Redefining Diabetic Cardiomyopathy: Perturbations in Substrate Metabolism at the Heart of its Pathology

Lisa C. Heather[1†], Keshav Gopal[2,3,4], Nikola Srnic[1], John R. Ussher[2,3,4†]

[1]Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK
[2]Faculty of Pharmacy and Pharmaceutical Sciences,
University of Alberta, Edmonton, AB Canada
[3]Alberta Diabetes Institute, University of Alberta, Edmonton, AB Canada
[4]Cardiovascular Research Institute, University of Alberta, Edmonton, AB Canada

[†]Address for correspondence:
Lisa C. Heather, DPhil
Department of Physiology, Anatomy and Genetics
University of Oxford
Parks Road, Oxford, OX1 3PT
United Kingdom
tel: 44.1865.282048
email: lisa.heather@dpag.ox.ac.uk

John R. Ussher, PhD
Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta
2-020E Katz Centre for Pharmacy and Health Research
Edmonton, AB T6G 2E1
Canada
tel: 1.780.232.1002
email: jussher@ualberta.ca

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Abstract

Cardiovascular disease represents the leading cause of death in people with diabetes, most notably from macrovascular diseases such as myocardial infarction or heart failure. Diabetes also increases the risk of a specific form of cardiomyopathy referred to as diabetic cardiomyopathy (DbCM), originally defined as ventricular dysfunction in the absence of underlying coronary artery disease and/or hypertension. Herein, we provide an overview on the key mediators of DbCM, with an emphasis on the role for perturbations in cardiac substrate metabolism. We discuss key mechanisms regulating metabolic dysfunction in DbCM, with additional focus on the role of metabolites as signalling molecules within the diabetic heart. Furthermore, we discuss the pre-clinical approaches to target these perturbations to alleviate DbCM. With several advancements in our understanding, we propose "diastolic dysfunction in the presence of altered myocardial metabolism in a person with diabetes, but absence of other known causes of cardiomyopathy and/or hypertension", as a new definition for, or approach to classify, DbCM. However, we recognize that no definition can fully explain the complexity of why some individuals with DbCM exhibit diastolic dysfunction, whereas others develop systolic dysfunction. Due to DbCM sharing pathological features with heart failure with preserved ejection fraction (HFpEF), the latter of which is more prevalent in the diabetic population, it is imperative to determine whether effective management of DbCM decreases HFpEF prevalence.

Article Highlights

- Diabetic cardiomyopathy (DbCM) is characterized by diastolic dysfunction and perturbations in cardiac substrate metabolism, while being more prevalent in people with diabetes than previously recognized.
- Optimizing cardiac substrate metabolism is often associated with improvements in DbCM, and this improvement may be related to changes in flux, mitochondrial function, bioenergetics, and/or metabolite-regulated signalling processes.
- Heart failure with preserved ejection fraction is also more prevalent in people with diabetes and characterized by diastolic dysfunction, and whether interventions aimed specifically at treating DbCM can decrease the risk or progression of HFpEF is an important area for future investigation.

1. Introduction

Despite the complications of diabetes affecting many organs in the body, the leading cause of mortality in people with type 1 and type 2 diabetes (T1D/T2D) is cardiovascular disease. Diabetes increases the incidence of myocardial infarction (MI) and heart failure (1), with diabetic individuals who have not had a prior MI having comparable cardiovascular mortality rates to nondiabetic individuals who have had a previous MI (2). In part, this can be attributed to the macrovascular dysfunction, endothelial dysfunction, accelerated atherosclerosis and hypertension found in many diabetic individuals. In addition to these vascular complications, people with diabetes develop an often asymptomatic and undiagnosed diastolic dysfunction (3). This diastolic dysfunction is a hallmark of diabetic cardiomyopathy (DbCM), and is also a characteristic of heart failure with preserved ejection fraction (HFpEF). HFpEF is more prevalent within the diabetic population, however, we currently do not fully understand the mechanism(s) responsible for HFpEF, and have limited treatment options available for these individuals. As such, it is imperative we address whether treating diastolic dysfunction and alleviating DbCM in the early stages of T2D can influence the progression of HFpEF, which would have major implications for the burden imposed on our healthcare systems.

Herein we will provide an overview of the pathology of DbCM, highlighting some of the key mediators, with major emphasis on the role of perturbations in cardiac substrate metabolism. Furthermore, we will interrogate whether correcting these perturbations in cardiac substrate metabolism may represent viable targets for the treatment of DbCM. We will also consider the alternative role for disrupted metabolites, as signaling molecules regulating cell function in the heart. While our focus will primarily be DbCM in the setting of T2D, we will also consider these aspects in the context of T1D.

2. What is Diabetic Cardiomyopathy?

The clinical phenotype of DbCM was first described by Rubler and colleagues in the 1970s, from autopsy findings of four diabetic individuals with no evidence of MI, but signs of left ventricular (LV) hypertrophy, cardiomegaly, and congestive heart failure of unknown causes (4). This led to the definition of a DbCM: a condition in diabetic patients characterized by the presence of ventricular dysfunction, but in the absence of underlying coronary artery disease and/or hypertension. Our understanding of the clinical phenotype of DbCM has greatly improved in the 21st century (Fig. 1), aided by advances in the diagnostic capabilities of non-invasive imaging modalities (5; 6). Through these diagnostic advancements it has been found that a decline in

