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Metabolic remodelling of the failing heart in diabetes: shifting substrates and emerging therapeutics

Abstract

Heart failure (HF) remains a significant global health burden, with a disproportionately high prevalence and severity among individuals with diabetes mellitus (DM). Diabetic cardiomyopathy, a distinct clinical entity characterized by myocardial dysfunction in the absence of overt coronary artery disease or hypertension, underscores the critical contribution of metabolic dysregulation in disease pathogenesis. Under physiological conditions, the heart exhibits remarkable metabolic flexibility, efficiently switching between substrates—primarily fatty acids, glucose, lactate, ketone bodies, and amino acids—to meet its substantial energy demands via mitochondrial oxidative phosphorylation. This substrate utilization is finely regulated by hormonal signals, nutrient availability, and transcriptional control. However, in the failing heart, especially in the diabetic milieu, this flexibility is compromised. Key features of this maladaptive metabolic remodeling include mitochondrial dysfunction, impaired oxidative phosphorylation, and a shift toward inefficient glycolysis. Insulin resistance further impairs myocardial glucose uptake and promotes excessive fatty acid oxidation, leading to lipotoxicity and oxidative stress. Notably, recent studies have highlighted an increased reliance on ketone bodies as an alternative, oxygen-efficient energy source in diabetic heart failure. This review synthesizes current evidence on the pathophysiology of myocardial energy metabolism in diabetic HF and explores emerging therapeutic strategies aimed at restoring metabolic flexibility and enhancing cardiac efficiency.

Keywords: heart failure, diabetes mellitus, SGLT2 inhibitors, GLP-1 receptor agonists

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Introduction

Heart failure (HF) is a leading cause of morbidity and mortality globally, with a particularly high prevalence among individuals with diabetes mellitus (DM). Diabetic cardiomyopathy, characterized by structural and functional myocardial changes independent of coronary artery disease or hypertension, is a well-recognized clinical entity. The metabolic landscape of the failing diabetic heart undergoes significant shifts, contributing to energetic inefficiency and progressive myocardial dysfunction. As described by Lopaschuk et al[1].understanding cardiac energy metabolism—its substrates, mitochondrial dynamics, and compensatory responses—has critical implications for novel therapeutic approaches in diabetic heart failure.[1]

Normal cardiac energy metabolism

The human heart is a highly energy-demanding organ, requiring a continuous and substantial supply of adenosine triphosphate (ATP) to sustain its rhythmic contractions and maintain adequate perfusion throughout the body. Despite constituting only about 0.5% of total body mass, the myocardium consumes approximately 8–15% of total body oxygen at rest. This significant energy demand is met through a complex and tightly regulated system of substrate utilization and mitochondrial oxidative metabolism, as highlighted by Yurista et al.,[2].

Metabolic Flexibility of the Heart

The healthy adult myocardium is often described as a "metabolic omnivore," reflecting its remarkable ability to utilize a variety of substrates for energy production. These substrates include fatty acids (60–70%), glucose (20–30%), lactate (10–15%), ketone bodies (5–10%), and amino acids (minimal under normal conditions). The exact contribution of each substrate to ATP generation is dynamic and fluctuates depending on physiological conditions such as feeding versus fasting, rest versus exercise, and normoxia versus hypoxia. As noted by Wang et al.,[3], this substrate flexibility is a key adaptive feature of the heart, allowing it to maintain energy production across varying metabolic states.[3]

Fatty acid oxidation (FAO)

Long-chain fatty acids (LCFAs) are the predominant substrate in the normal, oxygenated adult heart. These fatty acids are either derived from the circulation (as free fatty acids bound to albumin or as triglyceride-rich lipoproteins) or from intracellular lipid stores. LCFAs enter cardiomyocytes through passive diffusion and via transport proteins such as CD36 (cluster of differentiation 36), FATP (fatty acid transport proteins), and FABP (fatty acid-binding proteins). Inside the cytosol, fatty acids are activated to fatty acyl-CoA by acyl-CoA synthetase.

