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Mitochondrial energy metabolism in diabetic cardiomyopathy: Physiological adaption, pathogenesis, and therapeutic targets

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Abstract

Diabetic cardiomyopathy is defined as abnormal structure and function of the heart in the setting of diabetes, which could eventually develop heart failure and leads to the death of the patients. Although blood glucose control and medications to heart failure show beneficial effects on this disease, there is currently no specific treatment for diabetic cardiomyopathy. Over the past few decades, the pathophysiology of diabetic cardiomyopathy has been extensively studied, and an increasing number of studies pinpoint that impaired mitochondrial energy metabolism is a key mediator as well as a therapeutic target. In this review, we summarize the latest research in the field of diabetic cardiomyopathy, focusing on mitochondrial damage and adaptation, altered energy substrates, and potential therapeutic targets. A better understanding of the mitochondrial energy metabolism in diabetic cardiomyopathy may help to gain more mechanistic insights and generate more precise mitochondria-oriented therapies to treat this disease.

Keywords: Mitochondria; Mitochondrial energy metabolism; Diabetic cardiomyopathies; Physiology; Physiological adaption; Pathogenesis; Therapeutics

Introduction

The prevalence of diabetes mellitus (DM) has been steadily increasing for decades, with approximately 536.6 million people living with DM (diagnosed or undiagnosed) worldwide in 2021, according to the International Diabetes Federation (IDF).[1] Among the DM-related complications, cardiovascular disease is one of the leading causes of death.[2] In turn, as an independent risk factor, diabetes confers a two-fold excess risk of adverse outcomes and is with higher mortality when combined with cardiovascular diseases.[3–5]

In 1927, Rubler *et al*[6] proposed the existence of diabetic cardiomyopathy based on the finding that four adult diabetic patients who suffered from congestive heart failure were in the absence of diseases in coronary artery, valvula, and peripheral vasculature. It is widely accepted that one of the hallmarks of the diabetic cardiomyopathy is left ventricular (LV) diastolic dysfunction, which is often detected earlier than systolic dysfunction even in asymptomatic patients with well-controlled DM.[7–9] Genetic culprits, such as abnormal miRNA and epigenetics, have been reported to regulate the phenotypes of diabetic cardiomyopathy.[10] Also, there are multiple inherited cardiovascular diseases with dilated, hypertrophic, and restrictive phenotypes. Although they shared similar phenotypes with diabetic cardiomyopathy, these patients are often without a history of diabetes.[11]

With the development of non-invasive diagnostic devices, such as magnetic resonance imaging and echocardiography, structural changes including myocardial fibrosis and hypertrophy are gradually recognized as the main

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characteristics of diabetic cardiomyopathy.[12,13] Research into the pathophysiological mechanisms underlying diabetic cardiomyopathy highlights the importance of insulin resistance, mitochondrial respiratory chain dysfunction, ATP synthesis disorder, metabolic inflexibility, oxidative stress, and impaired calcium handling. However, there is no specific treatment for the patients with diabetic cardiomyopathy. So far, the treatment strategies are mainly aimed at blood glucose control and preventing risk factors associated with the progression of cardiovascular diseases. Importantly, the etiological differences between type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) complicate the pathogenesis, cardiac phenotype, and therapies of the cardiomyopathies. Accumulating studies demonstrate that T1DM patients mainly display diastolic dysfunction, while T2DM patients manifest systolic impairment and myocardial structure changes.[14,15] There are also studies proposed that these functional changes should be viewed as a progressive process rather than a specific phenotype of one type of diabetes.[16] Moreover, T1DM is usually accompanied by enhanced autophagy in the heart, whereas it is suppressed in T2DM diabetes.[17] Despite these differences, both types of diabetes lead to increased extracellular glucose and greater reliance on fatty acid (FA) oxidation.[18] Therefore, targeting at mitochondrial metabolism for diabetic cardiomyopathy treatment may hold therapeutic potential for both T1DM and T2DM patients.

As an energy-consuming organ, the heart relies predominantly on mitochondria to fulfil the energy demand. Dysfunction in mitochondria and energy substrates reprogramming are implicated as a central driver for the onset and progression of diabetic cardiomyopathy. Here, we review the current knowledge of the reprogrammed mitochondrial energy metabolism in diabetic cardiomyopathy by elaborating how the changed catabolism of glucose, FAs, lactate, ketone bodies, and branched-chain amino acids (BCAAs) participates in or counteracts the pathogenesis, and highlighting the emerging mitochondrial metabolism targeted therapies.

Mitochondrial Dysfunction in Diabetic Cardiomyopathy

Mitochondria are primary cellular power sources and play an essential role in meeting the elevated energy requirements and vital activities of cardiomyocytes. Metabolic diseases disrupt mitochondrial function which is important for the maintenance of normal heart function. In diabetic hearts, metabolic deficits significantly and negatively impact the mitochondria. Mitochondria respond to high glucose levels and insulin resistance by altering their biogenesis and dynamics. However, failed compensation results in the accumulation of reactive oxygen species (ROS), leading to intracellular calcium disturbances, calcium homeostasis dysregulation, and cellular damage [Figure 1].

Abnormal mitochondrial dynamics

It has been reported that mitochondrial activity is impaired in diabetic patients and preclinical diabetic models, and maintaining mitochondrial integrity effectively improves energy production.[19–21] Mitochondrial dynamics regulate mitochondrial capacity and function. Specifically, mitochondrial fission leads to mitochondrial fragmentation, whereas mitochondrial fusion contributes to mitochondrial formation. In T2DM, the mitochondrial number increases; however, the mitochondria are smaller in size and are fragmented, suggesting an imbalance in mitochondrial quality control.[22] The diabetic hearts are reported to exhibit an increased rate of mitochondrial fission, which results in numerous fragmented mitochondria. Another study suggested that the rapid formation of small mitochondria, induced by high glucose levels, occurs as a response to increased metabolic flux.[23] This process is regulated by the posttranslational modifications of the dynamic relative protein 1 (DRP1).[24] Also, the DRP1-mediated macrophage stimulating 1 (MST1) pathway is involved in the development of diabetic cardiomyopathy.[25] Furthermore, recent research suggests that Ca^{2+} release-activated calcium channel protein 1 (ORAI1) plays an important role in diabetic cardiomyopathy by regulating calcium homeostasis. The cardioprotective effect of ORAI1 inhibition on mitochondrial dysfunction and diabetic cardiomyocyte hypertrophy occurs via the ORAI1/DRP1 signaling pathway.[26] In diabetic cardiomyopathy, mitochondrial fusion decreases, as indicated by a significant decrease in mitofusion 2 (MFN2) expression. The overexpression of MFN2 in diabetic hearts has been shown to reduce ROS production and normalize fission. And MFN2 expression can be regulated via the peroxisome proliferator-activated receptor α (PPARα).[27]

