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Mitochondrial Dysfunction and its Impact on Diabetic Heart

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Abstract

Mitochondrial dysfunction and associated oxidative stress is strongly linked to cardiovascular, neurodegenerative, and age associated disorders. More specifically cardiovascular diseases are common in patients with diabetes and significant contributor to the high mortality rates associated with diabetes. Studies have shown that the heart failure risk is increased in diabetic patients even after adjusting for coronary artery disease and hypertension. Although the actual basis of the increased heart failure risk is multifactorial, increasing evidences suggest that imbalances in mitochondrial function and associated oxidative stress play an important role in this process. This review summarizes these abnormalities in mitochondrial function and discusses potential underlying mechanisms.

1. Introduction

Over the last 20 years, our understanding of the pathophysiology of chronic heart failure has advanced substantially. However, heart disease still remains the number one cause of morbidity and mortality in the industrialized world, affecting over 27 million people in the United States alone [1]. Furthermore, the prevalence of Type 2 diabetes is reaching pandemic proportions, with estimates that by the year 2025 nearly 300 million adults will be affected by diabetes mellitus [2, 3]. Patients with diabetes are at increased risk of cardiovascular diseases associated mortality [4, 5]. Previously, it has been shown that patients with chronic heart failure and type 2 diabetes have almost two times higher risk of all cause of mortality that of similar patients without diabetes. To put this in context, if a patient with chronic heart failure (CHF) suffers from type 2 diabetes, their risk of cardiovascular-associated death is over two times higher [4, 6]. Interestingly, in many cases diabetic patients also develop heart failure even in the absence of cardiovascular risk factors such as hypertension and coronary artery disease [7, 8]. Recently the term “diabetic cardiomyopathy” is used to refer the

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cardiovascular dysfunction in diabetic patients that is out of proportion to their underlying vascular disease [9]. Mitochondria serve as the power houses of a cell and recent reports implicate mitochondrial injury to be a major player in the pathophysiology of diabetic heart disease [10, 11]. Therefore strategies to attenuate mitochondrial injury might be a potential therapeutic target for diabetic heart disease.

2. Mitochondrial dysfunction in diabetic heart

The mitochondrion serves a critical role as a platform for energy transduction, signaling, and cell death pathways related to common cardiovascular diseases such as heart failure [12]. Cardiac dysfunction in diabetic patients is caused by multiple pathologic mechanisms. Interestingly, all these mechanisms are associated with mitochondrial injury, which has been proposed to be an underlying cause, in the pathophysiology of diabetic heart disease [10, 11]. Indeed, numerous animal and human studies demonstrated the frequent appearance of damaged mitochondria in the diabetic hearts [13–15]. Dysfunctional mitochondria can cause more ROS production and release pro-death factors such as cytochrome C, apoptosis inducing factor, and Smac/DIABLO [15, 16]. Various ROS scavengers or antioxidants are able to reduce cardiomyocyte death and attenuate diabetic cardiac injury in experimental animal models [16, 17]. However, the antioxidant-based therapies have generally not been successful in diabetic patients [18, 19], suggesting that simply antagonizing existing ROS by antioxidants is not sufficient to abrogate diabetic cardiac injury. A potentially more effective treatment strategy may be to enhance the overall capacity of mitochondrial quality control to maintain a pool of healthy mitochondria that are needed for supporting cardiac contractile function in diabetic patients.

Recent evidences suggest that cardiac dysfunction in diabetic patients is linked to metabolic abnormalities and more often associated with mitochondrial dysfunction [20]. Diabetes and obesity, the major metabolic disorders, are characterized by high levels of circulating free fatty acids, which results in increased cardiac fatty acid uptake, storage and metabolism [21–23]. In heart, free fatty acids have taken up by cardiac cells such as cardiomyocytes, which are normally catabolized in mitochondrial and in some circumstances, peroxisomal fatty acid β -oxidation (FAO) pathways. Fatty acids are also incorporated into triglycerides (TAG) pools and are ultimately oxidized through β -oxidation flux [24, 25]. Peroxisome proliferator-activated receptor alpha (PPAR α), which is upregulated in diabetic hearts, plays significant role in modulating TAG flux [21, 24, 25]. In general, heart does not store significant amounts of lipid, however, it can accumulate triglycerides when fatty acid supply is high. Both in diabetic patients and animal models, the myocardial triglyceride content is notably increased compared to healthy controls [26–28].