The fatty acyl-CoA is then shuttled into the mitochondria via the carnitine shuttle system:

I. CPT1 (carnitine palmitoyltransferase 1) on the outer mitochondrial membrane converts fatty acyl-CoA to acylcarnitine.

II. Acylcarnitine is transported across the inner mitochondrial membrane via CACT (carnitine-acylcarnitine translocase).

III. CPT2 reconverts it to fatty acyl-CoA within the mitochondrial matrix.

Inside the mitochondria, β-oxidation cleaves two-carbon units from the fatty acyl-CoA, generating acetyl-CoA, NADH, and $FADH_2$. Acetyl-CoA enters the tricarboxylic acid (TCA) cycle, and the reduced cofactors (NADH, $FADH_2$) feed electrons into the electron transport chain (ETC). This culminates in oxidative phosphorylation, producing approximately 106–129 molecules of ATP per molecule of palmitate (a 16-carbon fatty acid), making FAO highly energy-rich but oxygen-costly, as outlined by Wen et al[4].

Glucose oxidation

Glucose contributes 20–30% of myocardial energy under resting conditions. It becomes the dominant substrate during conditions like ischemia, fetal development, and hypertrophy. Uptake and transport by insulin-dependent glucose uptake occurs primarily via GLUT4 (glucose transporter 4), while basal uptake is mediated by GLUT1. Insulin signaling enhances GLUT4 translocation to the sarcolemma, increasing glucose entry into the cardiomyocyte.

Glycolysis occurs in the cytosol, where glucose is broken down to pyruvate, producing a modest 2 ATP per glucose molecule. Under aerobic conditions, pyruvate is transported into mitochondria and converted to acetyl-CoA by pyruvate dehydrogenase (PDH). Acetyl-CoA then enters the TCA cycle and the electron transport chain (ETC), yielding approximately 36 ATP per glucose molecule. Notably, glucose oxidation is more oxygen-efficient than fatty acid oxidation—producing more ATP per mole of O_2 consumed, which proves particularly advantageous during ischemic conditions, as so thoughtfully elucidated by Heinen et al[5].

Lactate metabolism

Traditionally considered a mere byproduct of anaerobic metabolism, lactate has now emerged as a vital oxidative substrate within the myocardium. Under aerobic conditions, circulating or glycolytically derived lactate is taken up by cardiomyocytes via monocarboxylate transporters (MCTs), particularly MCT1. Once inside the cell, lactate is converted back to pyruvate by lactate dehydrogenase (LDH) and subsequently oxidized in the mitochondria. Lactate clearance is markedly enhanced during periods of exercise and physiological stress, underscoring its role as a flexible and auxiliary energy source—a concept eloquently presented.[6]

Ketone body oxidation

Ketone bodies—primarily β-hydroxybutyrate and acetoacetate—are synthesized in the liver during periods of fasting, prolonged exercise, or ketogenic metabolic states. These circulating ketones enter cardiomyocytes via monocarboxylate transporter 1 (MCT1). Within the cell, β-hydroxybutyrate is oxidized to acetoacetate, which is subsequently converted into acetoacetyl-CoA by the enzyme SCOT (succinyl-CoA:3-ketoacid coenzyme A transferase). Acetoacetyl-CoA is then cleaved into two acetyl-CoA molecules that fuel the tricarboxylic acid (TCA) cycle. Notably, ketone oxidation is remarkably oxygen-efficient, producing more ATP per molecule of O_2 consumed than both fatty acid and glucose oxidation—a metabolic advantage elegantly described by Zhang et al[7].

Amino acid oxidation

Although a relatively minor contributor under normal physiological conditions, certain amino acids—such as glutamate and leucine—can serve as oxidative fuels by converting into intermediates of the tricarboxylic acid (TCA) cycle during periods of metabolic stress or starvation. Nevertheless, owing to their limited oxidative capacity and the metabolic burden associated with their catabolism, the contribution of amino acids to myocardial energy production remains marginal in the healthy heart, as insightfully articulated by Rubio et al[8].

