

# Effects of Lipid Overload on Heart in Metabolic Diseases




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## ABSTRACT

Metabolic diseases are often associated with lipid and glucose metabolism abnormalities, which increase the risk of cardiovascular disease. Diabetic cardiomyopathy (DCM) is an important development of metabolic diseases and a major cause of death. Lipids are the main fuel for energy metabolism in the heart. The increase of circulating lipids affects the uptake and utilization of fatty acids and glucose in the heart, and also affects mitochondrial function. In this paper, the mechanism of lipid overload in metabolic diseases leading to cardiac energy metabolism disorder is discussed.

## Introduction

Metabolic diseases (MetDs), which include metabolic syndrome, pre-diabetes, and type 1 and 2 diabetes, are a series of pathological conditions characterized by abnormal glucose use in the body. Multiple clinical studies have shown that metabolic syndrome and prediabetes both increase the risk of cardiovascular disease and all-cause mortality [1–5], and that cardiac function and structure have changed in prediabetes patients [6–9]. In fact, obesity, insulin resistance, and hyperglycemia are independent risk factors for the development of diabetic cardiomyopathy (DCM), which is the leading cause of death in MetDs [10, 11]. DCM, mainly manifested as cardiac systolic dysfunction, is an important factor in the development of heart failure [12].

Cardiac energy metabolism disorder is considered to have a very important effect on the function and structure of the heart. Under normal physiological conditions, the use of fatty acids and glucose by myocardium is strictly regulated. However, under pathological conditions, the metabolism of fatty acids and glucose in cardiomyocytes changes significantly. The increase of fatty acid metabolism caused mitochondrial damage, leading to serious heart damage [13]. Both clinical and animal studies have reported increased uptake and utilization of lipids and accumulation of fat in heart in metabolic syndrome/diabetes [14–16]. The purpose of this review is to explain the role of lipids in cardiac energy metabolism and to elucidate a series of pathologic changes that occur in the heart when lipid overload occurs.

\* An Yan and Guinan Xie contributed equally to this work.

## Cardiac Energy Metabolism in the Healthy Heart

The heart converts chemical energy from fatty acids and glucose into mechanical energy for actin-myosin interactions. Due to the higher productivity fatty acids provide 70% of the ATP needed by the heart. Fatty acids are the main energy fuel for the heart, followed by glucose [17]. Interestingly, in the immature stage of cardiomyocyte the main energy comes from glycolysis [18, 19]. As cardiomyocytes continue to differentiate and mature, they gradually begin to rely on oxidative phosphorylation for energy. When the heart is saturated with energy requirements, excess glucose is stored as glycogen. When the heart is low on energy, stored glycogen can be disintegrated as fuel to produce ATP [20]. As the result of highly dependence on fatty acid explains why chronic changes in fatty acid metabolism can have profound effects on cardiac function. In conclusion, the selection, utilization, and storage of myocardial fuel is a complex physiological process.

Cardiac energy metabolism mainly includes three parts: substrate utilization, oxidative phosphorylation, and high-energy phosphate metabolism [21]. If the energy produced does not meet the heart's needs, it can gradually lead to a decline in heart function and even heart failure [21]. Mitochondrial ATP supply to myocardium requires the support of two important processes: metabolic fuel uptake and mitochondrial structural and functional integrity. A defect in either link can quickly lead to a decline in cardiac function. Under the stimulation of insulin and myocardial mechanical contraction, fatty acid translocase FAT/CD36 and GLUT4 are transported from endoplasmic reticulum to the cell membrane to uptake most of the fatty acids and glucose into the cardiomyocytes [22]. Fatty acid acyl-coenzyme A (Fa-CoA) is synthesized by fatty acids under the action of Fa-CoA synthetase but cannot enter the mitochondria directly. Fa-CoA is first transferred to carnitine by carnitine palmitoyltransferase-1 (CPT-1), and then acylcarnitine enter the mitochondria directly, where it is converted back to Fa-CoA by carnitine palmitoyltransferase-2 (CPT-2) in the inner membrane of mitochondria. After entering the mitochondria, Fa-CoA is oxidized to acetyl-CoA through  $\beta$ -oxidation [23]. Glucose produces pyruvate, which then enters the mitochondria and enters the tricarboxylic acid (TCA) cycle. Acetyl CoA is the confluence of fatty acid and glucose metabolism and can enter the TCA cycle freely to produce reducing agents NADH and FADH<sub>2</sub>, and transfer electrons to the mitochondrial respiratory chain for oxidative phosphorylation [24]. Because enzymes involved in fatty acids and glucose metabolism inhibit the oxidation of the other fuel, neither fuel disintegrates at the same time [25].