Myocardial energy substrate preference (glucose versus fatty acid) normally varies in a dynamic manner to meet the tremendous energy needs of the mammalian heart. In healthy heart vast majority of ATP is generated by oxidation of fatty acids (FAs) and glucose in mitochondria [29] [30–32]. During normal circumstances, nonesterified or free fatty acids (FAs) are the preferred substrate in the adult myocardium, supplying 60–90% of total ATP [29, 33–36]. FAs derived from circulating triglyceride-rich lipoproteins and albumin bound nonesterified FAs are oxidized in the mitochondrial matrix by FA β -oxidation (FAO)

process, while pyruvate derived from glucose and lactate is oxidized by the pyruvate-dehydrogenase (PDH) complex, present within the inner mitochondrial membrane. The final product, acetyl-CoA, derived from both pathways, ultimately enters the tricarboxylic acid (TCA) cycle to generate ATP [12, 37]. In heart failure with reduced ejection fraction, both animal models and human studies demonstrate alterations in the otherwise versatile capacity of the myocardium to use alternative substrates. Emerging data demonstrated a reduced cardiac fatty acid use during heart failure. Previous studies in different heart failure models showed a reduced mRNA and protein expression of FA transporters [38–41]. FA uptake has been reported to reduce both in high-salt-diet-induced heart failure and by rapid pacing [39, 42]. Finally both in animal models and human subjects strongly advocate that FA oxidation is significantly reduced during cardiovascular abnormalities [38–41]. In contrast, the data on cardiac glucose use are less consistent [43–45]. In the presence of systolic dysfunction, cardiac glucose uptake was decreased in mice after aortic constriction [43], while unchanged in rats with myocardial infarction [46], and increased in Dahl salt-sensitive rats [39]. The impaired glucose oxidation that parallels systolic dysfunction might be attributable in part to mitochondrial dysfunction, reduced expression of genes involved in glycolysis and glucose oxidation, or decreased abundance of the PDH complex [39, 47]. Osorio et al showed increased glucose oxidation rates in failing dog hearts induced by rapid pacing [46], and Dávila-Román et al demonstrated higher total rates of glucose use in patients with idiopathic dilated cardiomyopathy [48]. Thus the changes in glucose oxidation in cardiac myocytes may depend on both the stage and the pathogenesis of heart failure.

Interestingly, during uncontrolled diabetes, cardiac energy substrate preference becomes constrained because of the need for insulin for myocardial glucose uptake. Glucose utilization in the diabetic heart is diminished at least in part because of insulin resistance, impaired pyruvate dehydrogenase activity, and reduced glucose transporter (e.g. Glut4). Thus, the diabetic heart relies almost exclusively on mitochondrial FAO for ATP synthesis. This reliance on FAO has potentially detrimental consequences, which includes impaired mitochondrial respiratory function. Mitochondria are the center of both fatty acid and glucose metabolism and thus are likely to be impacted by impaired metabolism associated with diabetes. Previously studies have demonstrated the mitochondrial abnormalities in skeletal muscle of insulin resistant and diabetic humans. Furthermore, reduced expression of targets genes associated with mitochondrial oxidative phosphorylation (OXPHOS) [49–51] peroxisome-proliferator-activated receptor (PPAR) gamma, co-activator-1 α (PGC-1 α) was observed during heart failure in diabetes [52]. PGC-1 α is a master metabolic regulator that coordinates gene expression for pathways involved in mitochondrial biogenesis and respiratory function (Figure-1) [52]. Shulman and colleagues demonstrated a reduction in ATP synthesis and mitochondrial content in severely insulin-resistant offspring of Type 2 diabetes [53, 54]. Kelley et al., found impaired mitochondrial enzyme activities and reduced mitochondrial size and number in skeletal muscle from diabetic patients [55, 56]. In sum, these studies strongly implicate impaired mitochondrial function and biogenesis both in diabetic animals and human patients.