Integration and regulation of substrate use

The heart's selection of fuel is not random but is tightly regulated by a complex interplay of hormonal, allosteric, and transcriptional factors:

Hormonal regulation

I. Insulin promotes glucose uptake and oxidation while suppressing lipolysis and fatty acid oxidation (FAO).

II. Catecholamines (epinephrine, norepinephrine) stimulate lipolysis, elevating circulating free fatty acids (FFAs) and enhancing FAO.

III. Thyroid hormones regulate mitochondrial biogenesis and oxidative capacity.

Allosteric and transcriptional regulation

I. AMPK (AMP-activated protein kinase) detects cellular energy deficits (high AMP/ATP ratio) and stimulates both FAO and glucose uptake.

II. PPARα (Peroxisome proliferator-activated receptor alpha) drives the expression of genes involved in FAO.

III. PDH kinase (PDK) inhibits pyruvate dehydrogenase (PDH), thereby favoring FAO under conditions of glucose scarcity.

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Randle cycle (glucose–fatty acid cycle)

First described by Randle et al., this cycle illustrates the reciprocal inhibition between FAO and glucose oxidation:

I. High FAO increases acetyl-CoA and NADH, which inhibit PDH and suppress glucose oxidation.

II. Conversely, increased glycolytic flux downregulates FAO.

This finely tuned metabolic crosstalk ensures optimal ATP generation in accordance with substrate availability and cellular demands, as eloquently outlined by Actis et al[9].

Mitochondria: the energetic hub

All oxidative substrates ultimately converge at the mitochondria, where the tricarboxylic acid (TCA) cycle, electron transport chain (ETC), and ATP synthase operate in harmony to generate the ATP essential for cardiac contraction. Mitochondria occupy approximately 30–40% of cardiomyocyte volume, and their densely packed cristae provide an expansive surface area to support oxidative phosphorylation. Strategically positioned between myofibrils, myocardial mitochondria are ideally located to deliver ATP directly to the contractile machinery. The heart's oxygen consumption (VO_2) correlates linearly with its ATP demand, underscoring the fundamental importance of mitochondrial integrity to cardiac performance.

This intricately regulated, multi-substrate metabolic system equips the heart to sustain its immense and continuous energy demands, both at rest and under stress. However, as elegantly described by Zhang et al. (2023), disruption of this metabolic equilibrium—as observed in diabetes and heart failure—leads to a state of metabolic inflexibility, impaired energy efficiency, and progressive cardiac dysfunction (Figure 1).[10]

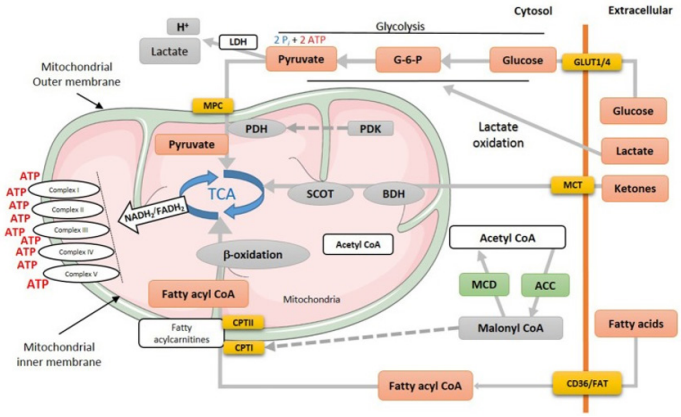

Figure 1 Energy production in normal heart. [Adapted from: Karwi QG, Uddin GM, Ho KL, Lopaschuk GD. Loss of Metabolic Flexibility in the Failing Heart. Front Cardiovasc Med. 2018 Jun 6;5:68.][11]