diastolic function is a key feature of DbCM, often in the absence of systolic dysfunction. Impairments in diastolic function have been identified early in the progression of diabetes, and were previously overlooked as this group of asymptomatic individuals would not be routinely investigated for cardiac dysfunction (3). The prevalence of diastolic dysfunction in T2D has been reported to range from as low as 20% to nearly 80%, depending on the diagnostic criteria used and patient group studied (7-10). In addition to LV hypertrophy, DbCM is also characterized by increased wall thickness, diffuse myocardial fibrosis and intramyocyte lipid accumulation (11). Despite the advances in our understanding of DbCM, what remains unclear is the progression of cardiac complications in people with diabetes, and how the different structural and functional changes progress longitudinally with diabetes duration. In addition, developments in the field have been hindered by the lack of a universally accepted and consistently applied definition of DbCM. Individuals with HFpEF have symptoms of heart failure in the absence of systolic dysfunction (ejection fraction >50%), and often display evidence of LV diastolic dysfunction and increased LV filling pressures (12). Development of HFpEF is particularly prevalent in diabetic individuals, with a recent study reporting 45% of HFpEF cases were in patients with diabetes (13). Phenomapping of HFpEF patients has identified a large subgroup characterized by a “metabolic, obese” phenotype (14). Diabetic individuals with HFpEF have a higher prevalence of hypertension, pulmonary diseases, and renal dysfunction, while also having more severe cardiac remodeling with higher filling pressure and diastolic dysfunction compared with non-diabetic individuals with HFpEF (15; 16). In addition, females are more susceptible to HFpEF and diastolic dysfunction than males (17). Despite an overlap in clinical features between DbCM and HFpEF (Fig. 1), there are symptomatic differences, especially in relation to the severe exercise intolerance and exertional dyspnea in the latter. Clinical studies directly comparing DbCM versus HFpEF in individuals with diabetes are needed, and we currently lack longitudinal studies in the population to determine whether DbCM increases risk for HFpEF and may explain why the abovementioned measures are exacerbated in those with diabetes.

3. Mediators of Diabetic Cardiomyopathy

Our understanding of the principal mechanisms underlying DbCM have been primarily uncovered using animal models of obesity/insulin resistance. Several preclinical models are available for investigating DbCM, of which their strengths and weaknesses have been extensively reviewed (18). A number of dysfunctional cellular processes have been identified within the diabetic myocardium. These include abnormal substrate metabolism, mitochondrial dysfunction and oxidative stress, dyslipidemia and lipotoxicity, increased fibrosis, inflammation,

microvascular/endothelial dysfunction, endoplasmic reticulum stress, abnormal calcium handling, and glucotoxicity (Fig. 2), many of which promote cardiomyocyte death and have been extensively reviewed in (3). It is highly unlikely that these mechanisms exist in isolation and possibly interact to propagate DbCM. As an example, impaired insulin signaling drives abnormal substrate metabolism, which can lead to mitochondrial dysfunction, driving oxidative damage and lipotoxicity (19; 20). Identification of the cellular processes that are "drivers" and which are "passengers" of DbCM progression is needed, as this would allow for better identification of druggable targets for pharmacotherapy. Almost universally, changes in cardiac substrate metabolism are observed in human and animal models of both T1D and T2D. The following sections of this Perspectives article will thus focus on these metabolic changes within the diabetic myocardium, and whether they represent targets for potential pharmacotherapy.

4. Cardiac Substrate Metabolism Perturbations in Diabetic Cardiomyopathy

The healthy adult heart is a metabolically flexible organ capable of switching between substrates including fatty acids, carbohydrates, amino acids and ketones according to the underlying physiological state (21). The majority of ATP generated from substrate oxidation comes from breakdown of fatty acids in the fasted state, whereas carbohydrates become a more dominant fuel source following feeding [see reviews (22-24)]. In individuals with either T1D or T2D, profound changes in cardiac metabolism have been identified (Fig. 3).

4.1 Fatty acid metabolism in the diabetic myocardium

Clinical studies analyzing arterial and coronary sinus blood samples from people with T1D without coronary artery disease observed elevated myocardial fatty acid uptake compared with healthy individuals (25; 26). Similarly, positron emission tomography (PET) imaging studies reported increased fatty acid oxidation and utilization within the myocardium of individuals with T2D (27). In animal models of diabetes, isolated heart perfusions using radioisotopes have demonstrated increased myocardial fatty acid oxidation rates (28; 29). This was accompanied by increased incorporation of fatty acid into the triacylglycerol (TAG) pool and other lipid intermediates, indicative of cardiac lipotoxicity (30; 31). Increased myocardial TAG content has also been confirmed in individuals with T2D using magnetic resonance spectroscopy (MRS), and was found to be an independent predictor for diastolic dysfunction (32). Extensive research in the 21st century has led to significant advancements in our understanding of the molecular mechanisms that drive excess cardiac fatty acid oxidation in diabetes. An early event in the pathogenesis is increased fatty acid uptake across the sarcolemma, predominantly regulated by fatty acid

translocase (FAT/CD36). FAT/CD36 translocates between intracellular vesicles and the membrane, and in diabetes it is permanently relocated to the membrane, thereby facilitating excessive fatty acid uptake to fuel oxidation and esterification (33).

Transcriptional upregulation of multiple genes involved in fatty acid uptake, oxidation and storage are mediated by the transcription factor peroxisome proliferator-activated receptor α (PPARα), resulting in a coordinated increase of fatty acid metabolism in diabetes (34). Lipid intermediates are endogenous agonists for PPARα, thereby fatty acids transcriptionally regulate their own fate. Key studies by Finck *et al*. demonstrated that cardiac-specific PPARα overexpression in mice recapitulated a DbCM phenotype, providing seminal evidence that the metabolic changes within the heart were sufficient on their own to induce cardiac dysfunction (34).

4.2 Glucose metabolism in the diabetic myocardium

It should be noted that there is extensive intracellular cross-talk between the oxidation of different fuels, to limit substrate wasting and futile cycling. This cross-talk forms the basis of the "Glucose-Fatty Acid cycle" reported first by Shipp *et al*. in the heart (35), then later linked with muscles and adipose tissue by Randle *et al*. and referred to as the "Randle cycle" (36). Furthermore, increased levels of fatty acid intermediates can suppress the utilization of glucose directly by allosterically or covalently regulating enzymes of glucose metabolism.