Mitophagy is the process of clearing damaged mitochondria and is among the most important steps in maintaining mitochondrial quality. During mitophagy, damaged parts of mitochondria fuse with lysosomes and are eliminated. Several studies have suggested that aberrant mitochondrial dynamics and mitophagy are primary metabolic deficits responsible for initiating pathological changes in the heart.[28] As previously mentioned, decreased mitophagy has been observed in prediabetic mice. In high-fat diet (HFD)-induced diabetes, the initiation of mitophagy by injection of Tat-Beclin1 attenuates mitochondrial dysfunction, improves lipid metabolism, and protects against cardiac dysfunction.[29] Additionally, in a diabetic cardiomyopathy animal model, MST1 deficiency was shown to stimulate mitophagy via the sirtuin3 (SIRT3)/Parkin pathway and alleviate the impaired heart phenotype.[30] In a streptozotocin (STZ)-induced diabetes mouse model, mitochondrial injury and cardiac dysfunction were shown to result from suppressed mitophagy, which occurs via the forkhead box O3 (FOXO3)/Parkin signaling pathway. These results suggest that mitophagy plays a protective role in diabetic cardiomyopathy. *In vitro*, SIRT3 overexpression normalized FOXO3 and Parkin expression, activated mitophagy, and inhibited mitochondrial damage and apoptosis.[31] Overall, these results indicate that SIRT3 and MST1 play crucial regulatory roles in mitochondrial dynamics and mitophagy during the development of diabetic cardiomyopathy and may serve as therapeutic targets.[32]