In the normal heart, mitochondrial ATP production is fuelled primarily by fatty acids, glucose, and ketone bodies through tightly regulated metabolic pathways. Fatty acids enter cardiomyocytes via CD36 (cluster of differentiation 36) and FAT (fatty acid translocase), and are transported into mitochondria through the CPT (carnitine palmitoyltransferase) system. Once inside, they undergo β-oxidation to form acetyl-CoA, which feeds into the TCA (tricarboxylic acid) cycle. Glucose enters the cell via GLUT1 or GLUT4 (glucose transporter types 1 and 4) and is converted to pyruvate by glycolysis. Pyruvate is shuttled into mitochondria by MPC (mitochondrial pyruvate carrier) and converted into acetyl-CoA by PDH (pyruvate dehydrogenase), whose activity is regulated by PDK (pyruvate dehydrogenase kinase). Ketone bodies such as β-hydroxybutyrate enter the heart via MCT (monocarboxylate transporter) and are metabolized by BDH (β-hydroxybutyrate dehydrogenase) and SCOT (succinyl-CoA:3-oxoacid CoA-transferase) to produce acetyl-CoA. Additionally, enzymes like ACC (acetyl-CoA carboxylase) and MCD (malonyl-CoA decarboxylase) regulate fatty acid oxidation by modulating malonyl-CoA levels. The convergence of these pathways at acetyl-CoA entry into the TCA cycle ensures a continuous supply of NADH and $FADH_2$ for the electron transport chain, maintaining the high ATP demands of the contracting heart.[11]

Mitochondrial dynamics and quality control

In the healthy heart, mitochondrial integrity is maintained through a delicate balance of mitochondrial dynamics—fusion and fission—and quality control (mitophagy). Fusion, mediated by mitofusins 1 and 2 (Mfn1/2) and optic atrophy 1 (OPA1), allows for the exchange of mitochondrial components, while fission, driven by dynamin-related protein 1 (Drp1), facilitates the removal of damaged organelles. In diabetic cardiomyopathy, this balance is profoundly disrupted; excessive fission and impaired mitophagy lead to the accumulation of fragmented, dysfunctional mitochondria that produce high levels of reactive oxygen species (ROS), further exacerbating energy deficiency and cellular damage.[12]

Metabolic remodeling in heart failure

Heart failure disrupts this delicately balanced metabolic orchestration. A defining feature of the failing myocardium is impaired mitochondrial oxidative phosphorylation, leading to diminished ATP production despite an elevated energy demand. As observed by Neubauer[13],this "engine out of fuel" phenomenon reflects the heart's progressive loss of energetic capacity. Further compounding the issue, mitochondrial biogenesis is downregulated, and electron transport chain functionality is compromised, resulting in profound energy starvation at the cellular level, as detailed by Doenst et al[14].

In an initial compensatory response, the heart increases glycolytic flux in an attempt to offset the shortfall in oxidative metabolism. However, glycolysis alone cannot satisfy the myocardium's high energy requirements, culminating in bioenergetic failure. Moreover, the mismatch between accelerated glycolysis and impaired glucose oxidation leads to proton accumulation and impaired excitation–contraction coupling, further exacerbating cardiac dysfunction.[13,14]

The pathogenic role of advanced glycation end-products (AGEs)

Hyperglycemia in diabetes accelerates the non-enzymatic glycation of proteins and lipids, forming Advanced Glycation End-products (AGEs). These compounds play a critical pathogenic role by cross-linking with the extracellular matrix (increasing myocardial stiffness) and directly modifying intracellular enzymes. Crucially, AGEs have been shown to inhibit key glycolytic enzymes, such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH). This inhibition creates a metabolic "bottleneck," further impairing the heart's ability to utilize glucose efficiently and shifting the metabolic burden toward oxidative stress-inducing pathways.[15]

The diabetic heart: a shift towards lipotoxicity and ketone utilization

In diabetic patients, myocardial metabolism undergoes distinct alterations even before structural changes in the heart become evident. Insulin resistance hampers glucose uptake via GLUT4 transporters, thereby reducing glucose oxidation. As a result, the myocardium shifts toward a greater reliance on fatty acid oxidation (FAO), fueled by elevated plasma free fatty acids and upregulated expression of PPARα-regulated enzymes, as described by Carley et al[16].

