

(Ploumi *et al.*, 2017). Instead of *de novo* generation, new mitochondria arise from pre-existing ones through a multi-step process involving mitochondrial fusion and fission. Consequently, mitochondrial biogenesis controls replication of mitochondrial DNA (mtDNA) and transcription and translation of mtDNA-related genes (Taherzadeh-Fard *et al.*, 2011; Cameron *et al.*, 2016), as well as synthesis, import, and assembly of mitochondrial proteins encoded by nuclear DNA (nDNA) (Bruggisser *et al.*, 2017). Moreover, a perturbed mitochondrial function may induce cell apoptosis and death, with autophagy being the most predominant process (Vafai and Mootha, 2012).

Maintaining mitochondrial integrity and function is critical for cellular physiologies particularly in the heart, which has high energy demands. Normal cardiac contractile function depends on mitochondrial oxidative phosphorylation to generate ATP, 60% of which from FFA oxidation and 40% originating from other fuel substrates including glucose, lactate, ketone bodies, and amino acids (De Jong and Lopaschuk, 2017). In contrast, normal cardiac diastolic function mainly depends on glucose oxidation (Sun *et al.*, 2016). In diabetic heart, mitochondrial stress result in ultrastructural abnormalities, bioenergetic deficiency, impaired mitochondrial biogenesis and imbalanced mitophagy. Myocardium energy consumption shifts from FFA oxidation toward ketone body utilization, a characteristic of the failing heart (Cook *et al.*, 2017). Conversely, mitochondrial dysfunction in diabetic heart may be explained by reduced ATP production and ROS damage, leading to cardiac structural, electrical, and functional disorder (Fig. 2) (Jia *et al.*, 2018a; Berthiaume *et al.*, 2019; Dillmann, 2019). Because disruption of mitochondrial quality control is a predominant mechanism implicated in decreased ATP generation and elevated ROS damage in CVD, therapeutics aimed at maintaining and/or restoring mitochondrial quality and related cellular processes are of significant importance (Li *et al.*, 2021a; Ji *et al.*, 2022). Specifically, pharmacological control of mitochondrial biogenesis is a promising strategy for a wide range of acute and chronic heart diseases characterized by mitochondrial dysfunction.