Accordingly, in people with T1D who exhibited increased myocardial fatty acid extraction, there was also a simultaneous decrease in glucose extraction (25; 26). Using non-invasive imaging modalities, decreased myocardial glucose metabolism was also found in people with T2D (37-40). Moreover, the limited glucose that was metabolized was preferentially converted to lactate, rather than being oxidized in the mitochondria (28). This has been further confirmed using cutting-edge hyperpolarized MRS techniques, which demonstrated decreased flux of cytosolic pyruvate into mitochondrial acetyl CoA via pyruvate dehydrogenase (PDH) in people with T2D (41). In preclinical animal models, the changes in glucose metabolism closely recapitulate those seen in humans, whereby both glycolysis and glucose oxidation are downregulated in isolated perfused hearts from mice and rats with T2D (28; 29; 42; 43). Complementing these *ex vivo* studies, *in vivo* measurements of pyruvate oxidation using hyperpolarized [1-^{13}C]pyruvate also demonstrate decreased flux through PDH in both the T1D and T2D rodent heart (44; 45).

Mechanistically, changes in sarcolemmal glucose transport regulate glucose entry to the heart, and have been heavily implicated in the metabolic changes in diabetes. Glucose transporter 4 (GLUT4) protein expression and sarcolemmal localization are both decreased in T1D and T2D animal models (46; 47). A key node for metabolic control in the heart is mitochondrial PDH, regulating the coupling between glycolysis and glucose oxidation. There is now unequivocal evidence that decreased myocardial PDH activity is a major factor in the robust impairment of glucose oxidation in DbCM. Post-translational modifications (PTMs) play a major role in its regulation, with PDH kinase (PDK)-mediated phosphorylation suppressing PDH activity, whereas PDH phosphatase (PDP)-mediated dephosphorylation increases its activity. Increases in myocardial PPARα activity not only contribute to molecular increases in fatty acid oxidation, but also to decreases in glucose oxidation via increased transcription of *Pdk4* (34; 48). Additionally, in mice with T2D, increases in myocardial PPARα activity may stimulate transcription of the mitochondrial calcium uniporter complex inhibitory subunit (MCUb), which impairs PDH activity by decreasing mitochondrial calcium levels (49). More recently, it has also been demonstrated that the transcription factor forkhead box protein O1 (FoxO1) contributes to elevations in myocardial *Pdk4* transcription and impaired PDH activity in obesity/T2D (50-52). Finally, increased acetyl CoA concentrations in the diabetic heart, generated from increased fatty acid oxidation, activate PDK4 and thereby suppress PDH activity, demonstrating one of the key nodes of regulation within the “Randle cycle”.

4.3 Branched chain amino acid and ketone metabolism in the diabetic myocardium

It is becoming increasingly recognized that cardiovascular pathologies are also associated with perturbations in branched-chain amino acid (BCAA) and ketone metabolism (53), the former of which also contributes to the pathology of T2D. However, both have been comparatively understudied in the diabetic heart versus fatty acid and carbohydrate metabolism, while myocardial amino acid metabolism in general has been ignored. Nonetheless, it has been reported that branched-chain α-ketoacid CoA dehydrogenase protein expression is decreased in hearts from genetically obese rats, suggestive of an impairment in myocardial BCAA metabolism (54).

With regards to myocardial ketone metabolism contrasting finding have been reported. Studies in rodents and humans have reported increased myocardial β-hydroxybutyrate levels and reduced expression and activity of the ketone oxidation enzyme, β-hydroxybutyrate dehydrogenase 1 (BDH1) (55). Conversely, *in vivo* studies using hyperpolarized [3-

^{13}C]acetoacetate observed increased myocardial ketone utilization in a genetic non-obese rat model of T2D (56). These discrepancies may be explained by the fact that acetoacetate oxidation is not dependent on BDH1 activity but that of SCOT, the activity of which is elevated in T2D (56; 57).

4.4 Myocardial energetics in diabetes and mitochondrial dysfunction

Phosphorus spectroscopy allows for measurements of cardiac energetics, to understand how changes in substrate flux ultimately impact myocardial ATP and phosphocreatine (PCr) concentrations. Studies in individuals with T2D have shown a decrease in the myocardial PCr/ATP ratio, which is further exacerbated upon exercise (58; 59). In animal models, decreased PCr/ATP ratios have been measured *in vivo* in mice with T2D, while decreases in both ATP and PCr concentrations have been reported in rats with T2D (60; 61).

The decrease in myocardial energetics in diabetes is consistent with mitochondrial dysfunction, though it remains unclear the precise interplay between the aforementioned perturbations in substrate metabolism and mitochondrial dysfunction in DbCM. Disturbances to the mitochondrial network have been identified, associated with imbalances in fission/fusion homeostasis, as mitochondrial content is increased but fragmented (3; 62). In addition, there is increased mitophagy in response to high fat feeding, which appears to be an adaptive response to ensure mitochondrial quality control (63). There are also increases in reactive oxygen species and oxidative stress, with strategies to prevent this including increasing catalase expression, inhibiting NADPH oxidases, or using antioxidants, all of which lead to improvements in mitochondrial and cardiac function in diabetes (64).

5. Impact of Disturbed Metabolites Beyond Traditional Metabolism

In addition to their traditional roles as substrates for ATP production, increasing evidence suggests that certain metabolites function as substrates for and as modulators of non-metabolic cellular processes. The relative excess or absence of certain metabolites in the diabetic heart dysregulates these metabolite-controlled processes, providing an alternative mechanism linking the metabolic perturbations to the functional changes within the diabetic myocardium. In this next section we describe selected examples of metabolites directly regulating epigenetics, PTMs and transcription factors in DbCM (Fig. 4).