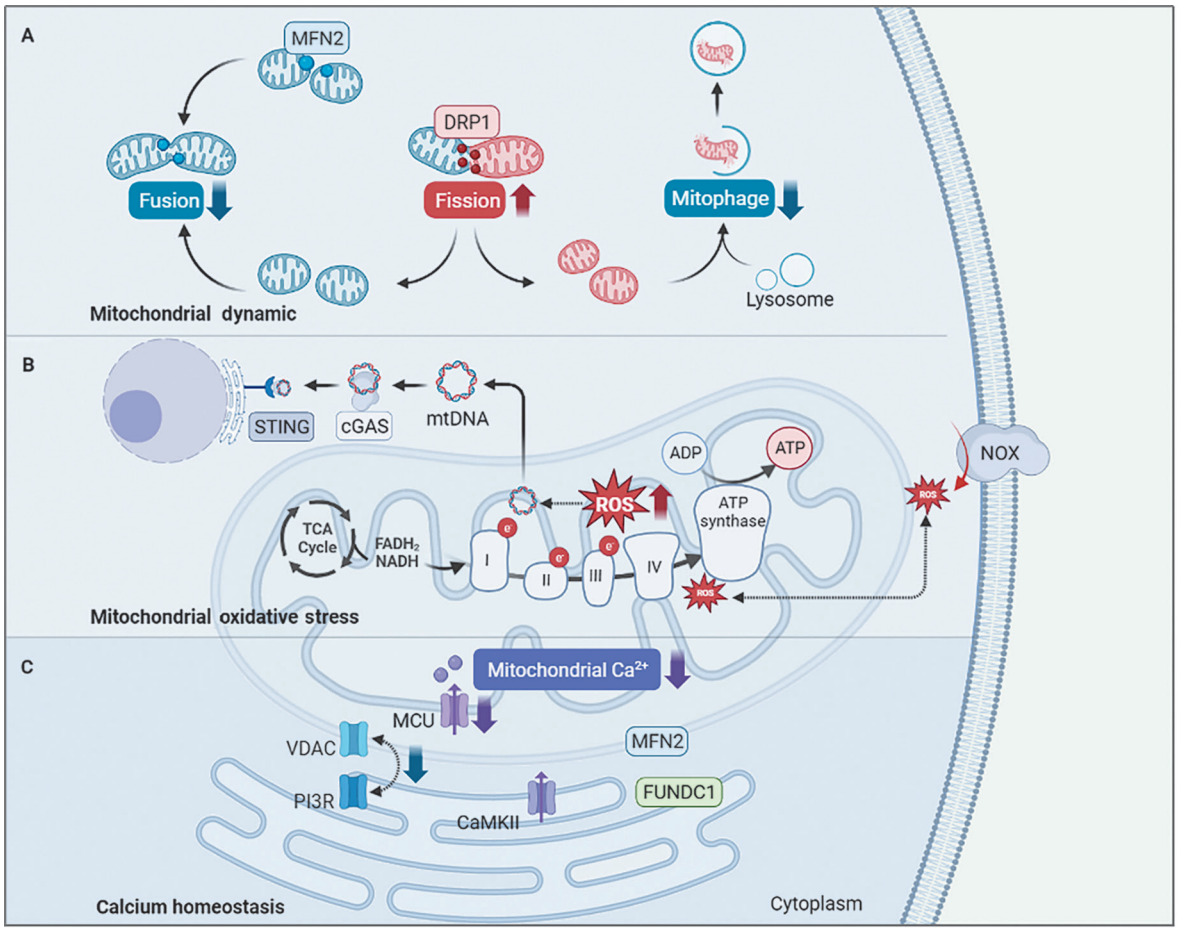

Figure 1: Mitochondrial modulation of diabetic cardiomyopathy. (A) Abnormal mitochondrial dynamics including decreased fusion, increased fission, and reduced mitophagy. (B) The enhanced metabolic flux and impaired electron transport chain result in the increased production of mitochondrial ROS which stimulates the efflux of mtDNA and interacts with cytoplasmic ROS. (C) Unbalanced mitochondrial Ca^{2+} homeostasis results from damaged Ca^{2+} channels in the inner and outer mitochondrial membranes and abnormal endoplasmic reticulum-derived Ca^{2+}. CaMKII: Calmodulin kinase II; cGAS: GMP-AMP synthase; DRP1: Dynamic relative protein 1; $FADH_2$: 5,10-methylenetetrahydrofolate reductase; FUNDC1: FUN14 domain containing 1; IP3R: Inositol 1,4,5-triphosphate receptor; MCU: Mitochondrial Ca^{2+} uniporter; MFN2: Mitofusion 2; NADH: Nicotinamide adenine dinucleotide reduced; NOX: Nicotinamide adenine dinucleotide phosphate oxidase; ROS: Reactive oxygen species; STING: Stimulator of interferon gene; TCA: Tricarboxylic acid; VDAC: Voltage-dependent anion channel.

Increase in mitochondrial oxidative stress

ROS and oxidative stress are extensively involved in the onset of diabetic cardiomyopathy because of their detrimental interactions with numerous macromolecules.[33] In diabetic hearts, inappropriate energy compensation increases the flux of reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) into the mitochondrial respiratory chain, resulting in excessive electron and ROS production.[34] In animal models and diabetic patients, elevated cardiac ROS causes mitochondrial fragmentation, cristae disruption, swelling, and damage to various biological pathways.[35,36] Mitochondria are an important source of ROS, and in experimental models of diabetic cardiomyopathy, the use of mitochondrial antioxidants, such as MitoTEMPO, offers cardioprotection.[37] Moreover, it was shown that mitochondrial ROS generated in db/db mice increased the transport of mtDNA into the cytoplasm and activated the GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) signaling pathway. Treatment with an STING inhibitor can improve cardiac dysfunction, indicating that STING may be a potential therapeutic target.[38,39]

Crosstalk between different cellular ROS sources is likely to exist; therefore, mitochondrial ROS production may be regulated by ROS from other sources. Nicotinamide adenine dinucleotide phosphate oxidases (NOXs) are considered major sources of cellular ROS and are involved in several pathological conditions.[40] NOX activity is increased in T1DM and T2DM and has been reported to contribute to the development of cardiomyopathy.[41,42] NOX4 upregulation aggravates mitochondrial superoxide accumulation and damages mitochondrial membrane potential.[26] The use of a mitochondrial ROS scavenger was shown to improve diabetic myocardium and decrease NOX2 expression. Moreover, in hyperglycemic hearts, mitochondrial superoxide formation was inhibited by the genetic inhibition of NOX2.[43]

Unbalanced mitochondrial calcium homeostasis

Mitochondrial Ca^{2+} plays an essential role in cardiac excitation–contraction coupling and signal conduction. In diabetic hearts, calcium homeostasis and Ca^{2+} transporters are disturbed, resulting in abnormal cardiac diastolic function.[44] The alteration of mitochondrial Ca^{2+} in diabetic

cardiomyopathy is still under debate; both increased and decreased cardiac mitochondrial Ca^{2+} levels have been reported in human and animal models of T1DM and T2DM. Mitochondrial Ca^{2+} overload and subsequent cell apoptosis can damage cardiomyocytes and impair heart function.[45,46] The decrease of mitochondrial Ca^{2+} could reduce the activity of pyruvate dehydrogenase (PDH), resulting in decreased glucose utilization, increased FA utilization, and impaired ATP production.[47] Therefore, the disturbance of mitochondria Ca^{2+} compromises mitochondrial bioenergetics and exacerbates oxidative stress, which drives the pathogenesis of diabetic cardiomyopathy.[48] Importantly, the level of mitochondrial Ca^{2+} uniporter (MCU) protein, a channel responsible for mitochondrial Ca^{2+} uptake located in the inner mitochondrial membrane, is also reduced.[49] Studies have reported that increased MCU levels reverse hyperglycemia-induced metabolic alterations with recovered mitochondrial Ca^{2+} concentration and mitochondrial membrane potential, which in turn reduces oxidative stress and apoptosis.[50,51] In db/db diabetic mice, overexpression of mitochondrial calcium uptake 1 (MICU1), the MCU subunit, improves cardiac function, reduces myocardial fibrosis and cardiac hypertrophy.[52]

Recent studies have revealed that disturbed mitochondrial calcium homeostasis results from reticulum–mitochondrial Ca^{2+} coupling dysregulation via the mitochondria-associated membrane (MAM). The most important tethering complex is the inositol 1,4,5-triphosphate receptor (IP3R)/voltage-dependent anion channel (VDAC), which mediates the transfer of Ca^{2+} in MAMs.[53] Furthermore, high-fat and high-sucrose diet-induced diabetic mice exhibited decreased IP3R–VDAC interaction.[54] In diabetic hearts, MAM and MFN2 expressions are downregulated and have been proposed as potential therapeutic targets for diabetic cardiomyopathy.[55] However, contradictory results suggest that enhanced MAM levels are detrimental to mitochondrial dysfunction. Recently, an outer mitochondrial membrane protein, FUN14 domain containing 1 (FUNDC1), was reported to be involved in the pathogenesis of diabetic cardiomyopathy. It was shown that high glucose levels induced the formation of MAMs via the Fundc1 pathway, resulting in mitochondrial fragmentation and apoptosis.[56] Furthermore, Ca^{2+}/calmodulin kinase II (CaMKII), the key mediator of Ca^{2+} homeostasis, is involved in diabetic-impaired Ca^{2+} handling and cardiac muscle contraction, which mediates Ca^{2+} release from the sarcoplasmic reticulum into the cytoplasm.[57]