The mitochondrial function has been directly studied in multiple animal models of diabetes. In chronic Type 1 diabetes (OVE26 mice) mice model, it was demonstrated that mice had evidence of mitochondrial biogenesis that was coupled to a reduction in mitochondrial

function and mitochondrial ultrastructural defects [57]. Mitochondrial state III respiration is significantly reduced in type 2 diabetic animal models (db/db and ob/ob) [58–60]. Furthermore, there is evidence for increased cardiac mitochondrial biogenesis with ultrastructural defects in insulin resistance and diabetes animals [59, 61–64]. In summary, the animal model investigations provide precise and convincing evidence that mitochondrial function is impaired in the hearts of animals with insulin resistance and diabetes. In contrast, due to limited availability of human heart samples and multiple variant, cardiac mitochondrial function has been under studied in human subjects. Nonetheless, a number of studies provide indirect evidence for altered cardiac mitochondrial function in diabetic patients. Diamant et al. studied high-energy phosphate metabolism and cardiac function in asymptomatic well-controlled diabetic men and controls using MRI and ^{31}P nuclear magnetic resonance spectroscopy (NMRS). They demonstrated a reduction in multiple indexes of diastolic function by MRI in the diabetic patients; these functional changes were associated with a reduction in the cardiac phosphocreatine/ATP ratios [65]. A reduction in cardiac phosphocreatine/ATP ratios has also been demonstrated in hearts of diabetic patients with normal cardiac function by echocardiography [66, 67], suggesting that changes in mitochondrial function may precede the reduction in contractility. In another study, Anderson et al. demonstrated in the left atrial appendage tissue from Type 2 diabetic patients undergoing coronary bypass surgery that mitochondrial respiratory function was impaired and hydrogen peroxide emission was increased, suggesting an increase in oxidative stress [68, 69]. Together with human data demonstrating altered lipid metabolism, these studies strongly implicate mitochondrial dysfunction in the human diabetic heart. In following sections, the potential mechanisms that contribute to mitochondrial dysfunction and leading to cardiovascular abnormalities in diabetes will be discussed.

3. Mechanism of mitochondrial dysfunction in diabetic heart

3.1. Altered energy metabolism

Heart is maximum energy consuming organ of the body and thus a subtle energy deficits can rapidly induced contractile dysfunction. The uninterrupted ATP generation is dependent on the continuous supply of oxygen and fuel substrates and on the integrity of oxidative phosphorylation (OxPhos), which produces virtually all the hearts' ATP. [70–72] While the heart can switch its substrate [fatty acids (FAs), glucose, ketones, lactate, amino acids] preference depending on workload, oxygen supply and hormones, its main energetic substrate is FAs (60–70%) as discussed in preceding section. Due to high-energy demand, cardiomyocytes has a relatively higher number of mitochondria compared to other cells. Due to insulin resistance in type 2 diabetes, diabetic heart has increased rate of fatty acid oxidation. Previous studies have shown an increased expression of nuclear receptor transcription factor, PPAR α / δ / β . PPARs is an important transcriptional regulator of fatty acid uptake and oxidation. In fact PPAR α regulates most of the enzymes involved in fatty acid oxidation. PPAR α knock out mice showed reduced fatty acid oxidation rate. Interestingly, cardiac specific PPAR α overexpression significantly reduced enzymes involved in mitochondrial oxidative phosphorylation. Sack et al. [73] reported the down-regulation of genes required for myocardial FAs use in human hearts and rats with progressive heart failure. Davila-Roman et al. used in vivo imaging with positron emission

tomography (PET) to confirm reduced FAs oxidation with increased dependence on glucose metabolism in patients with compensated dilated cardiomyopathy [48]. As heart failure progresses, myocardial insulin resistance develops [74], further compromising the versatility of substrate use and increasing the metabolic stress on the heart. Importantly, chronic heart failure patients with decreased systemic insulin sensitivity have a worse prognosis [75]. Notably, increase in FAO may be detrimental, as it requires more oxygen and generate plenty of ROS (Figure 2). Intriguingly, diabetic animals showed reduced cardiac efficiency, with increased myocardial oxygen consumption (V_{O_2}) associated with increased FAO [59, 76–78]. The increased demand for oxidizing fatty acids and the reduction in cardiac efficiency may contribute to contractile dysfunction in the diabetic heart. Furthermore, the altered substrate flexibility and the change in oxygen consumption potentially may contribute to increased mortality following ischemic damage in diabetic patients.