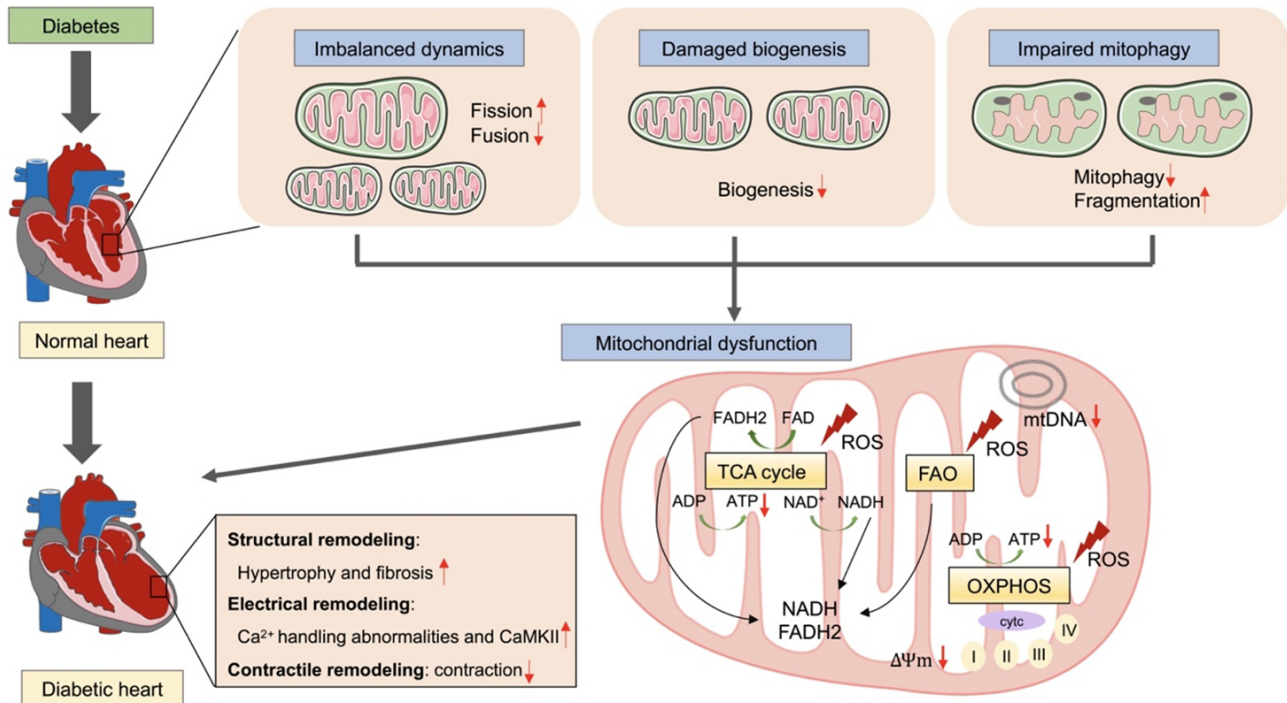


**Fig. 1.** Cardiac metabolic remodeling in response to diabetes. Diabetic hearts are suffered from both hyperglycemia and high fat levels, leading to reduced glucose uptake and oxidation, but increased FFA uptake and oxidation. These metabolic remodeling eventually contribute to cardiac structural, electrical, and functional disorders. FFA, free fatty acid.

## MITOCHONDRIAL BIOGENESIS AND DIABETIC CARDIOMYOPATHY

### Mitochondrial biogenesis

Mitochondrial biogenesis is orchestrated by the growth and division of pre-existing organelles and requires co-ordination between both mitochondrial and nuclear genomes. Interestingly, the two genomes are synthesized by the transcriptional co-regulator peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), a master regulator of mitochondrial biogenesis and maturation. PGC-1 $\alpha$  expression is regulated by activation of transcription factors acting on mitochondrial genes including myocyte enhancer factor 2 (MEF2) (Moore *et al.*, 2003), forehead box class-O3 (FoxO3) (Nakae *et al.*, 2008), the silent information regulator 1 (SIRT1, Thirupathi and de Souza, 2017), and cAMP response element-binding protein (CREB) (Herzig *et al.*, 2001), and several other signaling inducers including AMPK, AKT-eNOs, calmodulin-dependent protein kinase IV (CaMK IV), calcineurin A, and protein kinase A (Angus *et al.*, 2005; Gleyzer and Scarpulla, 2016; Yao *et al.*, 2016; Popov, 2020). PGC-1 $\alpha$  is also regulated by multi-post-translational modifications including acetylation, methylation,



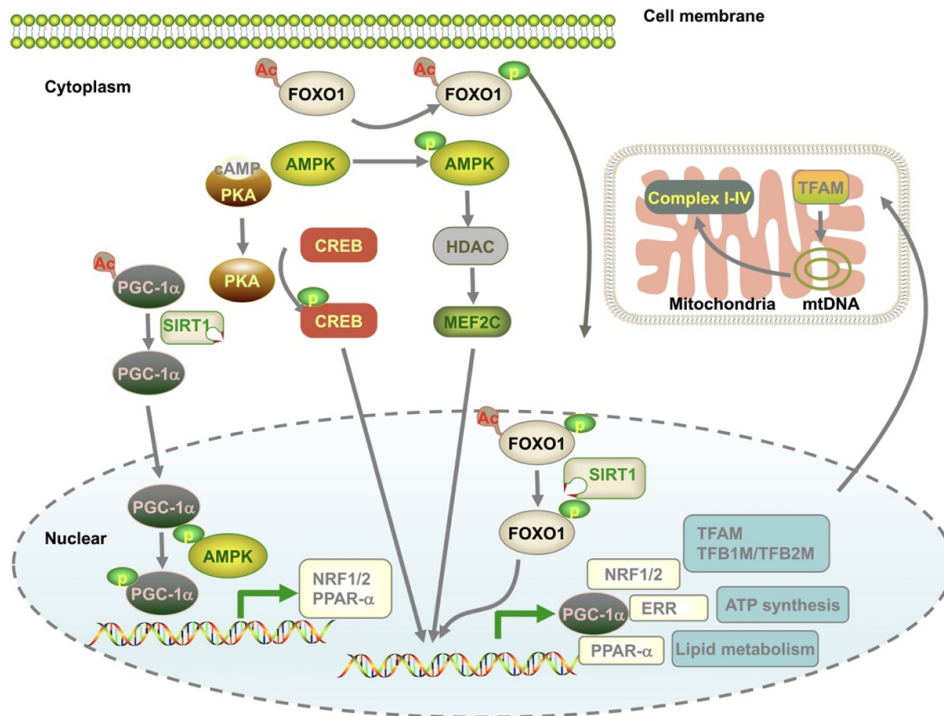
**Fig. 2.** The role of mitochondrial dysfunction in the development of diabetic cardiomyopathy. In diabetic heart, mitochondria are suffered from imbalanced dynamics, damaged biogenesis, and impaired mitophagy. Conversely, mitochondrial dysfunction may be explained by reduced ATP production and ROS damage, leading to cardiac structural, electrical, and functional disorder. ADP, adenosine-diphosphate; ATP, adenosine-triphosphate; TCA, tricarboxylic acid cycle; FAO, Fatty Acid Oxidation; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; mtDNA, mitochondrial DNA.