Altered Fuel Preference and Cardiac Energetics in Diabetic Cardiomyopathy

In diabetic hearts, ATP production fails to meet myocardial demands because of altered mitochondria and substrate utilization. During the early stages of diabetes, metabolic abnormalities are initiated in the myocardium, including impaired insulin signaling, reduced glucose utilization, and enhanced myocardial FA oxidation. Moreover, the utilization of lactate, ketone bodies, and BCAAs are altered and play regulatory roles in metabolic flexibility. These altered metabolites with damaged mitochondria promote myocardial injury and contribute to cardiac dysfunction [Figure 2].[58,59]

Impaired myocardial insulin signaling

Impaired insulin signaling, a complex network covering multiple interactions, is a key pathophysiological abnormality in diabetic cardiomyopathy.[60] Under physiological conditions, insulin stimulates glucose uptake in the heart to maintain glucose homeostasis via the insulin receptor substrate 1 (IRS1)/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway. Activation of the PI3K/AKT pathway increases myocardial substrate flexibility and energy homeostasis. In cases of insulin resistance and DM, cluster of differentiation 36 (CD36), the protein involved in FA uptake, is preferentially localized to the cell membrane, whereas the glucose transporter 4 (GLUT4) is primarily located in the cytoplasm, resulting in enhanced dependency on FA utilization.[61] Another pathway implicated in cardiac hypertrophy and associated with impaired IRS1 signaling is the mammalian target of rapamycin (mTOR)/S6 kinase 1 (S6K1) pathway. S6K1 pathway activation can improve cardiac performance by enhancing myocardial glucose utilization and diastolic function recovery.[62] Furthermore, impaired insulin signaling has a significant effect on mitochondrial biogenesis and function. Insulin deficiency decreases the synthesis of mitochondrial proteins, decreasing ATP production via the mTOR/PPARγ coactivator 1α (PGC1α).[63] Moreover, in an HFD model, cardiac contractile function can be reversed by inhibiting the insulin/G protein-coupled receptor kinase (GRK2) pathway.[64]

Multiple fates of glucose in diabetic cardiomyopathy

Impaired glucose utilization in diabetic cardiomyocytes is mediated by reduced glucose uptake, glycolytic activity, and pyruvate oxidation; however, intracellular glucose remains at a high concentration.[65] Diabetes is characterized by reduced insulin receptor expression and a decrease in GLUTs, primarily GLUT4.[66] In HFD/STZ-induced rats, it was recently reported that the duodenal jejunal bypass surgery mitigates diabetic cardiomyopathy via enhancing GLUT 4-mediated glucose uptake.[67]

Following transport into cardiomyocytes, glucose is broken down through glycolysis to yield pyruvate. Phosphofructokinase (PFK) is one of the most important rate-limiting enzymes of glycolysis, which catalyzes the conversion of fructose-6-phosphate to fructose 1,6-bisphosphate. The reduced PFK activity and the increase in the levels of glucose-6-phosphate and fructose-6-phosphate in the myocardium have pathological consequences because they serve as pathological pathway substrates involved in the development of diabetic cardiomyopathy.[68] In DM animal models, the activity of PDH, which is another rate-limiting enzyme involved in myocardial glucose metabolism, is reduced.[69] In the HFD/STZ-induced diabetes rat model, a dose-dependent relationship was observed between cardiac PDH activity and STZ concentration, suggesting that PDH is associated with diabetic myocardium damage. Interestingly, in diabetes,