5.1 Modulation of epigenetics

Epigenetic alterations refer to changes in chromosome structure or composition without changing the nucleotide sequence, which can contribute to disease pathogenesis by changing gene expression through the reversible covalent modification of DNA or histones. DNA cytosine methylation is increased in DbCM compared with healthy cardiac tissue (65), and this has been linked to decreased α-ketoglutarate (αKG) synthesis in diabetes. αKG is a positive allosteric activator of the demethylation complex thymine DNA glycosylase–ten eleven translocation protein 1 (TDG-TET1), and decreased αKG production in diabetes limits DNA demethylation within the heart.

PTMs of histones have been implicated in changing the transcriptional landscape in diabetes by regulating chromatin remodeling. Histone acetylation is regulated by a family of acetyltransferase and deacetylase enzymes, which confer changes in transcription of target genes. Histone deacetylase 4 is regulated by increased glucose concentrations via flux through the hexosamine biosynthetic pathway, which can change gene expression in the diabetic heart (66). Histone lysine lactylation is a newly described epigenetic modification mediated by addition of a lactyl group derived from lactate (67), which has been shown to be elevated in skeletal muscle biopsies from insulin resistant individuals. In these individuals, protein lactylation correlated with markers of anaerobic glycolysis, and could be recapitulated by culturing cells with elevated lactate or glucose (68). However, the specific myocardial proteins undergoing this modification in DbCM have yet to be determined.

5.2 Regulators of protein function and location

As metabolites function as substrates for many protein PTMs, alterations in intermediary metabolism contribute to DbCM pathogenesis by inappropriately increasing or decreasing protein PTMs and detrimentally altering a protein's structure, stability, localization, or intermolecular interactions. Elegant work by Bertrand and colleagues have identified post-translational acetylation of proteins involved in protein trafficking as a driver for metabolic dysfunction in diabetes. Elevated acetyl CoA within the diabetic myocardium (47), derived from fatty acids, ketones and ketogenic amino acids, drives acetylation of α-tubulin lysine resides, causing decreased GLUT4 translocation and myocardial glucose utilization (69; 70). Given the majority of intracellular acetyl CoA is located within the mitochondria, changes in mitochondrial protein acetylation driven by elevated fatty acid-derived acetyl CoA have also been reported in diabetes, modulating mitochondrial respiration and morphology (61; 71).

Another example of metabolite-derived PTMs in diabetes is O-GlcNAcylation, which involves the addition of β-N-acetylglucosamine to proteins, synthesized via the hexosamine biosynthetic pathway from sequential reactions involving glucose, glutamine and acetyl CoA. O-GlcNAcylation is increased in the rodent and human heart in diabetes and can be mimicked by increasing supply of glucose or glucosamine to cardiomyocytes (72; 73). A multitude of proteins involved in diverse cellular processes undergo O-GlcNAcylation, thus the current challenge remains to identify which of those modifications that are elevated in the diabetic heart are causative to pathology.

5.3 Transcriptional modulation

In addition to modifying a cell's epigenome, metabolites influence gene expression by modulating several transcription factors. Stabilization of the hypoxia-inducible factor (HIF)-1α transcription factor has been shown to be suppressed in the ischemic diabetic myocardium by the presence of elevated fatty acid concentrations (31; 47; 74). Fatty acids indirectly regulate HIF-1α by suppressing production of the Krebs cycle intermediates succinate and fumarate during hypoxia, which is needed for HIF-1α stabilization. Transcription factors have also been identified as targets for O-GlcNAcylation, and one such target that is excessively O-GlcNAcylated in diabetes is the homeodomain transcription factor, Nkx2.5, implicated in growth and repair (75). As mentioned previously, PPARs are master regulators of fatty acid metabolism that are activated by lipid intermediates, resulting in a viscous cycle of fatty acid influx driving increased capacity for fatty acid metabolism (76).

6. Targeting Cardiac Substrate Metabolism to Alleviate Diabetic Heart Disease

Numerous preclinical studies have demonstrated that correcting cardiac substrate metabolism perturbations can attenuate the progression of DbCM and improve outcomes. In this next section we provide examples of pharmacological approaches that directly manipulate these pathways (Fig. 3), for the treatment of DbCM in both animal and small scale human studies.

6.1 Targeting fat metabolism

Trimetazidine, an antianginal agent that decreases fatty acid oxidation secondary to an inhibition of 3-ketoacyl CoA thiolase, alleviates diastolic dysfunction in HFD-induced obese mice (77). Similarly, clinical studies employing trimetazidine treatment for 6 months in individuals with T2D and idiopathic dilated cardiomyopathy led to improvements in both systolic and diastolic function (78). Strategies to inhibit fatty acid uptake across the sarcolemma by blocking FAT/CD36 using sulfo-N-succinimidyl oleate decreased fatty acid metabolism in rodent models of T2D,

upregulating glycolysis and improving post-ischemic cardiac function (47). Blocking fatty acid uptake with sulfo-N-succinimidyl oleate also restored HIF1α activation and downstream hypoxic signalling in insulin resistant cardiomyocytes (74). Demonstrating the integrated nature of metabolic control, HIF-1α activation with molidustat (a drug developed for the treatment of anemia) decreased myocardial fatty acid oxidation and TAG accumulation in T2D rats (31).

6.2 Targeting glucose metabolism

Targeting defects in myocardial glucose metabolism has also shown benefit in preclinical studies. Activating mitochondrial PDH using the pan-PDK inhibitor, dichloroacetate (DCA), increased *in vivo* myocardial glucose oxidation rates in T2D rats, and alleviated diastolic dysfunction (44). Increased FoxO1 transcriptional activity also contributes to impaired myocardial PDH activity in T2D (50), as inhibition of FoxO1 with AS1842856 improved diastolic dysfunction in T2D mice (51). Of interest, AS1842856 treatment decreased *Pdk4* expression and subsequent PDH phosphorylation, while these benefits were abolished in mice with a cardiac-specific PDH deficiency, emphasizing that increases in glucose oxidation were responsible for the improved cardiovascular outcomes. Similar observations have been reported in T1D-related cardiomyopathy, as AS1842856 treatment also improved cardiac function in STZ treated rats (79). Treatment with an aldose reductase inhibitor AT-001 (currently under phase 3 clinical trials) improved diastolic dysfunction in mice with T2D, and while targeting this enzyme prevents the conversion of glucose to sorbitol, decreases in myocardial fatty acid oxidation were also reported (80). Of clinical relevance, GLP-1R agonists improve cardiovascular outcomes in people with T2D, and increased myocardial glucose oxidation rates have been observed in mice with T2D following systemic treatment with liraglutide, along with improvements in diastolic function (42). Recent findings have also demonstrated that treatment with the long-acting GLP-1R agonist, semaglutide, improved the Kansas City Cardiomyopathy Questionnaire clinical summary and 6-minute walk distance in individuals with HFpEF but without diabetes (81). Whether the observed benefit may be dependent on increases in myocardial glucose oxidation is unknown but an intriguing avenue for further interrogation.