Mitochondrial oxygen consumption is normally tightly coupled to ATP synthesis (via electron transport chain). The energy that is produced during electron transfer is used to create an electrochemical gradient by pumping protons from the mitochondrial matrix to the inter membrane space. These protons generally reenter the matrix via the ATP synthase/complex V (proton pump) and generate ATP from ADP (Figure 2). However, sometimes it is possible that protons bypass the ATPase system and reenter into matrix using uncoupling proteins (such as UCP-1, 2, 3, 4 and 5) [76]. This bypass system results in oxygen consumption that is not coupled to ATP production [79]. Recently, Boudina et al. demonstrated mitochondrial uncoupling in db/db mouse hearts [80]. This group has noted an increase in respiration in the setting of oligomycin, an inhibitor of the ATP synthase and an increase in proton leak from cardiac mitochondria isolated from db/db mice. Adding guanosine diphosphate (GDP), an inhibitor of UCPs, resulted in restoration of proton leak to wild-type levels, strongly suggesting that the increased uncoupling was mediated by UCPs. A second potential mediator of mitochondrial uncoupling is the adenine nucleotide translocator (ANT). Boudina et al. also found that atractyloside, an inhibitor of ANT-mediated uncoupling, altered proton leak in db/db mitochondria, suggesting that ANT may also contribute to uncoupling in diabetic hearts [80].

3.2. Oxidative stress and derangement of oxidative phosphorylation

Both preclinical and clinical studies suggest that ROS production is significantly enhanced in the failing myocardium [81, 82]. The majority of ROS in the heart appear to come from uncoupling of mitochondrial electron transport chain at the level of complexes I and III [81, 83, 84]. The activities of mitochondrial electron transport chain complexes are suppressed in HF, and disruption of mitochondrial bioenergetics function was found to increase ROS levels and oxidative DNA damage [85, 86], providing a possible pathophysiological link between mitochondrial dysfunction and ROS (Figure 2) [82, 87]. Thus, ROS generated by the mitochondria have the ability to modify multiple additional physiologic pathways. ROS can directly damage proteins by oxidation, or they can oxidize lipids to form lipid peroxidation products, which can induce protein or phospholipid damage. Therefore deficiencies in antioxidant system during diabetes may enhance the oxidative damage in cardiac cells. Previous studies have shown that mitochondrial ROS activates multiple pathways related to cellular damage in the setting of hyperglycemia [88–91]. An increase in 3-nitrotyrosine in

association with increased cell death has been noted in human myocardial samples [15, 92], as well as in a streptozotocin (STZ)-induced model of Type 1 diabetes [93]. Indeed, Cai et al. demonstrated a reduction in nitrosative damage with overexpression of metallothionein, an antioxidant protein, in STZ-treated mice [94]. Furthermore, Boudina et al. have reported an increase in mitochondrial H₂O₂ in db/db mice, in association with increased levels of MnSOD, suggesting that there is an increase in ROS production [80]. In addition, catalase overexpression protected cardiomyocyte contractility in the agouti model of type 2 diabetes. [95]. Taken together, studies discussed above suggest the potential role of oxidative stress in the myocardial dysfunction in diabetics.