phosphorylation, ubiquitination, and O-linked N-acetylglucosylation (Fig. 3) (Fernandez-Marcos and Auwerx, 2011). For the downstream signaling pathways, PGC-1 $\alpha$  binds to a series of nuclear transcription factors, including nuclear respiratory factor 1/2 (NRF1/2), estrogen-related receptor  $\alpha$  (ERR- $\alpha$ ), and PPARs (Biswas and Chan, 2010; Bruni *et al.*, 2010; Satoh *et al.*, 2013; Yang *et al.*, 2014). Stimulation of NRF1/2 activates the downstream factors involved in mtDNA transcription and replication [(transcription factor A mitochondrial (TFAM)], transcription factor B1 mitochondrial (TFB1M), and transcription factor B2 mitochondrial (TFB2M) (Biswas and Chan, 2010; Satoh *et al.*, 2013; Yang *et al.*, 2014), respiratory chain [cytochrome C oxidase subunit IV (COXIV) and cytochrome c (Bruni *et al.*, 2010)], and the mitochondrial protein import machinery (translocase of outer mitochondrial membrane 34kDa subunit, TOMM34) (Blesa *et al.*, 2008). For ERR- $\alpha$ , in cooperation with PGC-1 $\alpha$ , ERR- $\alpha$  regulates mitochondrial energy transduction and adenosine-triphosphate (ATP) synthesis, including fatty acid oxidation (FAO), tricarboxylic acid (TCA) cycle, and the electron transport chain/oxidative phosphorylation (ETC/OXPHOS) (Sakamoto *et al.*, 2020). The PPARs are PGC-1 $\alpha$  coactivators and can serve as critical regulators in the biogenesis of mitochondrial FAO and other cellular lipid metabolic pathways (Zhou *et al.*, 2018).

### Changes of mitochondrial biogenesis in diabetic cardiomyopathy

Cardiac mitochondrial biogenesis is a dynamic process. During physiological conditions, stimulation or inhibition of

mitochondrial biogenesis induced by either up- or down- regulation of transcriptional factors are exhibited according to different energy demands. While during pathological conditions, there are two sides regarding the disturbances of mitochondrial biogenesis: i) an impairment condition in which stimulation of mitochondrial biogenesis is required; ii) the abnormal worsen that a removal is necessary. In OVE26 mouse model of type 1 diabetic (T1DM) heart, impaired mitochondrial function and increased oxidative stress were observed as evidenced by increased mitochondrial area and reduced respiratory control ratio. However, these damaged mitochondria might be due to enhanced mitochondrial biogenesis exhibited as elevated mtDNA and mRNA levels for TFAM, cytochrome b, and cytochrome c in T1DM (Shen *et al.*, 2004). Alternatively, in streptozotocin (STZ)-induced T1DM heart mouse model, mitochondrial biogenesis was significantly impaired showed as dysregulated mitochondrial structure, reduced mtDNA, and decreased biogenesis-related mRNAs level (Tao *et al.*, 2020). In *ob/ob* mouse model of type 2 diabetic (T2DM) heart, significant mitochondrial disorders, reduced mtDNA and impaired mitochondrial biogenesis were identified in cardiomyocytes (Yan *et al.*, 2013). Nevertheless, in fat-enriched regimen and STZ injection-induced T2DM mice model, cardiac contractile dysfunction was associated with decreased mitochondrial oxygen consumption, as well as reduced ATP production, and despite enhanced mitochondrial biogenesis signaling (Marciniak *et al.*, 2014). In patients with T2DM, mitochondrial biogenesis appeared to be decreased in skeletal and heart samples, as shown by reduced mtDNA content and mitochondrial vol-