6.3 Targeting amino acid and ketone metabolism

There are limited studies investigating whether manipulating myocardial amino acid or ketone metabolism can improve outcomes in experimental DbCM. Dietary supplementation with lysine, leucine and arginine decreased myocardial wall thickness, thereby attenuating cardiac hypertrophy in insulin resistant rats (82). Ketone ester administration to T2D mice resulted in

improved diastolic and systolic function, associated with improvements in mitochondrial respiration (83). There has been much interest in SGLT2 inhibitors as manipulators of ketone metabolism, with clinical data demonstrating that they also improve cardiovascular outcomes in people with T2D. Treatment with the SGLT2 inhibitor, empagliflozin, ameliorates diastolic dysfunction in mice subjected to HFD-induced obesity (84), however, empagliflozin failed to increase myocardial ketone oxidation rates in mice with T2D (85). Thus, it remains unclear whether the beneficial effects of SGLT2 inhibition involve changes in ketone metabolism, or whether this has simply been a metabolic "red herring".

6.4 Furthering our understanding of metabolic control in DbCM

It has often been posited that decreasing fatty acid oxidation or increasing glucose oxidation will improve the efficiency of contractile function, due to the lower O_2 cost of generating ATP from glucose versus fatty acids. Whether this is relevant in DbCM where some of the primary pathological features are diastolic dysfunction and cardiac fibrosis is difficult to ascertain. It would seem prudent to determine how decreasing or increasing fatty acid and glucose oxidation, respectively, impacts the molecular control of ventricular relaxation, which is a highly energy dependent process (86). Furthermore, as correcting these metabolic perturbations can be associated with alleviation of cardiac fibrosis (51), it would also be relevant to determine whether changes in fatty acid and/or glucose oxidation in cardiomyocytes or fibroblasts directly impact fibrogenesis. Another key area of consideration revolves around the previously described non-energetic aspects of metabolic intermediates and PTMs, as they may influence signaling and biological processes. For example, titin is a major protein of the cardiac sarcomere susceptible to several PTMs that regulates diastolic function. Understanding how dysregulated metabolism may influence the cardiac sarcomere may identify novel areas for investigation in diabetes.

7. Future Considerations and Redefining Diabetic Cardiomyopathy

As highlighted throughout this Perspectives article, a plethora of preclinical and clinical studies support that DbCM is characterized by several perturbations in cardiac substrate metabolism and the presence of diastolic dysfunction. However, there have been limited studies comparing DbCM from HFpEF in diabetes. Research in this area is needed to answer (1) whether DbCM is predictive or a precursor to HFpEF in T2D, (2) whether effective management of DbCM at its onset will decrease the prevalence of HFpEF, or (3) whether DbCM is truly its own unique clinical entity? Recent studies identified a stepwise decrease in diastolic function and PCr/ATP ratio when comparing control, T2D and HFpEF patients, but exercise only induced transient pulmonary

406 congestion in the HFpEF patients (87). This would suggest changes in energy metabolism are
407 following a trajectory via DbCM to HFpEF, however, the number of HFpEF patients with diabetes
408 in this study was limited.
409
410 What is also lacking is a clear and consistently applied definition of DbCM. It has been suggested
411 that with an improved understanding of the pathology that characterizes DbCM, perhaps the
412 condition should be re-termed “diabetic heart disease” (3). A limitation of this approach is that the
413 term diabetic heart disease could be falsely construed to include all cardiovascular diseases
414 associated with diabetes (not just those affecting the myocardium but also the vascular diseases).
415 Therefore, our recommendation is that the term DbCM simply be redefined, of which we propose
416 the definition “diastolic dysfunction in the presence of altered myocardial metabolism in a person
417 with diabetes, but absence of other known causes of cardiomyopathy and/or hypertension”. While
418 advancements in non-invasive imaging technologies such as ^{13}C hyperpolarized MRS and PET
419 imaging allow for assessment of myocardial glucose oxidation and fatty acid oxidation,
420 respectively, these are unlikely to see routine use in clinical management in the foreseeable
421 future. Thus, validation of metabolic biomarkers reflective of the perturbations in cardiac energy
422 metabolism may serve as a more feasible approach for diagnosing DbCM based on this definition.
423 Additionally, further research characterizing the metabolic phenotype in diabetic patients with
424 HFpEF will assist in unravelling the relationship between DbCM and HFpEF. Nonetheless, even
425 this new definition cannot universally distinguish DbCM, as there will be individuals with diabetes
426 and systolic dysfunction more reminiscent of a heart failure with reduced ejection fraction
427 phenotype. Why one individual with DbCM may develop diastolic dysfunction whereas another
428 may develop systolic dysfunction remains unknown, and until appropriately designed larger
429 population studies are pursued, will remain an enigma in the field of cardiovascular endocrinology.
430
431 Taken together, it is becoming increasingly recognized that DbCM is more prevalent in people
432 with diabetes than previously accepted, and it is often present but undiagnosed in people with
433 prediabetes or early-stage T2D. Cardiovascular outcomes trials (CVOTs) for 2 glucose-lowering
434 medications, the SGLT2 inhibitors and GLP-1R agonists, reported decreased cardiovascular
435 events in people with T2D (88; 89). Despite these promising observations, it is important to note
436 that the majority of diabetic individuals included in CVOTs have established macrovascular
437 cardiovascular disease and have been diabetic for years. Conversely, people with prediabetes or
438 the early stages of T2D are comparatively understudied in CVOTs, and this population will need
439 to be considered in future studies.