3.3. MicroRNAs in regulation of mitochondrial dysfunction in diabetic heart

Recent studies have highlighted the therapeutic potential of microRNAs (miRNA) in diabetic cardiomyopathy [96], [97]. We and others have previously shown that microRNAs (miR) regulates multiple cellular processes such as proliferation, differentiation, cell metabolism, apoptosis and angiogenesis [98–104]. This review also summarizes the knowledge on the effects of miRNAs in diabetic cardiomyopathy.

miRNAs' biogenesis is characterized by a cleavage process catalyzed by Drosha, an RNase III, and its essential cofactor known as DGCR8 (DiGeorge syndrome critical region) [105–107]. After the cleavage process, an intermediate stem loop is released, known as the miRNA precursor or pre-miRNA. Pre miRNA hairpins are then recognized by Exportin-5 for nuclear export. At the cytoplasm, the pre-miRNA is cleaved by Dicer, an RNase III, into the mature form of 20–22 nucleotides [108]. This RNA is subsequently unwound by a helicase activity, binds to an Argonaute protein and gets incorporated as single-stranded RNA into the RNA-induced silencing complex (RISC) [108] which directs the miRNA to complementary sites within the 3' UTRs (untranslated region) of target mRNAs leading to translational repression or degradation of the target mRNA [102, 109]. Interestingly, miRNAs can act as translational activators as well [26]. Based on computational algorithms, around 60% of human transcripts contain potential miRNA-binding sites within their 3' UTRs. A "seed sequence" in the 5' end of the mature miRNA pairs to nucleotides 2 through 8 at the 3' UTR of target mRNAs [108]. However, miRNAs can interact with 5' UTRs, protein-coding sequences and introns. Furthermore, miRNAs can also localize to the nucleus, where they may regulate transcription/splicing of transcripts, or serve as signaling molecules between two cells through exosome transfer [110]. Although a single miRNA can target many genes, it is possible that multiple miRNAs can regulate a single gene. These studies suggest that miRNA transcription to maturation involves several coordinated steps and that deregulation in miRNA biogenesis and function might contribute to the development of cardiovascular diseases [111, 112].

Role of miRs in regulation of multiple cardiac remodeling genes has been well studied, however, a functional link between miRNA and diabetes-induced cardiac dysfunction is not well established. Recently altered miRs expression has been reported in isolated cardiac cells from diabetic rat heart [96]. Furthermore, antioxidant therapy (NAC treatment) significantly restored miRs (MiR-1, -133a, -133b, -499) expression and thus protects against diabetes-induced injury [96]. miRNA-141 plays important role by targeting inner

mitochondrial membrane phosphate transporter Slc25a3 (solute carrier family-25 member 3) gene, which provide inorganic phosphate to mitochondrial matrix and thus essential for mitochondrial ATP production. Further, Baseler et. al have demonstrated an elevated miR-141 levels in diabetic mouse heart [97]. Thus further concluded that, miRNA-141 can regulate Slc25a3 protein expression in diabetic heart and could be involved in the pathogenesis of diabetic cardiomyopathy [97]. Therefore inhibition of miR-141 could be a potential target to improve mitochondrial function in diabetic heart. A recent study has demonstrated an increased expression of miR-223 in left ventricular biopsies from diabetic patients. Further miR-223 directly targets Glut-4 mediated glucose metabolism in the heart [113]. Shan et al. (2010) demonstrated that the high glucose induced expression of miR-1 and miR-206 in cardiomyocytes. Further induction of the miR's resulted in increased cardiomyocyte cell death via directly targeting Hsp60 expression, contributing to hyperglycemia-induced cell death in cardiomyocytes [114]. Ingenuity miRNA pathway analysis in diabetic mice revealed that dysregulated miRNAs were implicated in myocardial signaling networks which can trigger apoptosis (miR-320b, miR-378, miR-34a), fibrosis (miR-125b, miR-150, miR-199a, miR-29b, miR30a), hypertrophic growth (miR-1, miR-150, miR-199a, miR-133a, miR-214, miR-29a, miR-125b, miR-221, miR-212), autophagy (miR-133a, miR-221, miR-212, miR30a), oxidative stress (miR-221, miR-146a, miR-34a, miR-210, miR-19b, miR-125b, miR27a, miR-155), and heart failure (miR-423, miR-499, miR-199a) [115]. These findings further signify the importance of miRNA in the diabetic heart disease.