**Fig. 3.** Mechanisms that contribute to mitochondrial biogenesis. Mitochondrial biogenesis is a well-controlled process and is coupled with a complex transcriptional network involving mitochondrial DNA and nuclear DNA. PGC-1 $\alpha$  is a master regulator and coordinates with several different pathways to meet the metabolic demand of the cells under various conditions. mtDNA, mitochondrial DNA.

ume (Karamanlidis *et al.*, 2010). The inconsistencies between mitochondrial biogenesis and mitochondrial function may be possibly explained by the evidence that diabetes impaired mitochondrial degradation and accumulation of damaged mitochondria. Furthermore, changes of mitochondrial number in diabetic hearts may affect the rates of mitochondrial fission and/or fusion (Liang and Kobayashi, 2016). Additionally, although up-regulation of related transcriptional factors is a key player in mitochondrial biogenesis, unflavored genes may be equally activated, resulting in detrimental effects depending on ligands specificity (Cameron *et al.*, 2016). Finally, energy demands of different cell types in diabetic hearts may also be one of the reasons. However, the extent and duration of energy demand in different cell types in diabetic hearts are uncertain till now. Hence, further experiments are needed to differentiate these possibilities.

**Stimulators and inhibitors of mitochondrial biogenesis in DCM**

In diabetic conditions, several stimulators or inhibitors of cardiac mitochondrial biogenesis have been identified within last decades. Examples of drugs or hormone substances are presented as follows (Table 1).

Melatonin, a hormone known for its antioxidant capacity, that protected against myocardial remodeling by preserving mitochondrial biogenesis in both type 1 and type 2 DCM model. A study indicated that melatonin could improve mitochondrial function through SIRT6 mediated AMPK-PGC-1 $\alpha$ -AKT axis in high-fat diet and STZ injection-induced rat model (Yu *et al.*, 2021) or mammalian Ste20-like kinase 1 (Mst1)/SIRT3 signaling in STZ injection-induced mice model (Zhang *et al.*,

2017). Another study showed that resveratrol, a SIRT1 activator, could increase the affinity of SIRT1 for both nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and the acetylated substrate. Resveratrol treatment significantly alleviated cardiac hypertrophy, improved mitochondrial biogenesis, and decreased cardiomyocyte apoptosis in DCM models induced by SIRT1 deletion. Resveratrol further enhanced PGC-1 $\alpha$  deacetylation and activated downstream targets (Ma *et al.*, 2017; Fang *et al.*, 2018).

Some other natural extracts were also assumed to regulate mitochondrial biogenesis. For instance, Li *et al.* (2021b) have reported that salidroside can protect against diabetic cardiac systolic function, improve insulin resistance, and rescue impaired mitochondrial biogenesis through SIRT3, AMPK/Akt, and PGC-1 $\alpha$ /TFAM signaling in high fat and STZ injection-induced mice models. Additionally, pterostilbene, an antioxidant in blueberries, was also reported to rescue myocardial inflammation, oxidative stress, and mitochondrial biogenesis in high glucose rat models through AMPK/NRF2/HO-1/PGC-1 $\alpha$  signaling (Kosuru *et al.*, 2018).

Notably, it has been demonstrated that chemical compounds, including miR-144 agonists, could improve mitochondrial biogenesis and suppress cardiomyocyte apoptosis via targeting Rac-1 in STZ-challenged heart samples. This study also found that decreased Rac-1 levels further induced AMPK phosphorylation and PGC-1 $\alpha$  deacetylation (Tao *et al.*, 2020). Another compound was tetrahydrobiopterin (BH4), prolonged BH4 supplementation could bind to CAMKK2 and activate AMPK/CaMK IV/CREB/PGC-1 $\alpha$  to rescue cardiac dysfunction, improve mitochondrial biogenesis, and correct morphological abnormalities of cardiac muscle in Otsuka long-evans