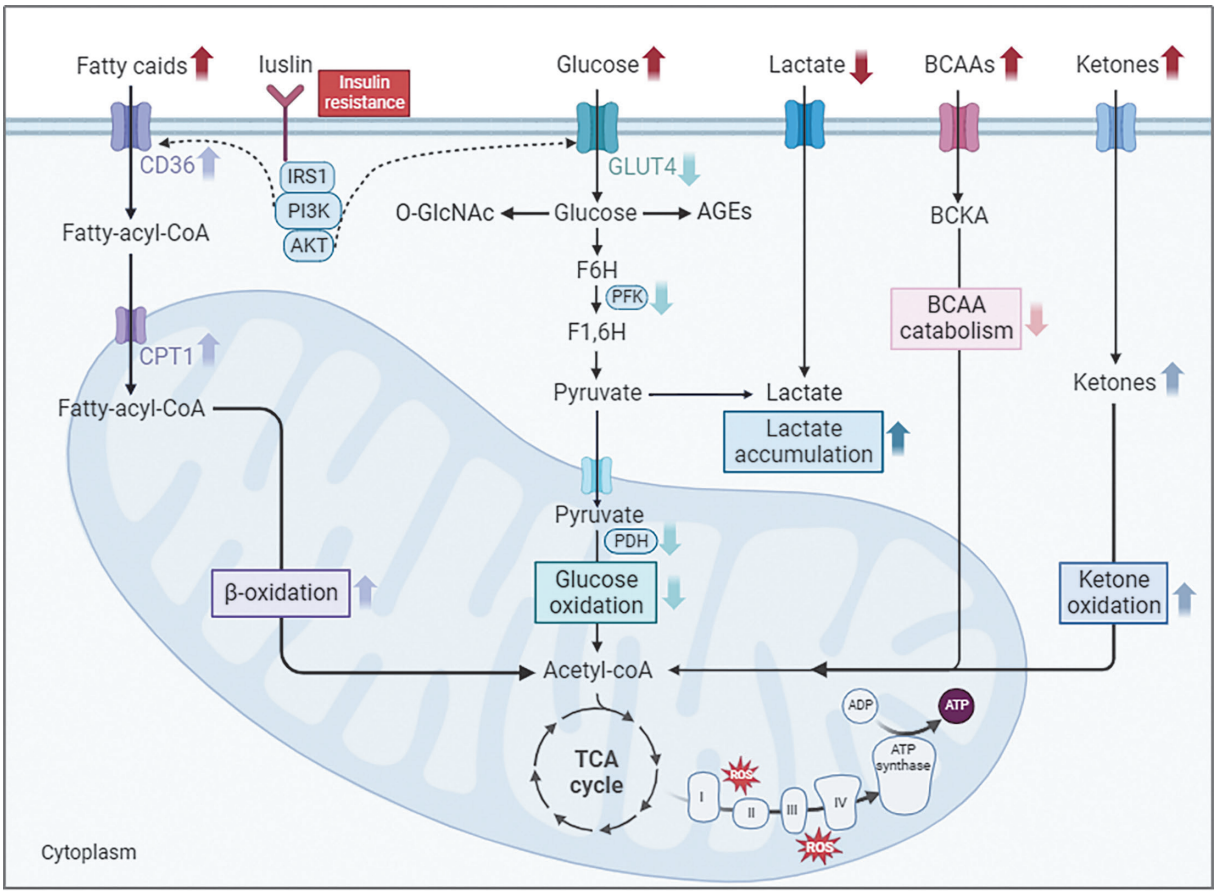

Figure 2: Overview of altered fuel preference and cardiac energetics in diabetic cardiomyopathy. At the top of the picture are the changes in each substrate in the blood. After entering the cardiomyocyte, substrates continue to the aerobic oxidation pathway or other metabolic pathways. An arrow facing up indicates an increase, and an arrow facing down indicates a decrease. The direction of the black arrow represents the process of metabolism, while the dotted arrow represents the regulatory effect. AGEs: Advanced glycation end-products; AKT: Protein kinase B; BCKA: α-Keto acid; CD36: Cluster of differentiation 36; CPT-1: Carnitine palmitoyl transferase 1; GLUT4: Glucose transporter 4; IRS1: Insulin receptor substrate 1; PDH: Pyruvate dehydrogenase; PFK: Phosphofructokinase; PI3K: Phosphoinositide 3-kinase; ROS: Reactive oxygen species.

FA and glucose metabolism interact, wherein increased cardiac FA oxidation inhibits PDH activity by phosphorylating the PDH complex via pyruvate dehydrogenase kinase (PDK). Recently, in a T2DM rat model, it was reported that administration of a PDK inhibitor restored myocardial PDH activity and improved cardiac diastolic function.[70]

The relationship between altered glucose utilization and diabetic cardiomyopathy is complicated. The formation of advanced glycation end-products (AGEs) contributes to glucotoxicity.[9] When there is excessive glucose that cannot be utilized, AGEs are formed via spontaneous reactions with excessive glucose in the absence of enzymes. Glycosylation of macromolecules, such as proteins, lipids, or nucleic acids, induces an irreversible form of posttranslational modification and functional properties. In a high glucose-induced diabetic cardiomyopathy model, AGE products were reported to directly bind to myeloid differentiation 2, a coreceptor of toll-like receptor 4, leading to an inflammatory response.[71] In a diabetic cardiomyopathy study, LCZ696, a new angiotensin receptor-neprilysin inhibitor was recommended for the treatment of symptomatic chronic heart failure as well as effectively protected against inflammation and apoptosis via the AGEs/NF-κB pathway.[72]

Under normal physiological conditions, a relatively minor amount of glucose is metabolized by the hexosamine biosynthesis pathway (HBP), resulting in the production of uridine 5′-diphospho-N-acetylglucosamine (UDP-GlcNAc). UDP-GlcNAc then provides O-linked β-N-acetylglucosamine (O-GlcNAc) for posttranslational modification, playing an important role in physiology and pathology.[73,74] Increasing evidence suggests that abnormal cardiac O-GlcNAc signaling mediates the adverse effects of diabetes on the heart.[75] PI3K and AKT are modified by O-GlcNAc, impairing the structural and functional characteristics of the diabetic heart.[76,77] Moreover, animal studies have revealed that the O-GlcNAcylation of numerous proteins, including DRP1, OPA1, and MFN2, is involved in mitochondrial dynamic alteration.[78] Furthermore, under hyperglycemic conditions, O-GlcNAc affects CaMKII activity and is linked to cardiac Ca^{2+} homeostasis.[79,80]

Increased FA dependency in diabetic cardiomyopathy

Disturbances in lipid metabolism are detected during the early stages of diabetes and cardiac diseases.[81,82] Circulating levels of FAs increase in both T1DM and T2DM[83,84] because of impaired insulin action in the lipolysis of adipose tissues and the liver.[85,86] In addition,

the increase in circulating FAs suppresses glucose uptake and oxidation. In diabetes, FAs enter cardiomyocytes via increased levels of sarcolemmal transport protein, CD36, which is responsible for lipotoxicity.[87] However, it is unclear whether CD36 is an effective therapeutic target. In the hearts of STZ-induced diabetic mice, CD36 knockdown resulted in reduced FA oxidation and an energetic compromise, suggesting that suppression of FA utilization is not beneficial but detrimental to cardiac energetics in diabetic cardiomyopathy.[88]

Increased myocardial lipid content has been observed in both patients and animal models of DM.[89,90] It is generally accepted that lipid levels predict LV remodeling and contractile dysfunction. Generally, FAs undergo esterification to form fatty acyl-CoA. Acetyl-CoA, which is produced via β-oxidation, enters the tricarboxylic acid (TCA) cycle to produce ATP. Preclinical studies have shown that insulin-resistant diabetic hearts consume more oxygen to meet the increased energy demand.[91] However, the increased dependence on cardiac FA oxidation negatively impacts cardiac efficiency because when compared to glucose, FA is a less efficient substrate.[92] Furthermore, increased β-oxidation inhibits cardiac glucose oxidation via the Randle cycle phenomenon, which further compromises cardiac efficiency. High FA oxidation rates can increase ROS production and exacerbate mitochondrial membrane uncoupling, resulting in damage to the mitochondrial structure and function.[93]

Changes in FA oxidation are associated with various transcription factors. Increased FA levels excessively activate PPARs, which play a significant role in regulating metabolism and act as potential therapeutic targets for diabetic cardiomyopathy.[94] PPARα mediates the induction of protein-encoding genes involved in FA uptake and β-oxidation, thereby promoting excessive ROS production, mitochondrial uncoupling, and mitochondrial fission dyshomeostasis. In db/db mice, microRNA-30c was reported to protect against diabetes by reducing excessive ROS production and myocardial lipid accumulation, and subsequently attenuating cardiac dysfunction via PPARα.[95] Echinacoside, a natural compound used to treat diabetic cardiomyopathy, was reported to show protective effects via the PPARα/carnitine palmitoyl transferase 1 (CPT-1) signaling axis.[96] Meanwhile, AMP-activated protein kinase (AMPK)/PPARα/PGC-1α mediates a protective effect against cardiac hypertrophy and dysfunction.[97] Several studies have suggested that PPARγ modulates cardiac energy metabolism through its effects on extracardiac tissues, such as adipose tissues. PPARγ activation promotes glucose uptake and triglyceride synthesis in adipose tissues, resulting in reduced circulating glucose and FA levels that directly affect cardiac PPARα activities.[98]