4. Clinical relevance and future prospective

As unexplained cardiomyopathy is possibly driven by T2DM itself, good diabetic control seems naturally important for preventing dilated cardiomyopathy. However, only animal studies have shown that achieving early normal glucose levels reduces the progress of diabetes associated heart failure, and that certain diabetic drugs can have specific anti-cardiac remodeling effects.[116, 117]. For example, in ex vivo mice hearts, glucose–insulin infusions improved glucose oxidation and contractile efficiency, while incretin based therapies (Liraglutide and Exendin-4) reversed oxidative stress and SERCA down-regulation [118, 119]. Very limited data is available in humans, and some of them are not reproduced with animal's findings. In a retrospective analysis, metformin use was associated with reduced natriuretic peptide (NPs) levels and lower cardiovascular morbidity and mortality [120, 121] while glucose–insulin–potassium trials yielded inconsistent results. [122] In contrast, increased hospitalizations due to heart failure were documented with thiazolidinediones (e.g. rosiglitazone) and sulfonyureas (e.g. glicazide). [122, 123] Thus, glycemic control alone might not be sufficient for preventing or managing heart failure. Because systolic dysfunction develops as diastolic cardiomyopathy progresses, and can itself accelerate DiCM independently by inducing mitochondrial dysfunction and oxidative stress, the mandated use of HF specific therapies is critical. They not only disrupt the vicious cycle between systolic failure and diastolic cardiomyopathy but certain agents such as β -blockers directly suppress oxidative stress and FAs metabolism [124]. However, because these agents are not suggested in the majority of patients (as their LV ejection fractions are adequate), alternative strategies are needed.

As discussed above, due to disrupted metabolism, increased FAs utilization occurs during Type 2 diabetes. Therefore, in cardiac cells, FAs metabolism can be regulated by drugs, which alter plasma-free FAs levels (lipoprotein lipase inhibitors), mitochondrial FAs uptake (CPT1 inhibitors) or FAs oxidation (β -oxidation inhibitors). In rats with Type 2 diabetes, acipimox and etomoxir reduced serum lipid levels and improved SERCA expression [125]. In diabetic heart failure patients, trimetazidine reduced natriuretic peptides and improved exercise capacity and LV function despite no change in cardiac perfusion [126, 127]. In a large clinical trial, ranolazine relieved angina more in diabetic than in non-diabetic patients [128]. Ranolazine also recovered LV function quicker in diabetic than in non-diabetic rats after myocardial infarction, with the benefits related to activation of the energy sensor, adenosine monophosphate kinase. [129] Besides inhibiting FAs utilization, directly stimulating glucose oxidation with dichloroacetate, a pyruvate dehydrogenase (PDH) activator, could also rebalance cardiac substrate uses in T2DM [130, 131].

Alternatively, inhibition of mitochondrial oxidative could be a potential therapeutic target to inhibit diabetic cardiomyopathy. In cell culture models of glucotoxicity and lipotoxicity, MitoQ (a mitochondrial targeted antioxidant) reduces oxidative stress, enhances oxidative phosphorylation (OxPhos) and stimulates cells survival. [132, 133] Alternatively, oxidative stress could be attenuated by boosting antioxidant defense system with agents such as resveratrol or N-acetyl cysteine (NAC), which improved cardiac oxidative phosphorylation in diabetic animals [134, 135]. Furthermore, direct ETC stimulation could also increase oxidative phosphorylation and improve heart function in diabetes.

Intriguingly, therapies designed to increase glucose uptake by overcoming insulin resistance or other mechanisms hold promise for improving myocardial energetics and preventing the progression of contractile abnormalities in heart. In this context, glucagon-like peptide (GLP)-1, a naturally occurring incretin peptide, enhances glucose uptake by stimulating insulin secretion and by enhancing insulin sensitivity in target tissues [136–138]. Administration of exogenous GLP-1 by continuous infusion in patients with type 2 diabetes causes an impressive increase in insulin sensitivity in both skeletal muscle and adipose tissue, with substantial improvements in both insulin-mediated glucose uptake [138] and insulin-independent glucose uptake [139]. Receptors for GLP-1 have also been identified in human myocardium [140], thereby identifying the heart as a potential target for GLP-1 action. Although native GLP-1 is very unstable, degradation resistant GLP-1 analogues are now widely used in clinic for the treatment of type 2 diabetes. Recently, LePore et al. [141] had shown that GPL-10 agonist (albiglutide) ameliorates myocardial metabolic abnormalities in chronic heart failure.