**Table 1.** Stimulators and inhibitors of mitochondrial biogenesis in animal DCM models

	Types	DCM models	Mechanisms	References
<b>Stimulators</b>				
Melatonin	T1DM	STZ injection mice	SIRT3/Mst1	Yu <i>et al.</i> , 2021
	T2DM	High-fat diet and STZ injection rats	SIRT6, AMPK-PGC-1 $\alpha$ -AKT	Zhang <i>et al.</i> , 2017
Resveratrol	T2DM	High-fat diet and STZ injection rats	SIRT1-PGC-1 $\alpha$ deacetylation	Fang <i>et al.</i> , 2018
		SIRT1 deletion mice	SIRT1-PGC-1 $\alpha$ deacetylation	Ma <i>et al.</i> , 2017
Salidroside	T2DM	High-fat and STZ-injection mice	SIRT3, AMPK/AKT/PGC-1 $\alpha$ -TFAM	Li <i>et al.</i> , 2021b
Pterostillbene	T1DM	High-glucose diet rats	AMPK/NRF2/HO-1/PGC-1 $\alpha$	Kosuru <i>et al.</i> , 2018
miR-144	T1DM	STZ-injection mice	Rac-1/AMPK/ PGC-1 $\alpha$	Tao <i>et al.</i> , 2020
BH4	T2DM	OLETF rats	CaMKK2-AMPK/CAMP/CREB/ PGC-1 $\alpha$	Kim <i>et al.</i> , 2020
<b>Exercise</b>				
Resistance	T2DM	OLETF rats	UCP2/UCP3	Ko <i>et al.</i> , 2018
Moderate	T2DM	Db/db mice	CXC3	Veeranki <i>et al.</i> , 2016
Ensurance	T2DM	Db/db mice	PGC-1 $\alpha$ -AKT	Wang <i>et al.</i> , 2015
<b>Inhibitors</b>				
ADMA	T2DM	High-fat and STZ injection rats	PGC-1 $\alpha$ phosphorylation and acetylation	Xiong <i>et al.</i> , 2020
	T1DM	STZ injection rats	NO/ PGC-1 $\alpha$	Xiong <i>et al.</i> , 2021

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; STZ, streptozotocin; OLETF, Otsuka long-evans Tokushima fatty; BH4, tetrahydrobiopterin; ADMA, asymmetric dimethylarginine.

tokushima fatty (OLETF) rat models (Kim *et al.*, 2020).

Interestingly, previous studies found that regular exercise conferred a multitude of cardiovascular benefits during diabetes. Resistance exercise, defined as repeatedly climbing a 1m grid ladder inclined at 85°, 20 times during each session, lasting 5 days/week for 12 weeks, was effective at maintaining diabetic cardiac contractility and function by enhancing mitochondrial biogenesis in OLETF rat models, which were accompanied by elevated superoxide dismutase 2 and reduced uncoupling protein (UCP) 2 and UCP3 levels (Ko *et al.*, 2018). Moderate-intensity exercise covering a daily distance of 330 meters at a speed of 10 m/min for 2 weeks and at a speed of 11 m/min for the rest of the 3 weeks for 5 days/week, could prevent db/db mice cardiac contractile functional deficiencies by improving mitochondrial biogenesis, sustaining trans-membrane potential and reducing excessive mitochondrial fission through the restoration of connexin 43 signaling (Veeranki *et al.*, 2016). Moreover, continuous exercise (1 h running/day at a speed of 10 m/min for 15 weeks) also preserved cardiac systolic function and enhanced mitochondrial biogenesis in the late stage of DCM in a db/db mouse model by activation of PGC-1 $\alpha$  and Akt signaling (Wang *et al.*, 2015). These results indicated that exercise with different intensities or durations might affect cardiac mitochondrial biogenesis to varying degrees. More recently, a large sample, community-dwelling study confirmed that an average of 12 min acute exercise elicited widespread metabolic changes central to cardiovascular disease and cardiometabolic health (Naylor *et al.*, 2020). However, whether acute exercise affect cardiac metabolic remodeling by regulating mitochondrial biogenesis is still uncertain, and the longevity of exercise-mediated cardiac benefits in diabetes needs to be further explored.