On the other hand, mitochondria consume oxygen and ADP to synthesize ATP through oxidative phosphorylation of complexes I, II, III, and IV located in the mitochondrial intima, and at the same time use energy released by electron transport process to establish proton gradient across the intima [26, 27]. NADH and succinic acid formed in the TCA cycle are oxidized by complexes I and II, transferring electrons to ubiquinone. Under the action of complex III, ubiquinone transfers electrons to cytochrome C, and finally electrons transfer to complex IV to reduce oxygen to water [27, 28]. During electron transport, protons are pumped out of the mitochondrial matrix and create an electrochemical gradient on the

mitochondrial lining. F<sub>0</sub>F<sub>1</sub>-ATP synthase uses the proton gradient to generate free energy to power the synthesis of ATP from ADP [28] (► Fig. 1).

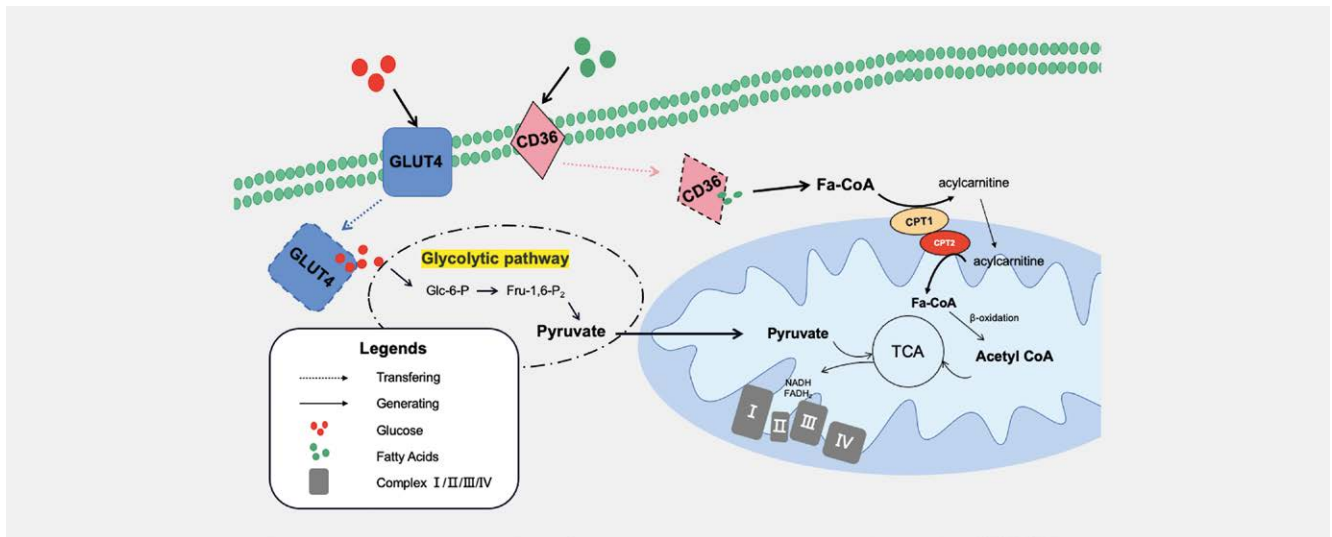
## Lipid Overload Resulted in Increased FAT/CD36 Translocation to the Cell Membrane and Decreased GLUT4