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Duality of Interest

The authors have no relevant conflicts to disclose.

References

1. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H: Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. The lancet Diabetes & endocrinology 2015;3:105-113
2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-234
3. Ritchie RH, Abel ED: Basic Mechanisms of Diabetic Heart Disease. Circ Res 2020;126:1501-1525
4. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A: New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 1972;30:595-602
5. Ho CY, Solomon SD: A clinician's guide to tissue Doppler imaging. Circulation 2006;113:e396-398
6. Lindsey ML, Kassiri Z, Virag JAI, de Castro Bras LE, Scherrer-Crosbie M: Guidelines for measuring cardiac physiology in mice. Am J Physiol Heart Circ Physiol 2018;314:H733-H752
7. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG: Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care 2001;24:5-10
8. Fang ZY, Schull-Meade R, Leano R, Mottram PM, Prins JB, Marwick TH: Screening for heart disease in diabetic subjects. American Heart Journal 2005;149:349-354
9. Yazici M, Ozdemir K, Gonen MS, Kayrak M, Ulgen MS, Duzenli MA, Yazici R, Soylu A, Gok H: Is there any relationship between metabolic parameters and left ventricular functions in type 2 diabetic patients without evident heart disease? Echocardiography 2008;25:675-682
10. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE: Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. Am J Cardiol 2004;93:870-875
11. Ng AC, Auger D, Delgado V, van Elderen SG, Bertini M, Siebelink HM, van der Geest RJ, Bonetti C, van der Velde ET, de Roos A, Smit JW, Leung DY, Bax JJ, Lamb HJ: Association between diffuse myocardial fibrosis by cardiac magnetic resonance contrast-enhanced T(1) mapping and subclinical myocardial dysfunction in diabetic patients: a pilot study. Circ Cardiovasc Imaging 2012;5:51-59
12. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, Group ESCSD: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-3726
13. Echouffo-Tcheugui JB, Xu H, DeVore AD, Schulte PJ, Butler J, Yancy CW, Bhatt DL, Hernandez AF, Heidenreich PA, Fonarow GC: Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: Findings from Get With The Guidelines-Heart Failure registry. Am Heart J 2016;182:9-20
14. Peters AE, Tromp J, Shah SJ, Lam CSP, Lewis GD, Borlaug BA, Sharma K, Pandey A, Sweitzer NK, Kitzman DW, Mentz RJ: Phenomapping in heart failure with preserved ejection fraction: insights, limitations, and future directions. Cardiovasc Res 2023;118:3403-3415
15. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Kober L, McKelvie RS, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray JJ: Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes According to Diabetes Status in Patients With Heart Failure and Preserved Ejection Fraction: A Report From the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation 2017;135:724-735

16. Lindman BR, Davila-Roman VG, Mann DL, McNulty S, Semigran MJ, Lewis GD, de las Fuentes L, Joseph SM, Vader J, Hernandez AF, Redfield MM: Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. J Am Coll Cardiol 2014;64:541-549
17. Wu MZ, Chen Y, Yu YJ, Zhen Z, Liu YX, Zou Y, Ho LM, Lin QS, Ng MY, Lam KS, Tse HF, Yiu KH: Sex-specific pattern of left ventricular hypertrophy and diastolic function in patients with type 2 diabetes mellitus. Eur Heart J Cardiovasc Imaging 2021;22:930-940
18. Heather LC, Hafstad AD, Halade GV, Harmancey R, Mellor KM, Mishra PK, Mulvihill EE, Nabben M, Nakamura M, Rider OJ, Ruiz M, Wende AR, Ussher JR: Guidelines on models of diabetic heart disease. Am J Physiol Heart Circ Physiol 2022;323:H176-H200
19. Boudina S, Bugger H, Sena S, O'Neill BT, Zaha VG, Ilkun O, Wright JJ, Mazumder PK, Palfreyman E, Tidwell TJ, Theobald H, Khalimonchuk O, Wayment B, Sheng X, Rodnick KJ, Centini R, Chen D, Litwin SE, Weimer BE, Abel ED: Contribution of impaired myocardial insulin signaling to mitochondrial dysfunction and oxidative stress in the heart. Circulation 2009;119:1272-1283
20. Tsushima K, Bugger H, Wende AR, Soto J, Jenson GA, Tor AR, McGlauflin R, Kenny HC, Zhang Y, Souvenir R, Hu XX, Sloan CL, Pereira RO, Lira VA, Spitzer KW, Sharp TL, Shoghi KI, Sparagna GC, Rog-Zielinska EA, Kohl P, Khalimonchuk O, Schaffer JE, Abel ED: Mitochondrial Reactive Oxygen Species in Lipotoxic Hearts Induce Post-Translational Modifications of AKAP121, DRP1, and OPA1 That Promote Mitochondrial Fission. Circ Res 2018;122:58-73
21. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC: Myocardial fatty acid metabolism in health and disease. Physiol Rev 2010;90:207-258
22. Goldberg IJ, Trent CM, Schulze PC: Lipid metabolism and toxicity in the heart. Cell Metab 2012;15:805-812
23. Ho KL, Karwi QG, Connolly D, Pherwani S, Ketema EB, Ussher JR, Lopaschuk GD: Metabolic, structural and biochemical changes in diabetes and the development of heart failure. Diabetologia 2022;65:411-423
24. Bayeva M, Sawicki KT, Ardehali H: Taking Diabetes to Heart—Deregulation of Myocardial Lipid Metabolism in Diabetic Cardiomyopathy. Journal of the American Heart Association 2013;2
25. Avogaro A, Nosadini R, Doria A, Fioretto P, Velussi M, Vigorito C, Sacca L, Toffolo G, Cobelli C, Trevisan R, et al.: Myocardial metabolism in insulin-deficient diabetic humans without coronary artery disease. Am J Physiol 1990;258:E606-618
26. Doria A, Nosadini R, Avogaro A, Fioretto P, Crepaldi G: Myocardial metabolism in type 1 diabetic patients without coronary artery disease. Diabet Med 1991;8 Spec No:S104-107
27. Mather KJ, Hutchins GD, Perry K, Territo W, Chisholm R, Acton A, Glick-Wilson B, Considine RV, Moberly S, DeGrado TR: Assessment of myocardial metabolic flexibility and work efficiency in human type 2 diabetes using 16-[18F]fluoro-4-thiapalmitate, a novel PET fatty acid tracer. Am J Physiol Endocrinol Metab 2016;310:E452-460
28. Aasum E, Hafstad AD, Severson DL, Larsen TS: Age-dependent changes in metabolism, contractile function, and ischemic sensitivity in hearts from db/db mice. Diabetes 2003;52:434-441
29. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, Cooksey RC, Litwin SE, Abel ED: Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology 2005;146:5341-5349
30. Pulinilkunnil T, Kienesberger PC, Nagendran J, Waller TJ, Young ME, Kershaw EE, Korbutt G, Haemmerle G, Zechner R, Dyck JR: Myocardial adipose triglyceride lipase overexpression protects diabetic mice from the development of lipotoxic cardiomyopathy. Diabetes 2013;62:1464-1477
31. Sousa Fialho MDL, Purnama U, Dennis K, Montes Aparicio CN, Castro-Guarda M, Massourides E, Tyler DJ, Carr CA, Heather LC: Activation of HIF1alpha Rescues the Hypoxic