Previous data have suggested inhibitors of mitochondrial biogenesis can down-regulate the expression level of associated-transcriptional factors or reduce signaling pathways such as AMPK. A study indicated that asymmetric dimethylarginine (ADMA), a nitric oxide (NO) synthase inhibitor, could inhibit myocardial mitochondrial biogenesis in a T2DM rat model in-

duced by high-fat feeding plus STZ injection. The underlying mechanisms might be related to decreased PGC-1 $\alpha$  promoter activity and activated PGC-1 $\alpha$  protein phosphorylation and acetylation (Xiong *et al.*, 2020). Moreover, ADMA accumulation was also associated with cardiac and mitochondrial dysfunction in parallel with decreased NO content and PGC-1 $\alpha$  level in a T1DM induced by STZ rat model (Xiong *et al.*, 2021).

Therefore, as mitochondrial biogenesis is a dynamically controlled process where mitochondrial quality, activity, and maintenance are constantly adapted to the cell's bioenergetic needs, and the role of the two opposite states (impairment or enhancement) of mitochondrial biogenesis in cardio-protection can give insights into novel therapeutics for DCM.

## MITOCHONDRIAL BIOGENESIS AND CLINICAL RELEVANCE IN DIABETIC CARDIOMYOPATHY

### Clinical evaluation of mitochondrial biogenesis

Mitochondrial biogenesis plays an essential role in DCM in both *in vitro* and *in vivo*, but its potential clinical relevance in DCM has not been fully elucidated. mtDNA synthesis reflects cell energy demands (Malik and Czajka, 2013; Melser *et al.*, 2015) and can be regarded as an early biomarker of mitochondrial biogenesis. In DCM, both mtDNA mutation accumulation and mtDNA copy number (mtDNAcn) disturbance can be used to explain the impaired mtDNA synthesis.

mtDNA mutations are a common cause of mitochondrial dysfunction. They are often present in only a fraction of mtDNA copies and act recessively to induce several diseases, including diabetic cardiac disorders. Compared to ordinary diabetic patients, patients with mtDNA mutation at base pair 3243 had more severe cardiac autonomic nervous dysfunction with sympathovagal imbalance as investigated by heart rate variability. Diabetic patients with mtDNA mutation exhibited smaller standard deviation of all R-R intervals (SDNN) index and smaller total and low-frequency spectra (Momiyama *et al.*, 2002). In addition to heart rate, diabetic patients with tRNA

(Leu (UUR)) gene mutation also showed cardiac structural and functional impairments as evidenced by a significantly thicker interventricular septum and lower fractional shortening than those without mutations (Ueno and Shiotani, 1999). Furthermore, variants at 16189 of mtDNA mutation were more likely to develop in diabetic patients with left ventricle hypertrophy (LVH) than that in diabetic patients without LVH (Moriyama *et al.*, 2003).

In addition to mtDNA mutation, mtDNAcn disturbance has been also suggested to be a potential biomarker for cardiovascular disease. In the blood, mtDNAcn was significantly reduced in patients with CAD and was associated with metabolic risk factors, including hypertension and glomerular filtration rate (GFR) (Bordoni *et al.*, 2021). In plasma, cell-free mtDNA was elevated in patients with CAD and DM compared to that in those without DM or healthy controls. Furthermore, mtDNA levels were positively correlated with fasting blood glucose levels in patients with CAD and DM (Liu *et al.*, 2016). Interestingly, recent evidence demonstrated that blood also contained circulating cell-free respiratory competent mitochondria (Al Amir Dache *et al.*, 2020), supporting the novel interest towards mtDNA measurement as an easy-accessible biomarker in CVD.

However, there are some limitations of current studies. First, only a small number of studies have focused on the relationship between circulating mtDNA and DCM in human beings. More large-scale clinical studies are warranted to infer the direct role of mtDNA in DCM. Second, the precise mechanism underlying the link between mtDNA damage and DCM is poorly elucidated. It is well recognized that mtDNA is a major target of ROS (Quan *et al.*, 2020). In diabetic conditions, hyperglycemia and insulin insistance increases oxygen metabolism at complexes I and III, leading to mitochondrial inner membrane hyperpolarization and excessive ROS production (Jia *et al.*, 2018a). Thus, we hypothesized that oxidative stress might be a causal factor in mtDNA damage in DCM, which ultimately resulted in mitochondrial dysfunction. Further research on mtDNA, ROS, DCM, and other implicated mechanisms is required. Third, although a positive link between the number of mitochondria and mtDNAcn has been confirmed (Lee and Wei, 2000), mtDNAcn is not always correlated with mitochondrial gene expression. Thus, mtDNAcn cannot be used as a reliable biomarker of mitochondrial abundance (Cayci *et al.*, 2012; Qiu *et al.*, 2013). Future mechanistic studies are necessary to clarify the real role of mtDNA in DCM.