Although the mechanism is unclear, it is widely believed that lipid overload causes insulin increase. Since CD36 is more sensitive to insulin than GLUT4, it induces CD36 transfer from endoplasmic reticulum to sarcomembrane when insulin is increased in circulation. In addition, a new study showed that excess lipids also induced CD36 translocation through upregulation of PKC $\zeta$  activity and TBC1D1 phosphorylation [29]. This change results in the persistence of CD36 in the sarcomembrane, which in turn promoted the myocardial fatty acid uptake rate [30]. Although there was an increase in CD36 expression in the sarcomere, there was no change in total expression. This was due to the transfer of CD36 from the endoplasmic reticulum to the sarcomere rather than increased protein expression [31, 32]. An increase in fatty acid transport was observed under a high-fat diet induced model, apparently prior to insulin resistance. Before insulin resistance, CD36 translocation increased under the action of lipids and insulin, while GLUT4 translocation is not affected [33]. Increased fatty acid oxidation and rapid intracellular lipid accumulation lead to increased protein acetylation levels and lipid intermediates, which inhibit insulin signaling at multiple levels [34–36]. When insulin resistance occurs, Akt2-mediated GLUT4 translocation is inhibited, leading to a decrease in glucose transport rate and a further increase in fatty acid uptake [33].

However, inhibition of fatty acid transport does not improve heart function. A study has shown that the specific ablation of CD36 on cardiomyocytes severely obstructs the utilization of fatty acids, leading to the over-dependence of the heart on glucose for energy and further accelerating the development of heart failure [37]. Therefore, the heart can only function properly when the use of fatty acids and glucose is in balance. Otherwise, too much fatty acids or glucose can cause heart damage. Re-balancing substrate uptake is an effective therapy to correct cardiometabolic disorder [38]. It has also been shown that supplementing or promoting non-lipid myocardial metabolic substrates can improve the state of high-fat induced cardiac energy metabolism imbalance. In vitro and in vivo studies have demonstrated that specific amino acid supplementation (lysine, leucine, arginine) reinternalized CD36 to the endosomes by regulating the mTORC1-v-ATPase axis, reduces myocardial lipid uptake and reverses/prevents lipid accumulation [39].

## Excessive Fatty Acid Utilization Affects Myocardial Energy Efficiency

Clinical data show that a significant decrease in myocardial glucose uptake in T2DM patients is associated with predominant lipid utilization [40]. In db/db mouse heart, oxidation of fatty acids relative to glucose was reported to have increased by 64% [41], providing more than 90% of the heart's ATP [42]. The flow of glycolysis and glycogen decomposition decreased by a factor of two and three [41].



► **Fig. 1** Uptake and utilization of fatty acids and glucose in the healthy heart.

The effects of fatty acid oxidation on the heart have been elucidated in several reviews [24, 43, 44], which will not be repeated in this review. Circulating lipid overload promotes CD36-mediated myocardial fatty acid uptake and reduces GLUT4 translocation. This leads to increased uptake of fatty acids and reduced glucose in the myocardium. On the other hand, the expression of PPAR $\alpha$  and enzymes involved in  $\beta$ -oxidation were upregulated by fatty acid stimulation, which further promoted the increase of myocardial fatty acid oxidation flux [45–47]. Due to the increased dependence of cardiomyocytes on fatty acids, the ratio of cardiac fatty acid oxidation to glucose oxidation increases, which foiled the development of DCM. Glutaredoxin 3 (Grx3) is generally thought to protect cardiomyocytes from oxidative stress-induced damage by regulating REDOX states in mammals [48, 49]. But a new study found that Grx3 is also an important part of regulating cardiac metabolism. Grx3 regulates the balance of cardiac energy metabolism by up-regulating the expression of proteins related to fatty acid uptake, transport and oxidation and down-regulating the expression of proteins related to glucose uptake and utilization [50].

Fatty acids are more productive than glucose, producing more ATP per carbon molecule, but they also require more oxygen [23]. In diabetes, increased oxidation of fatty acids causes the heart muscle to consume scarce oxygen more quickly. When the situation develops further – hypoxia becomes more serious – fatty acid oxidation gradually decreases, and excessive dependence on fatty acids for energy leads to myocardial systolic dysfunction and myocardial hypertrophy, which is the energy metabolism process in the development of DCM. Prostaglandin E receptor (EP4) is one of the receptors of prostaglandin E2, which is widely expressed in cardiomyocytes. Recent studies have shown that EP4 changes CD36 expression in HFD-induced DCM by regulating FOXO1/CD36 signaling axis and improves cardiac fatty acid metabolism and ATP production [51].