Lactate in diabetic cardiomyopathy

Lactate is produced during glycolysis and is a potential substrate for ATP production in cardiomyocytes.[99] The decreased uptake of lactate and impaired pyruvate oxidation was observed in patients with diabetes and diabetic animal models, resulting in reduced lactate metabolism. Metabolomics and hyperpolarized [1-^{13}C]pyruvate magnetic resonance spectroscopy were performed in hyperglycemic mouse hearts, and lactate accumulation was observed.[100] In addition, it was demonstrated that the cardioprotective effects of sodium-glucose transporter 2 (SGLT2) inhibitors are accompanied by a decrease in cardiac lactate production.[101] These studies suggest that lactate accumulation, with decreased lactate utilization, correlates with myocardial damage. Importantly, a recent study on non-diabetic ventricular myocardium showed that chronic lactate exposure leads to decreased FA transport and increased ROS production.[102] It has been suggested that lactate is not only an energetic substrate but also a valuable signaling molecule. Lactylation, a novel type of posttranslational modification mediated by lactate, has gradually become the focus of metabolic disorders.[103] However, comprehensive studies on lactate metabolism in diabetic cardiomyopathy have not been conducted.

Ketone bodies as an alternative energy in diabetic cardiomyopathy

Although ketone bodies contribute only to a modest percentage of cardiac energy metabolism, compared to FAs, they are more efficient substrates and are considered excellent metabolic fuels.[104] Ketones, such as β-hydroxybutyrate (β-OHB), play important roles in maintaining bioenergetic homeostasis in diabetic cardiomyopathy.[105] It is generally accepted that plasma and cardiac ketone bodies are increased in patients with diabetes and diabetic animal models.[106] Studies have revealed that increased ketone body oxidation is beneficial in heart failure, it reduces inflammation and maintains energy homeostasis.[107] However, ketone body metabolism in diabetic hearts remains controversial. Most studies have reported an increase in ketone utilization.[108] Generally, an increase in ketone body oxidation provides fuel for aerobic oxidative metabolism. In addition, increased β-OHB oxidation decreases histone deacetylase activity and hypertrophic signaling. Recently, in STZ-induced diabetic rats, a ketogenic diet (KD) was shown to improve cardiac function by increasing ketone utilization, suppressing FA metabolism, and decreasing inflammation.[109] Ketone bodies may play a regulatory role in other energy substrates. A study by our laboratory revealed that an increase in ketone body availability rescued mitochondrial dysfunction and fibrosis and inhibited FA uptake in insulin-resistant hearts.[110]

In contrast, some studies have reported that increased ketone body oxidation may have detrimental effects on mitochondrial protein acetylation, impairing cardiac energetics and decreasing mitochondrial oxidative phosphorylation.[111] In lean diabetic GotoKakizaki rats, a long-term low-carbohydrate low-protein KD appeared to exacerbate diabetic cardiomyopathy associated with maladaptive cardiac metabolic modulation and lipotoxicity. Furthermore, diabetic animals that were fed a KD not only showed lower blood glucose and insulin levels but also showed reduced myocardial oxidation of ketone bodies and glucose compared to that observed in chow-fed diabetic rats with cardiac hypertrophy.[112] In a

recent study, in an STZ- and HFD-induced model, β-OHB dehydrogenase (BDH1) and succinyl-CoA:3-oxoacid CoA transferase (SCOT) expressions were reduced, suggesting a discrepancy between ketone body availability and utilization.[113] Interestingly, this research also revealed potential crosstalk between glucose and ketone body utilization. The researchers developed four diabetic animal models and showed increased glucose availability improves ketone body utilization.

Furthermore, it is remarkable that the rate-limiting ketogenic enzyme 3-hydroxy-3-methylglutaryl CoA synthase 2 (HMGCS2) plays a role in diabetic hearts because it is primarily expressed in the liver. RNA sequencing results from both patients with diabetes and diabetic animals have suggested elevated HMGCS2 levels in myocardial tissue.[114,115] Interestingly, in an *in vitro* model, HMGCS2 silencing attenuated diabetic cardiomyopathy by increasing cell viability, inhibiting apoptosis, and inhibiting oxidative stress.[116] These findings suggest that ketone body utilization and ketogenesis play important roles in the pathogenesis of diabetic cardiomyopathy, however, further studies are required to identify their underlying mechanisms.

BCAAs play a diverse role in diabetic cardiomyopathy

Recently, BCAA metabolism has been considered to have an emerging role in the pathogenesis of diabetes, and many studies suggest that BCAAs and BCAA intermediates are biomarkers of insulin resistance and T2DM.[117] Several studies have reported that circulating BCAA levels, including those of leucine, isoleucine, and valine, are elevated in diabetes.[118,119] In diabetes, BCAA oxidation is reduced with decreased BCAA metabolic enzyme expression and contributes to a small proportion of ATP production in the heart.[120] Data from our laboratory indicated that the chronic accumulation of BCAAs, resulting from defective BCAA catabolism, reduced glucose metabolism by inactivating PDH, which rendered the heart vulnerable to ischemic injury.[121] An increasing number of studies have consistently revealed novel mechanisms underlying BCAA catabolism in the regulation of energy metabolism. Accumulated BCAAs may play regulatory roles in the modulation of glucose and FA metabolism in the heart.[122] Moreover, BCAA intermediates, such as branched-chain α-keto acid (BCKA), were recently proposed to contribute to insulin resistance development.[123] The specific effect of BCKA on myocardial injury may be due to decreased cell survival and increased apoptosis via mTOR–Akt pathway inactivation.[124]