**Glucose-lowering drugs and mitochondrial biogenesis**

Various pharmacological and genetic preclinical models of DM have documented the detrimental effects of DM on the myocardium, which extend well beyond hyperglycemia (Murtaza *et al.*, 2019). Veteran Affairs Diabetes Trial (VADT) clinical trials confirmed that there was no evidence of a legacy effect

or mortality benefit with intensive glucose control in patients with T2DM (Reaven *et al.*, 2019). Therefore, recent clinical and experimental studies have described the evolving landscape of some glucose-lowering drugs with cardio-protective properties such as sodium-glucose co-transporter-2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase-4 inhibitors (DPP-4is). These cardio-protective effects may be achieved by “pleiotropic actions” that go beyond glucose control. Currently, emerging evidence showed that one of the “pleiotropic actions” may consist of maintaining mitochondrial biogenesis (Table 2).

**Sodium-glucose co-transporter-2 inhibitor:** SGLT2is are novel glucose-lowering drugs that act via specific renal action by inducing glucosuria, independently of insulin (Li and Zhou, 2020). Large clinical studies such as Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) (Zinman *et al.*, 2014), Canagliflozin Cardiovascular Assessment Study (CANVAS) (Neal *et al.*, 2017), and Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) (Wiviott *et al.*, 2019) have confirmed the protective effects of taking SGLT2is in reducing CV mortality and hospitalization for heart failure in T2DM patients. Recent evidence indicated that SGLT2is might perform a cardio-protective function by regulating mitochondrial function in diabetic models (Peng *et al.*, 2020; Yurista *et al.*, 2020). In eleven-week-old female db/db mice, empagliflozin was shown to normalize mitochondrial ultrastructural anomalies, including the disorganized appearance of sarcomeres, decreased matrix electron density, loss and fusion of cristae, and increased mitochondrial fragmentation (Habibi *et al.*, 2017). In high-fat diet-induced obese insulin-resistant rats, administration of dapagliflozin for 4 weeks before cardiac ischemic/reperfusion injury attenuated mitochondrial ROS production, swelling, and depolarization. Furthermore, data also suggested that dapagliflozin also improved mitochondrial ultrastructure by reducing mitochondrial fragmentation and cristae loss (Tanajak *et al.*, 2018). In STZ-induced diabetic rats on a high-fat diet, empagliflozin was demonstrated to ameliorate the atrial structure and electrical remodeling through increasing mitochondrial respiratory function and mitochondrial biogenesis. Consequently, empagliflozin prevented the inducibility of atrial fibrillation (AF) by activating the PGC-1 $\alpha$ -NRF1-TFAM signaling pathway (Shao *et al.*, 2019), which played a crucial role in mitochondrial biogenesis. However, the exact roles of mitochondrial biogenesis in the occurrence and progression of ischemic cardiomyopathy or AF in diabetic patients remain unclear. It is still uncertain whether these benefits are from direct cardiac or systemic effects or if they are drug-specific effects of empagliflozin or a class effect of SGLT2is, all of which need further exploration.

**Table 2.** Glucose-lowering drugs and mitochondrial biogenesis

Drugs	Types	Diabetic models	Mechanisms	References
Empagliflozin	T2DM	High-fat and STZ injection rats	PGC-1 $\alpha$ -NRF1-TFAM	Habibi <i>et al.</i> , 2017
Alogliptin	T1DM	Alloxan-induced rabbits	PGC-1 $\alpha$ -NRF1-TFAM	Zhang <i>et al.</i> , 2018
Metformin	T1DM	High glucose-induced cardiomyocytes	PGC-1 $\alpha$ -NRF1-TFAM	Packer, 2020
Pioglitazone	T1DM	Alloxan-induced mice	PGC-1 $\alpha$	Zhang <i>et al.</i> , 2021

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; STZ, streptozotocin.

**Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs):** As well known, DPP-4is inhibit the enzyme degrading 2 gut-derived incretin hormones, GLP-1, and glucose-dependent-insulinotropic polypeptide (Scheen, 2018). Functionally, DPP-4i can stimulate insulin secretion and repress glucagon secretion in a glucose-dependent manner, contributing to glucose-lowering effects. Nauck *et al.* (2017) found that in diabetic myocardium DPP-4is had protective effects against cardiovascular (CV) risk factors, including body weight, blood pressure, postprandial lipemia, inflammation, and oxidative stress. Mitochondrial biogenesis has been reported to be involved in the cardioprotective actions of DPP-4i. In alloxan-induced diabetic rabbits, DPP-4i alogliptin alleviated cardiac ventricular hypertrophy, diastolic dysfunction, and interstitial fibrosis, which were associated with increased mitochondrial biogenesis via PGC-1 $\alpha$ /NRF1/TFAM signaling pathway and improved mitochondrial function as evidenced by decreased mitochondrial ROS production, sustained mitochondrial membrane depolarization, and elevated mitochondrial swelling (Zhang *et al.*, 2018).

GLP-1 is classically viewed as the primary substrate of DPP-4 and capable of modulating CV function. In a myocardial infarction mouse model study, DPP-4i (MK-0626) and GLP-1A (Exendin-4) were found to exert favorable effects to preserve mitochondrial quality and biogenesis in skeletal muscle, and both were inhibited by GLP-1 antagonist [Exendin-(9-39)], indicating that DPP-4i/GLP-1 receptor signaling could be a potential treatment target for HF patients with exercise intolerance via mitochondrial biogenesis (Takada *et al.*, 2016). Furthermore, GLP-1RAs could reduce established CV risk factors in T2DM, such as hyperglycemia, obesity, dysfunctional lipid profile, and high blood pressure (Marso *et al.*, 2016; Kristensen *et al.*, 2019; Verma *et al.*, 2020). However, whether GLP-1RAs' potential cardioprotective effects are derived from mitochondrial biogenesis is an area of growing interest.

**Other glucose-lowering drugs:** In addition to SGLT2is, GLP-1RAs, and DPP-4is, other antihyperglycemic drugs also act on mitochondrial biogenesis, which we describe briefly below. Metformin is a widely prescribed antihyperglycemic drug. In diabetic hearts, metformin promoted mitochondrial autophagy and ameliorates cardiomyocyte dysfunction, whose actions can either be dependent or independent of AMPK (Packer, 2020). Furthermore, in high glucose-induced cardiomyocytes, metformin also stimulated mitochondrial biogenesis as evidenced by increased expression of mitochondrial biogenesis-related transcription factors (PGC-1 $\alpha$ , NRF1, and TFAM) (Liu *et al.*, 2020), but the detailed mechanisms of metformin regulating mitochondrial function in DCM remained unclear. PPAR $\gamma$  agonist, pioglitazone, mimicked the effect of PGC-1 $\alpha$ , prevented atrial structural remodeling, and lowered the incidence of inducible AF, which were associated with improved mitochondrial structure and elevated mitochondrial biogenesis in diabetic mice induced by alloxan monohydrate. (Zhang *et al.*, 2021).

## CONCLUSIONS AND PERSPECTIVES

In conclusion, mounting evidence shows that the dysfunction of mitochondrial biogenesis is a major contributor to the development of DCM. However, it is necessary to determine whether changes in mitochondrial biogenesis are maladaptive

or adaptive by using gain- and loss-of-function experiments to target mitochondrial biogenesis for therapeutics in DCM successfully. Furthermore, as mitochondrial homeostasis is controlled by several mechanisms, including mitochondrial dynamics, mitophagy, and biogenesis, identifying relative contributions, molecular underpinnings, and coordination between different processes is crucial. Animal models indicate that regulating mitochondrial biogenesis of the human diabetic hearts may be appropriate targets for future interventions. Finally, more studies are needed to examine the potential role and mechanisms of novel glucose-lowering treatments on mitochondrial biogenesis in patients with DCM.

## CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

## ACKNOWLEDGMENTS

This research was funded by the National Natural Science Foundation of China (NSFC) grants 82170356, China Postdoctoral Science Foundation grant 2018M642317, Post-Doctoral Foundation of Jiangsu Province grant 2018K095B, Six Talent Peaks Project of Jiangsu Province grants WSN-202 and WSW-183, Changzhou Sci&Tech Program grant CJ20210091, Maternal and Child Health Research Project of Jiangsu Province grant F201803.

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