However, this preferential use of fatty acids comes at a steep metabolic cost. FAO requires more oxygen per molecule of ATP generated compared to glucose, thereby reducing the heart's overall

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energetic efficiency. Furthermore, the accumulation of toxic lipid intermediates—such as ceramides and diacylglycerol—contributes to lipotoxicity, mitochondrial uncoupling, and cardiomyocyte apoptosis, as outlined by Schulze et al[17].

More recently, emerging evidence has highlighted the role of ketone bodies, particularly β-hydroxybutyrate, as a potentially adaptive fuel in the failing diabetic heart. Ketone oxidation is more oxygen-efficient than FAO, producing greater ATP per unit of oxygen consumed. In heart failure, both hepatic ketogenesis and myocardial expression of ketone-metabolizing enzymes such as BDH1 and SCOT are upregulated, signaling a metabolic reprogramming toward ketone utilization. This shift, as suggested by Yurista et al[18], may serve as a compensatory mechanism in response to impaired glucose oxidation and the inefficiency of fatty acid metabolism.[16–18]

Molecular targeting: The SIRT6-FoxO1-zDHHC4-CD36 axis

New molecular insights have identified the FoxO1-zDHHC4-CD36 axis as a primary driver of myocardial lipid overload. In the diabetic state, increased FoxO1 activity promotes the expression of zDHHC4, an acyltransferase that mediates the S-acylation of the fatty acid transporter CD36. This modification facilitates the permanent translocation of CD36 to the sarcolemma, leading to uncontrolled fatty acid uptake and subsequent lipotoxicity. Pharmacological activation of SIRT6 has emerged as a promising strategy to inhibit this axis by deacetylating FoxO1, thereby reducing CD36-mediated lipid uptake and restoring metabolic homeostasis.[19]

Molecular and mitochondrial alterations in diabetic HF

Beyond shifts in substrate utilization, mitochondrial structure and function are profoundly altered in diabetic heart failure. Chronic exposure to elevated glucose and fatty acid levels fosters oxidative stress, damages mitochondrial DNA, and disturbs the delicate balance of mitochondrial fusion and fission. The resulting overproduction of mitochondrial reactive oxygen species (ROS) leads to protein nitration, impaired ATP synthase activity, and the pathological opening of the mitochondrial permeability transition pore (mPTP)—a cascade that ultimately promotes cardiomyocyte death, as comprehensively described by Zhou and Tian[20]. In addition, insulin resistance attenuates critical metabolic regulators such as AMPK and PGC-1α, both of which are essential for mitochondrial biogenesis and substrate adaptability. The culmination of these disturbances is a metabolically inflexible, ROS-generating, and energy-deficient myocardium—one that is ill-equipped to maintain energetic and functional homeostasis under conditions of stress.[20]

Pharmacological targeting of cardiac energy metabolism

SGLT2 inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors—such as empagliflozin and dapagliflozin—have transformed the therapeutic landscape of heart failure management. Originally developed as antihyperglycemic agents, these drugs have demonstrated substantial reductions in heart failure hospitalization and cardiovascular mortality, regardless of diabetic status, as reported by McMurray et al[21].

The mechanisms underlying these benefits extend well beyond glycemic control. SGLT2 inhibitors are proposed to:

I. Enhance ketone body availability and oxidation

II. Improve mitochondrial function and biogenesis

III. Reduce cytosolic Na^+ and Ca^{2+} overload, thereby enhancing myocardial contractility

IV. Attenuate oxidative stress and inflammation

Empagliflozin, in particular, has been shown to increase myocardial ketone oxidation, potentially augmenting cardiac energy efficiency while lowering oxygen consumption—a mechanism thoughtfully reviewed by Verma and McMurray[22].[21,22]