## Effect of Lipid Overload on Mitochondrial Function

Mitochondria, as biological energy metabolic centers in eukaryotic organisms, provide the site for a variety of biochemical processes, including oxidative phosphorylation (OXPHOS), the tricarboxylic acid cycle, fatty acid  $\beta$ -oxidation, calcium treatment, and heme biosynthesis [52]. Mitochondrial structural integrity is critical to its function and vitality, but mitochondrial damage has been observed in a variety of metabolic diseases. Mild diastolic/systolic dysfunction occurs in prediabetic heart, accompanied by impaired mitochondrial function, including impaired mitochondrial respiration and ATP production, and decreased mitochondria, etc. [53, 54]. When myocardial insulin resistance or diabetes occurs, by increasing mitochondrial division and reducing mitochondrial fusion, reducing mitochondrial oxidative capacity, increasing ROS production and mitochondrial decoupling, mitochondrial function is impaired, leading to mitochondrial damage, myocardial cell death, and cardiac dysfunction [55–58].

Chronic elevated blood glucose provides an environment for myocardial ischemia and hypoxia, resulting in impaired mitochondrial function of cardiomyocytes [59]. As myocardial contraction and membrane potential ion pump require energy from mitochondria, cardiomyocytes are particularly sensitive to hypoxic injury [60, 61]. Therefore, previous studies have suggested that the main cause of mitochondrial function impairment in metabolic diseases is oxidative stress injury caused by ischemia and hypoxia, but the damage of lipid overload to mitochondria cannot be ignored. Under normal conditions, mitochondrial structural integrity maintains a steady state of synthesis and degradation under the control of a variety of mitochondrial fusion and fission proteins. Mitofusin 1 (MFN1), Mitofusin 2 (MFN2), and protein Optic Atrophy 1 (OPA1) are the key GTPases of mitochondrial fusion, among which the first two are responsible for mitochondrial outer membrane fusion [62, 63], and OPA1 regulates mitochondrial inner membrane fusion

[64]. Excessive fatty acid uptake in cardiomyocytes can reduce the expression of mitochondrial fusion genes MFN1, MFN2, and OPA1, resulting in mitochondrial structure remodeling, and inhibit the activity of respiratory chain complex I and oxidative phosphorylation [65]. Dynamin-related protein 1 (Drp1) is a large GTP enzyme that mediates mitochondrial division. Drp1 acts on the outer membrane of mitochondria through receptor proteins and activates downstream signaling pathways through multiple phosphorylation sites to promote mitochondrial fission [52]. Recent studies have found that excess lipids activate Drp1 through acetylation and increase mitochondrial translocation, leading to myocardial cell dysfunction and death [66]. In vitro experiments also confirmed that the increase of FA in myocardium significantly reshaped the mitochondrial network, resulting in the accumulation of slender mitochondria with reduced diameter in myocardium cells, and induced mitochondrial dynamic changes mediated by the post-translational modifications of mitochondrial protein, DRP1 and OPA1, leading to mitochondrial dysfunction [67].

## Cardiolipotoxicity

Excessive lipid accumulation in the non-adipose cells of the cardiovascular system leads to cell dysfunction and cell death, a process known as lipotoxicity. When excess lipids are deposited in the heart, they can lead to myocardial cell apoptosis and cardiac systolic dysfunction [68]. Excessive fatty acids can selectively absorb and store fatty acids by upregulating GSK-3 $\alpha$  and phosphorylating PPAR $\alpha$  at Ser280 of its ligand binding domain, promoting fat accumulation, which is the basis for the development of the metabolic disease lipotoxic cardiomyopathy [69].