Conclusion

Mitochondria are taking the center stage in cardiovascular research for novel therapeutics, as their dysfunction appears early and invariably in the development of hypertrophy and HF (Figure 3). Maintenance of mitochondrial integrity and biogenesis against cardiac insults and reduction in mitochondrial ROS production during diabetic cardiomyopathy are the promising directions to take in account for therapy. Although, in past decades, much advancement has been made in biomedical and pharmaceutical research, still several

questions remained unanswered and suggest us for more systematic preclinical and clinical investigations to develop the better therapeutics to control the cardiovascular complications in diabetic patients.

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Abbreviations

CHF	Chronic heart failure
ROS	Reactive oxygen species
TGA	Triglycerides
FAO	Fatty acid β oxidation
PDH	Pyruvate dehydrogenase
TCA	Tricarboxylic acid
ATP	Adenosine triphosphate
ADP	Adenosine diphosphate
GDP	Guanosine diphosphate
OXPHOS	Oxidative phosphorylation
PPARα	Peroxisome proliferator-activated receptor alpha
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
ANT	Adenine nucleotide translocator
miR	microRNA
NAC	N-acetyl cysteine
Slc25a3	solute carrier family-25 member 3
T2DM	type-2 diabetes
GLP-1	Glucagon-like peptide
ACC	Acetyl-Coenzyme A carboxylase
AMPK	5AMP-activated protein kinase
CoA	Coenzyme A
FAs	Fatty acids

GLUT	glucose transporter
PI3K	Phosphatidylinositol 3-Kinase
ROS	Reactive oxygen species
UPCs	Uncoupling proteins

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Highlights

- Mitochondrial function is impaired in diabetic cardiomyopathy.
- Dysfunctional mitochondria triggers cardiac cells death in diabetic heart disease.
- Fatty acid and glucose metabolism are impaired in diabetic heart disease.
- PGC-1 α a master metabolic regulator of mitochondrial biogenesis and respiratory function is dysregulated in diabetic cardiomyopathy.
- Dysregulated microRNAs contribute to impaired mitochondrial function diabetic heart.

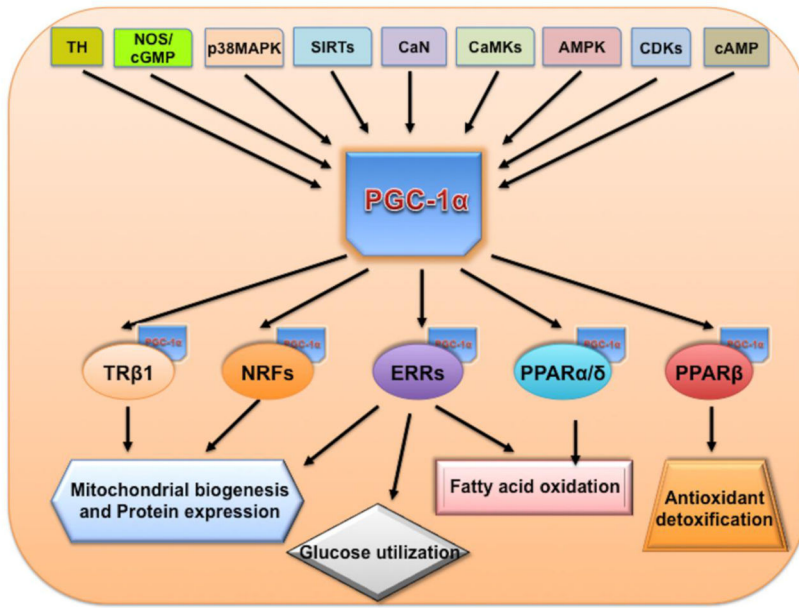


Figure 1. PGC-1 α regulatory cascade. Thyroid hormone, nitric oxide synthase, MAP kinase, sirtuins, calcinurin (CaN), CAMK, AMPK, CDK and β -adrenergic stimulus have been shown to influence the PGC1 α activity. PGC1 α then co-activate transcription factors such as PPAR α / β , NRFs, TRb1 etc which is known to regulate different aspects of energy metabolism including mitochondrial biogenesis, fatty acid oxidation and antioxidant defense system.