BCAA supplementation is often beneficial in energy expenditure. However, the effects of BCAA treatment on diabetes may depend on the components and dose. BCAA intake offers potential metabolic profile benefits, and a high BCAA intake may be associated with a decreased risk of diabetes.[125] A previous study suggested that supplementation with specific amino acids rescues insulin resistance in the heart via the mTOR pathway.[126] However, several studies have also revealed that elevated BCAA levels may be a risk factor for diabetic heart disease.[127–129] In a prospective cohort study, the association between BCAA consumption and the risk of T2DM was investigated and the authors reported that higher dietary intake of BCAAs is associated with an increased risk of T2DM.[130] It is suggested that increased BCAA levels activate the mTOR/p70S6K pathway and promote IRS-1 phosphorylation at multiple serine sites.[131] These observations strongly suggest that deficient BCAA catabolism in diabetic cardiomyopathy plays an important role and remains to be experimentally confirmed.

Emerging Mitochondrial Energy Metabolism Targeted Interventions in Diabetic Cardiomyopathy

Current diabetic cardiomyopathy treatment strategies are primarily aimed at controlling blood glucose levels, preventing risk factors associated with the progression of cardiovascular diseases, such as obesity and hypertension, and treating heart failure once it is diagnosed. Therefore, although diabetes is an independent predictor of heart failure, there is no specific clinical treatment designed to treat diabetes-induced heart failure. Several pharmacological agents currently demonstrate direct cardiovascular effects. The beneficial effects of anti-hyperglycemic agents such as glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) have been shown to have direct cardioprotective effects against diabetic cardiomyopathy. Experimental studies on the mechanisms underlying mitochondrial energy metabolism, such as lipid metabolism, KD, and ROS generation, reveal potential therapeutic targets [Table 1].

Glucose-lowering therapies

Hormones are used as glucose-lowering agents in diabetic patients because of their pleiotropic effects, including increased insulin secretion, suppression of glucagon secretion, and decreased appetite. GLP-1, a commonly used hormone, is an incretin hormone derived from L-cells of the distal ileum and colon in response to food intake. GLP-1 RAs have displayed beneficial cardiac effects in patients with diabetes improving the structural and functional disorders of the heart.[132,133] Studies that specifically investigated the effects of GLP-1 RAs on the diabetic myocardium are limited. Recently, studies have demonstrated that GLP-1 RA has a direct effect on cardiac ventricular excitability.[134] In STZ-induced diabetic mice, GLP-1 RA reduced ROS production and oxidative stress.[135] Moreover, in an HFD/STZ-induced diabetes model, GLP-1 RA was reported to protect cardiac function by ameliorating lipotoxicity in diabetic cardiomyopathy via the PPARα pathway.[136] Therefore, GLP-1 RA, which has been safely used in clinical treatment, has the potential to be used as a specific treatment for diabetic cardiomyopathy.

Clinically, SGLT2is have been widely used as glucose-lowering agents to improve hyperglycemia in T2DM patients by primarily increasing urinary glucose excretion. In the patients with diabetes, empagliflozin was shown to improve clinical outcomes and reduce cardiovascular disease-related mortality.[137,138] Similarly, canagliflozin and dapagliflozin have shown cardioprotective effects

Table 1: Summary of emerging mitochondrial energy metabolism targeted interventions in diabetic cardiomyopathy.

Studies	Agents	Object	Target	Mechanism	Potential effects on diabetic heart
Lambadiari *et al*[132]	Liraglutide	Human	GLP-1 RAs	–	Improved LV myocardial strain, LV twisting and untwisting
Bizino *et al*[133]	Liraglutide	Human	GLP-1 RAs	–	Educed early LV diastolic filling and LV filling pressure
Ang *et al*[134]	Exendin-4	Rats	GLP-1 RAs	Acetylcholine	Reduced ventricular arrhythmic potential
Wang *et al*[135]	AP5	Mice	GLP-1 RAs	AMPK/PI3K/Akt	Improved the survival rate of primary cardiomyocytes
Wu *et al*[136]	Exendin-4 and saxagliptin	Mice	GLP-1 RAs	ROCK/PPARα	Reversed cardiac remodeling and dysfunction
Wanner *et al*[137]	Empagliflozin	Human	SGLT2is	–	Reduced mortality in established cardiovascular disease
Oka *et al*[138]	Empagliflozin	Human	SGLT2is	–	Improved LV global longitudinal strain
Matsutani *et al*[139]	Canagliflozin	Human	SGLT2is	–	Improved LV diastolic function
Brown *et al*[140]	Dapagliflozin	Human	SGLT2is	–	Reduced LV mass and LV hypertrophy
Wang *et al*[141]	Empagliflozin	Mice	SGLT2is	Improved mitochondrial function	Prevented cardiac dysfunction, inhibited cardiac hypertrophy and fibrosis
Arow *et al*[142]	Dapagliflozin	Mice	SGLT2is	Calcium transport	Improved systolic function
Khalaf *et al*[143]	Dapagliflozin	Rats	SGLT2is	PPARγ	Reduced fibrosis
Kearney *et al*[144]	Cholesterol-lowering therapy	Human	Lipid-lowering therapies	–	Reduced myocardial infarction or coronary death, coronary revascularization, and stroke
Abdel-Hamid *et al*[146]	Atorvastatin	Rats	Lipid-lowering therapies	Apoptosis	Decreased LV wall thickness and heart weight
Yang *et al*[147]	Fibroblast growth factor-21	Mice	Lipid-lowering therapies	AMPK/AKT2/NRF and AMPK/ACC/CPT-1	Prevented cardiac dysfunction, hypertrophy, morphological abnormalities, and fibrosis
Cao *et al*[148]	CMHX008	Mice	Lipid-lowering therapies	PPARγ	Improved ejection fraction and cardiac hypertrophy
Trang *et al*[109]	KD	Rats	KD	PERK/p-eIF2α and Bax/Bcl-2	Reduced myocardial fibrosis
Guo *et al*[149]	KD	Mice	KD	PI3K/Akt	Ameliorated cardiac dysfunction
Zhou *et al*[150]	Melatonin	Mice	Mitochondrial-targeted	Syk/COX-1/SERCA	Improved diabetic myocardial function, reduced cardiac fibrosis, and preserved cardiomyocyte viability
Ni *et al*[37]	Mito-TEMPO	Mice	Mitochondrial-targeted	ERK1/2	Reduced adverse cardiac changes and mitigated myocardial dysfunction