555 Response and Reverses Metabolic Dysfunction in the Diabetic Heart. Diabetes 2021;70:2518-
556 2531
557 32. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, Romijn JA, de Roos
558 A, Lamb HJ: Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2
559 diabetes mellitus. J Am Coll Cardiol 2008;52:1793-1799
560 33. Luiken JJ, Dyck DJ, Han XX, Tandon NN, Arumugam Y, Glatz JF, Bonen A: Insulin induces
561 the translocation of the fatty acid transporter FAT/CD36 to the plasma membrane. Am J Physiol
562 Endocrinol Metab 2002;282:E491-495
563 34. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X, Gross RW, Kozak
564 R, Lopaschuk GD, Kelly DP: The cardiac phenotype induced by PPARalpha overexpression
565 mimics that caused by diabetes mellitus. J Clin Invest 2002;109:121-130
566 35. Shipp JC, Opie LH, Challoner D: Fatty Acid and Glucose Metabolism in the Perfused Heart.
567 Nature 1961;189:1018-1019
568 36. Randle PJ, Garland PB, Hales CN, Newsholme EA: The glucose fatty-acid cycle. Its role in
569 insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785-789
570 37. Lautamaki R, Airaksinen KE, Seppanen M, Toikka J, Luotolahti M, Ball E, Borra R, Harkonen
571 R, Iozzo P, Stewart M, Knuuti J, Nuutila P: Rosiglitazone improves myocardial glucose uptake in
572 patients with type 2 diabetes and coronary artery disease: a 16-week randomized, double-blind,
573 placebo-controlled study. Diabetes 2005;54:2787-2794
574 38. McGill JB, Peterson LR, Herrero P, Saeed IM, Recklein C, Coggan AR, Demoss AJ,
575 Schechtman KB, Dence CS, Gropler RJ: Potentiation of abnormalities in myocardial metabolism
576 with the development of diabetes in women with obesity and insulin resistance. J Nucl Cardiol
577 2011;18:421-429; quiz 432-423
578 39. Rijzewijk LJ, van der Meer RW, Lamb HJ, de Jong HW, Lubberink M, Romijn JA, Bax JJ, de
579 Roos A, Twisk JW, Heine RJ, Lammertsma AA, Smit JW, Diamant M: Altered myocardial
580 substrate metabolism and decreased diastolic function in nonischemic human diabetic
581 cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance
582 imaging. J Am Coll Cardiol 2009;54:1524-1532
583 40. Voipio-Pulkki LM, Nuutila P, Knuuti MJ, Ruotsalainen U, Haaparanta M, Teras M, Wegelius
584 U, Koivisto VA: Heart and skeletal muscle glucose disposal in type 2 diabetic patients as
585 determined by positron emission tomography. J Nucl Med 1993;34:2064-2067
586 41. Rider OJ, Apps A, Miller J, Lau JYC, Lewis AJM, Peterzan MA, Dodd MS, Lau AZ, Trumper
587 C, Gallagher FA, Grist JT, Brindle KM, Neubauer S, Tyler DJ: Noninvasive In Vivo Assessment
588 of Cardiac Metabolism in the Healthy and Diabetic Human Heart Using Hyperpolarized (13)C
589 MRI. Circ Res 2020;126:725-736
590 42. Almutairi M, Gopal K, Greenwell AA, Young A, Gill R, Aburasayn H, Al Batran R, Chahade JJ,
591 Gandhi M, Eaton F, Mailloux RJ, Ussher JR: The GLP-1 Receptor Agonist Liraglutide Increases
592 Myocardial Glucose Oxidation Rates via Indirect Mechanisms and Mitigates Experimental
593 Diabetic Cardiomyopathy. Can J Cardiol 2021;37:140-150
594 43. Mansor LS, Mehta K, Aksentijevic D, Carr CA, Lund T, Cole MA, Le Page L, Sousa Fialho
595 Mda L, Shattock MJ, Aasum E, Clarke K, Tyler DJ, Heather LC: Increased oxidative metabolism
596 following hypoxia in the type 2 diabetic heart, despite normal hypoxia signalling and metabolic
597 adaptation. J Physiol 2016;594:307-320
598 44. Le Page LM, Rider OJ, Lewis AJ, Ball V, Clarke K, Johansson E, Carr CA, Heather LC, Tyler
599 DJ: Increasing Pyruvate Dehydrogenase Flux as a Treatment for Diabetic Cardiomyopathy: A
600 Combined 13C Hyperpolarized Magnetic Resonance and Echocardiography Study. Diabetes
601 2015;64:2735-2743
602 45. Schroeder MA, Cochlin LE, Heather LC, Clarke K, Radda GK, Tyler DJ: In vivo assessment
603 of pyruvate dehydrogenase flux in the heart using hyperpolarized carbon-13 magnetic resonance.
604 Proc Natl Acad Sci U S A 2008;105:12051-12056