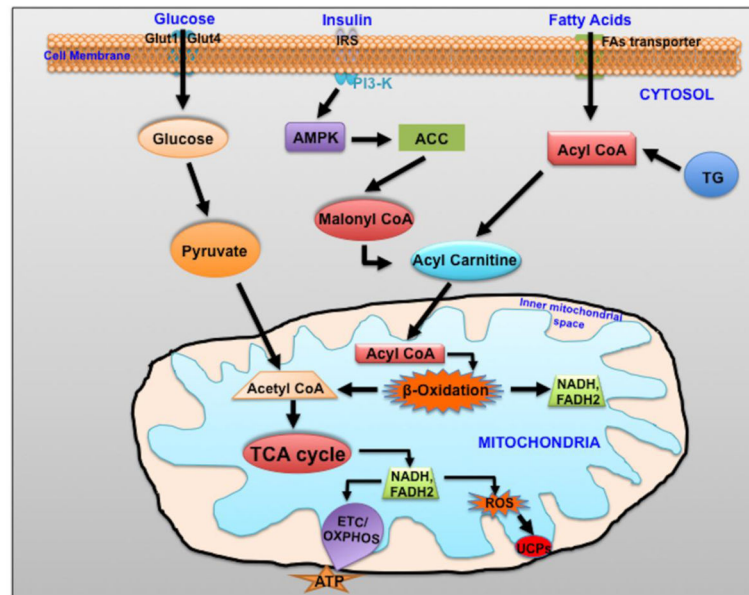


Figure 2. Schematic diagram showing cardiomyocyte energetics. In the diabetic heart, high free fatty acids and insulin resistance alleviated FAs oxidation. ACC: Acetyl-Coenzyme A carboxylase, AMPK: 5AMP-activated protein kinase, CoA: Coenzyme A, FAs: Fatty acids, GLUT: glucose transporter, PI3K: Phosphatidylinositol 3-Kinase, ROS: Reactive oxygen species, TCA: Tricarboxylic acid cycle, TG: triglycerides: UPCs: uncoupling proteins.

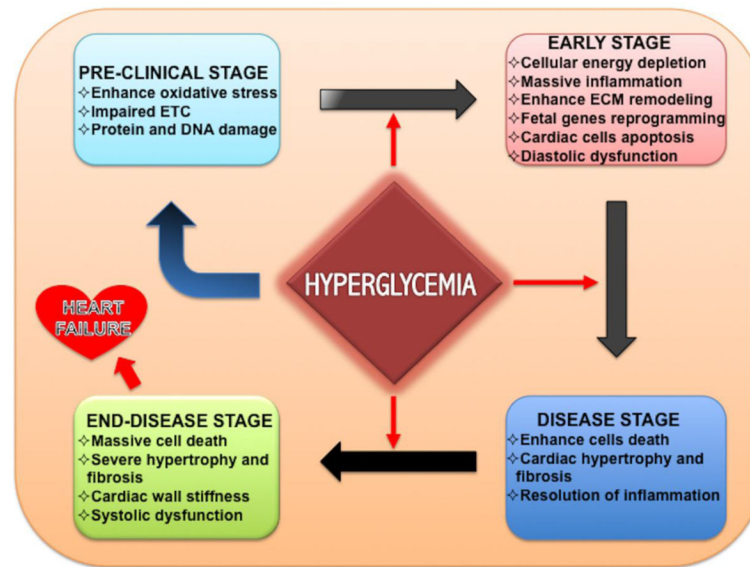


Figure 3. Stages of heart failure in diabetics. Early stress stimulus enhances inflammatory milieu in myocardium, which triggers the mitochondrial dysfunction, oxidative stress and ultimately heart failure.