As a storage form of fat, triacylglycerol (TAG) itself has no direct lipid toxicity to myocardium. However, the lipid intermediates produced in the process of TAG synthesis and decomposition are believed to be responsible for the lipid toxicity, as well as post-translational modification of proteins.

## Diacylglycerol (DAG)

Lipid intermediates are a class of signaling molecules produced during the intracellular accumulation of fatty acid, which regulate the energy supply and survival of cardiomyocytes. DAG is an important lipid intermediate in TAG synthesis and decomposition. It is widely believed that the activation of DAG-protein kinase C (PKC) induces insulin resistance (details will be described in the next section). Inhibiting the amount of DAG in myocardium may be an effective treatment. DAG acyltransferase (DGAT) is a key enzyme in the synthesis of DAG from 3-phosphoglyceride and acyl-CoA. A study has shown that partial inhibition of DGAT activity increases cardiac fatty acid oxidation but does not affect PPAR $\alpha$  signal transduction or cardiac systolic function. Complete inhibition of DGAT activity can eliminate cardiac lipid accumulation induced by high fat diet without adverse effects on basic cardiac function [70].

## Ceramide

Ceramides are the most widely studied sphingolipids involved in cardiac lipotoxicity. Studies have shown that ceramide levels in

circulation and myocardium are positively associated with the risk of cardiovascular events and mortality [71, 72]. When triglyceride stores are also saturated, acyl-CoA enters the ceramide biosynthesis pathway. Excessive ceramide can induce insulin resistance [35, 73], regulate the translocation of CD36 to the muscle membrane, inhibit the uptake of glucose and amino acids, reduce mitochondrial efficiency and slow lipolysis by blocking activation of hormonesensitive lipase (HSL) in cardiomyocytes [74].

## Long-chain acyl-CoA

Upon entry into cardiomyocytes, long-chain fatty acids bind with CoA molecules to form long-chain acyl-CoA (LCACoA). The direct lipid toxicity of LCACoA to cardiomyocytes has yet to be determined, and current reports indicate that LCACoA has a dual role in myocardial mitochondria. Palmitoyl CoA (PCoA) can induce the loss of  $\Delta\Psi_m$  outside the mitochondria and thus affect mitochondrial function [75]. PCoA can also limit the shuttle of ADP and ATP on the mitochondrial membrane by inhibiting the activity of ADP/ATP carriers on the mitochondrial membrane [76, 77]. However, during ischemia, ATP can be prevented from entering mitochondria for hydrolysis, which is a protective mechanism during ischemia [78]. However, in diabetes, the protective membrane potential of PCoA is inhibited, leading to increased ATP hydrolysis rate in diabetic heart during ischemia [78].

## Post-translational modifications (PTMs) of proteins

PTMs of proteins refers to a covalent process that a protein undergoes during or after translation, which can be regarded as a switch on which proteins function. Palmitoylation of proteins is the reversible linking of palmitate molecules to cysteine residues under the action of enzymes. Depending on the hydrophobicity of palmitate, the modified protein can be localized to specific submembrane. However, lipid overload can lead to aberrant/excessive palmitoylation of proteins, which negatively affects insulin signaling [79]. For example, hyperpalmitoylation of PKC $\epsilon$  leads to downregulation of insulin receptor expression and decreased insulin sensitivity [80]. CD36 hyperpalmitoylation promotes fatty acid uptake by increasing the number of CD36 on the cell membrane [81].

Acetylation of proteins is also a reversible modification. Since lysine acetyltransferase that mediates protein acetylation is produced by acetyl CoA, increased fatty acid metabolism leads to an increase in protein acetylation levels [34]. In the insulin signaling pathway, acetylation of Akt and its upstream regulator, phosphoinositol-dependent kinase 1 (PDK1), blocks insulin signaling and inhibits translocation of GLUT4 [82, 83].