Neurohormonal and cyclic GMP modulation

ARNI (Sacubitril/Valsartan): This Angiotensin Receptor-Neprilysin Inhibitor has revolutionized HF treatment by simultaneously inhibiting neprilysin (increasing natriuretic peptides) and blocking the renin-angiotensin-aldosterone system. Clinical evidence confirms that sacubitril/valsartan significantly reduces cardiovascular mortality and all-cause mortality in patients with HFrEF. Vericiguat: As a soluble guanylate cyclase (sGC) stimulator, Vericiguat enhances the cyclic GMP pathway, which is often impaired by oxidative stress in diabetes. The VICTORIA trial demonstrated that Vericiguat significantly reduces the risk of heart failure hospitalization and death in high-risk patients with a recent worsening HF event.[23]

Antifibrotic agents and MRAs

Mineralocorticoid Receptor Antagonists (MRAs): These remain a cornerstone of therapy, limiting the profibrotic effects of aldosterone. Novel Antifibrotics: Pirfenidone, a TGF-beta inhibitor, has shown potential in reducing myocardial extracellular volume and fibrosis in HFpEF. Similarly, Pamrevlumab, a monoclonal antibody targeting connective tissue growth factor (CTGF), is being investigated for its ability to attenuate the progressive structural remodeling seen in diabetic cardiomyopathy.[24]

Trimetazidine and ranolazine

These agents exert their therapeutic effects by partially inhibiting fatty acid oxidation (FAO) and promoting glucose oxidation, thereby enhancing myocardial energy efficiency. Trimetazidine achieves this by inhibiting 3-ketoacyl-CoA thiolase (3-KAT), a key enzyme in the β-oxidation pathway, while ranolazine modulates late sodium currents, indirectly favoring a metabolic shift toward glucose utilization. Both agents have shown clinical benefits in managing angina and heart failure, particularly in patients with ischemic diabetic cardiomyopathy, as demonstrated by Rosano et al[25].[25]

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists, widely recognized for their efficacy in glycemic control, may also exert cardioprotective effects through multiple metabolic and cellular mechanisms. These include improved insulin sensitivity, reduced systemic and myocardial inflammation, and enhanced myocardial glucose uptake. Additionally, some preclinical studies have suggested that GLP-1 agonists may enhance mitochondrial respiration, thereby contributing to improved cardiac energetics. These multifaceted cardiovascular benefits have been thoughtfully discussed by Ussher and Drucker[26].[26]

Addressing comorbidities: IV iron therapy

Iron deficiency is a common and debilitating comorbidity in diabetic HF, exacerbating mitochondrial dysfunction. Recent results from the FAIR-HF2 and HEART-FID trials (including updates from ACC 2025) confirm that intravenous iron therapy (e.g., ferric

carboxymaltose) significantly improves quality of life, functional capacity, and reduces the risk of HF hospitalizations, particularly in the first year of treatment.[27]

Future directions and challenges

While metabolic modulation in diabetic HF holds promise, several questions remain:

I. Is increased ketone utilization a beneficial adaptation or maladaptive consequence?

II. What are the long-term consequences of pharmacologically manipulating substrate pathways?

III. How can therapy be individualized based on metabolic profiling?

Emerging techniques such as cardiac PET imaging and metabolomics may aid in understanding myocardial fuel use in real time, guiding therapy. Additionally, gene editing (e.g., PGC-1α modulation), mitochondrial-targeted antioxidants (e.g., MitoQ), and exogenous ketone supplements are being explored as future interventions.

Conclusion

Cardiac energy metabolism in diabetic HF represents a paradigm of metabolic inflexibility, mitochondrial dysfunction, and substrate overload. In the normal adult heart, fatty acids are the dominant fuel, contributing 60–70% of ATP. Glucose, lactate, ketones, and amino acids provide metabolic flexibility. Insulin signaling, substrate availability, and energy demand dynamically regulate fuel use. Mitochondria are central to ATP production, redox homeostasis, and cell survival. The heart's shift from glucose to fatty acids and ketones in the failing diabetic state, while initially compensatory, can lead to inefficiencies and contribute to disease progression. Novel therapeutic strategies—especially those modulating substrate use and improving mitochondrial function—offer hope for improved outcomes. Continued translational research is essential to unravel the complexities of myocardial energetics and to personalize treatment in diabetic heart failure.

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Conflicts of interest

The author declares no conflicts of interest.

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