ACC: Acetyl-CoA carboxylases; AKT: Protein kinase B; AMPK: Adenosine 5′-monophosphate-activated protein kinase; Bax: BCL-2 associated X protein; Bcl-2: Pro-survival B cell lymphoma 2; COX-1: Mitochondrial complex I; CPT-1: Carnitine palmitoyl transferase 1; eIF2α: Eukaryotic initiation factor-2α; ERK: Extracellular signal-regulated kinase; GLP-1 RAs: Glucagon-like peptide 1 receptor agonists; HMG CoA reductase: 3-Hydroxy-3-methyl glutaryl coenzyme A reductase; KD: Ketogenic diet; LV: Left ventricular; NRF: Nuclear factor erythroid-derived 2-like 2; PERK: Pancreatic endoplasmic reticulum kinase; PI3K: Phosphoinositide 3-kinase; PPAR: Peroxisome proliferator-activated receptors; ROCK: Rho-associated kinases; SERCA: Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; SGLT2is: Sodium-glucose cotransporter-2 inhibitors; Syk: Spleen tyrosine kinase.

in patients with diabetes.[139,140] Increased attention has been given to the mechanism of cardioprotective effects of SGLT2is in diabetes. In animal studies, empagliflozin treatment has been shown to attenuate myocardial oxidative stress and improve mitochondrial function.[141] In diabetic mice, SGLT2i modulated FA and glucose metabolism and reduced inflammation, resulting in the alleviation of fibrosis and cardiac dysfunction.[142]

Moreover, therapy with dapagliflozin attenuates oxidative, inflammatory, and apoptotic activities by activating PPARγ in STZ-induced diabetic cardiomyopathy, confirming the direct protective effects of SGLT2is against diabetic cardiomyopathy.[143]

Lipid-modulating therapies

Statins are commonly used to manage cardiovascular complications in diabetes because of their low-density lipoprotein (LDL)-cholesterol-lowering effects. Comprehensive and consistent data have demonstrated the benefits of statin therapy to prevent adverse cardiovascular outcomes and reduce all-cause mortality.[144] Preclinical studies have shown that atorvastatin and fluvastatin exert beneficial effects on LV function and myocardial fibrosis by alleviating apoptosis and oxidative stress.[145,146] Experimental data also suggest that treating underlying myocardial lipotoxicity may also be a target to improve the outcomes of diabetic cardiomyopathy patients. In HFD/STZ-induced diabetic animals, statins were reported to have protective effects on the heart by suppressing FA β-oxidation via the CPT-1 pathway.[147] Moreover, a new PPARγ partial agonist, CMHX008, improved the ejection fraction of the heart in HFD-induced mice.[148]

Ketogenic therapies

KD is a low-glucose, HFD, which is beneficial to blood glucose control and reduces the burden of islet cells for diabetes. In recent years, studies of KD have shown a double-edged sword effect on cardiovascular disease, which may increase the risk of lipid metabolism disorder and ketoacidosis in patients with diabetes. Therefore, it is important to understand the specific mechanism of KD in diabetic heart. In animal experiments, the treatment of KD on STZ-induced diabetic rat showed a reduced myocardial fibrosis effect and it is probably through PERK and Bax/Bcl-2 pathway.[109] Moreover, KD treatment ameliorated cardiac dysfunction in db/db mice via PI3K–Akt pathway.[149] As KD is an exogenous supplement that stimulates the body to produce ketone bodies, other forms of ketone body therapy such as ketone esters are worth investigating to reduce the side effects of KD such as hyperlipidemia.

Mitochondrial-targeted therapies

The mitochondrial electron transport chain is a potential therapeutic target. A study on STZ-induced diabetic mice demonstrated melanin may exhibit the protective effects on the diabetic myocardium via a mitochondrial complex I-mediated pathway.[150] In addition, increasing evidence suggests that mitochondrial oxidative stress is a key contributor to the development of diabetic cardiomyopathy. However, the results of these studies have not been translated into clinical uses. Mito-TEMPO, a mitochondria-targeted antioxidant ROS scavenger, has been investigated as a potential treatment for diabetic cardiomyopathy in animals. In diabetic mice, the injection of mito-TEMPO reduced the elevation of H_2O_2 and protected against hyperglycemia-induced cardiomyocyte death via the downregulation of extracellular signal-related kinase phosphorylation.[37]

Conclusions and Perspectives

Mitochondrial energy metabolism plays a central role in the onset and development of diabetic cardiomyopathy. Energy substrate reprogramming in diabetes manifests as impaired glucose utilization and abnormal FA oxidation, accompanied by mitochondrial dysfunction and insufficient ATP production. Besides, emerging evidence shows that lactate, ketone bodies, and BCAAs are also actively involved in the pathogenesis of diabetic cardiomyopathy which not only serve as energy substrates but also play a role in molecular regulation. As ketogenic therapies showed the beneficial effects on the heart, these "minor" energetic substrates may serve as potential therapeutic targets for the treatment of diabetic cardiomyopathy. Furthermore, recent advances in technology, such as isotopic labeling and metabolic flux analysis, enable us to quantitatively determine changes in metabolic pathway fluxes and depict metabolic profile in ultra-high resolution, but not just the abundance of each metabolite, which may facilitate the reveal of more new specific targets. Still, many challenges are expected on the journey of translation, such as how to target a particular pathway without affecting the others and how to evaluate the efficacy of a potential candidate. Thus, the ultimate success in fighting diabetic cardiomyopathy is dependent on a thorough understanding of mitochondrial metabolism in the diabetic heart. Further efforts are encouraged and merited in this long expedition.

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Conflicts of interest

None.

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