## Insulin Resistance and Cardiac Energy Metabolism

Cardiomyocyte is a typical insulin-targeting cell. Chronic high fat intake promotes the development of insulin resistance in cardiomyocytes, leads to cardiometabolic dysfunction, and accelerates the development of left ventricular dysfunction and cardiac remodeling [84–86]. In diabetes, increased oxidation and storage of fatty

acids in the heart can lead to diastolic dysfunction, which is also associated with insulin resistance [23]. In the case of insulin resistance, reduced IRS-1 tyrosine phosphorylation reduces the activation of PI3K-Akt signaling pathway and inhibits downstream insulin-mediated metabolic regulation [86]. The decrease of Akt phosphorylation directly leads to the decrease of GLUT4 translocation, which reduces the uptake of glucose in myocardium [86, 87]. Reduced insulin signaling also inhibits glucose utilization by regulating the role of enzymes in the glycolysis pathway, such as hexokinase and phosphofructokinase 2 [88, 89]. Declines in myocardial glucose uptake and utilization have also been observed in patients with diabetes [90].

There are many studies that suggest that excess lipid induces insulin resistance through DAG and ceramide [35, 74, 91, 92], which greatly affects energy metabolism. DAG has been shown to be more associated with myocardial insulin resistance than ceramides [36]. DAG-mediated PKC activation is currently recognized as the main cause of DAG-induced insulin resistance. PKC activation reduces tyrosine phosphorylation of IRS-1 resulting in reduced insulin-PI3K-Akt signaling [91]. Ceramide inhibits Akt activity, affects GLUT4 translocation and glucose uptake by activating PKC $\zeta$  and protein phosphatase 2 (PP2A) [93, 94].

All in all, the insulin cascade forms a vicious circle, aggravating the heart's excessive dependence on fatty acids for energy and the acceleration of oxygen consumption. It has also been reported that, in addition to lipids, branched amino acids, iron overload can also lead to heart insulin resistance [95–97].

In addition to insulin, AMP-activated protein kinase (AMPK) also plays an important role in regulating substrate utilization. And insulin signal transduction are two relatively independent signaling pathways, but they also affect each other. The study showed that increased insulin sensitivity and increased glucose uptake and utilization were observed in mice with AMPK deletion [98]. Activated AMPK inhibits glycogen, fatty acid, and protein synthesis, and enhances glucose/fat uptake, mitochondrial metabolism, and autophagy by phosphorylating GLUT4/CD36, PGC-1 $\alpha$ /SIRT, and ACC2, respectively [99]. The interference of long-term excessive fatty acid level in the heart not only causes the change of PI3K-Akt-mediated insulin signaling, but also changes the AMPK-eNOS signaling. Although no studies have confirmed this, it can be inferred that FA can lead to cardiac energy metabolism disorders through AMPK even in the absence of insulin resistance.

## Concluding Remarks

The heart needs a balanced ratio of fatty acids to glucose metabolism. When that balance is disrupted, it triggers a cascade of butterfly effects that imbalance the energy metabolism of the heart, resulting in impaired cardiac function and structure. The disturbance of myocardial energy metabolism and lipid toxicity caused by lipid overload seriously affects cardiac function. Chronic lipid overload can lead to heart failure. First, excess lipid promotes FAT/CD36 uptake of fatty acids by increasing circulating free fatty acids through the action of insulin. Meanwhile, excessive intake of fatty acids up-regulated the expression of  $\beta$ -oxidation-related genes and enzymes and promoted the utilization of fatty acids. During this process, insulin resistance is induced by accumulating lipid toxicity,

which inhibits glut4-mediated glucose uptake and utilization. The increase of fatty acid/glucose oxidation ratio resulted in myocardial over-dependence on fatty acid for energy and increased oxygen consumption. In addition to affecting energy metabolism, lipid toxicity and hypoxia cause mitochondrial damage and reduce mitochondrial efficiency.

By elucidating the pathological changes of the heart caused by lipid overload at the cellular and molecular levels, it is helpful to identify potential therapeutic targets. In addition to explaining the mechanisms of lipid overdose-induced cardiac injury, this review also mentions some factors leading to lipid toxicity, among which the role of PTMs of proteins has attracted increasing attention in recent years. These new descriptions may provide new ideas for cardiometabolic intervention.

## Authors' Contributions

AY and GNX performed the literature review and wrote the manuscript. YW and LPG helped in the revision of the review. XYD conceived the review article. All authors approved the final version of the review.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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