605 46. Wright JJ, Kim J, Buchanan J, Boudina S, Sena S, Bakirtzi K, Ilkun O, Theobald HA, Cooksey
606 RC, Kandror KV, Abel ED: Mechanisms for increased myocardial fatty acid utilization following
607 short-term high-fat feeding. Cardiovasc Res 2009;82:351-360
608 47. Mansor LS, Sousa Fialho MDL, Yea G, Coumans WA, West JA, Kerr M, Carr CA, Luiken J,
609 Glatz JFC, Evans RD, Griffin JL, Tyler DJ, Clarke K, Heather LC: Inhibition of sarcolemmal
610 FAT/CD36 by sulfo-N-succinimidyl oleate rapidly corrects metabolism and restores function in the
611 diabetic heart following hypoxia/reoxygenation. Cardiovasc Res 2017;113:737-748
612 48. Hopkins TA, Sugden MC, Holness MJ, Kozak R, Dyck JR, Lopaschuk GD: Control of cardiac
613 pyruvate dehydrogenase activity in peroxisome proliferator-activated receptor-alpha transgenic
614 mice. Am J Physiol Heart Circ Physiol 2003;285:H270-276
615 49. Cividini F, Scott BT, Suarez J, Casteel DE, Heinz S, Dai A, Diemer T, Suarez JA, Benner CW,
616 Ghassemian M, Dillmann WH: Ncor2/PPARalpha-Dependent Upregulation of MCUb in the Type
617 2 Diabetic Heart Impacts Cardiac Metabolic Flexibility and Function. Diabetes 2021;70:665-679
618 50. Battiprolu PK, Hojayev B, Jiang N, Wang ZV, Luo X, Iglewski M, Shelton JM, Gerard RD,
619 Rothermel BA, Gillette TG, Lavandero S, Hill JA: Metabolic stress-induced activation of FoxO1
620 triggers diabetic cardiomyopathy in mice. J Clin Invest 2012;122:1109-1118
621 51. Gopal K, Al Batran R, Altamimi TR, Greenwell AA, Saed CT, Tabatabaei Dakhili SA, Dimaano
622 MTE, Zhang Y, Eaton F, Sutendra G, Ussher JR: FoxO1 inhibition alleviates type 2 diabetes-
623 related diastolic dysfunction by increasing myocardial pyruvate dehydrogenase activity. Cell Rep
624 2021;35:108935
625 52. Gopal K, Saleme B, Al Batran R, Aburasayn H, Eshreif A, Ho KL, Ma WK, Almutairi M, Eaton
626 F, Gandhi M, Park EA, Sutendra G, Ussher JR: FoxO1 regulates myocardial glucose oxidation
627 rates via transcriptional control of pyruvate dehydrogenase kinase 4 expression. Am J Physiol
628 Heart Circ Physiol 2017;313:H479-H490
629 53. Lopaschuk GD, Ussher JR: Evolving Concepts of Myocardial Energy Metabolism: More Than
630 Just Fats and Carbohydrates. Circ Res 2016;119:1173-1176
631 54. Ogawa T, Kouzu H, Osanami A, Tatekoshi Y, Sato T, Kuno A, Fujita Y, Ino S, Shimizu M,
632 Toda Y, Ohwada W, Yano T, Tanno M, Miki T, Miura T: Downregulation of extramitochondrial
633 BCKDH and its uncoupling from AMP deaminase in type 2 diabetic OLETF rat hearts. Physiol
634 Rep 2023;11:e15608
635 55. Brahma MK, Ha CM, Pepin ME, Mia S, Sun Z, Chatham JC, Habegger KM, Abel ED, Paterson
636 AJ, Young ME, Wende AR: Increased Glucose Availability Attenuates Myocardial Ketone Body
637 Utilization. J Am Heart Assoc 2020;9:e013039
638 56. Abdurrachim D, Woo CC, Teo XQ, Chan WX, Radda GK, Lee PTH: A new hyperpolarized
639 (13)C ketone body probe reveals an increase in acetoacetate utilization in the diabetic rat heart.
640 Sci Rep 2019;9:5532
641 57. Al Batran R, Gopal K, Capozzi ME, Chahade JJ, Saleme B, Tabatabaei-Dakhili SA, Greenwell
642 AA, Niu J, Almutairi M, Byrne NJ, Masson G, Kim R, Eaton F, Mulvihill EE, Garneau L, Masters
643 AR, Desta Z, Velazquez-Martinez CA, Aguer C, Crawford PA, Sutendra G, Campbell JE, Dyck
644 JRB, Ussher JR: Pimozide Alleviates Hyperglycemia in Diet-Induced Obesity by Inhibiting
645 Skeletal Muscle Ketone Oxidation. Cell Metab 2020;31:909-919 e908
646 58. Levelt E, Rodgers CT, Clarke WT, Mahmod M, Ariga R, Francis JM, Liu A, Wijesurendra RS,
647 Dass S, Sabharwal N, Robson MD, Holloway CJ, Rider OJ, Clarke K, Karamitsos TD, Neubauer
648 S: Cardiac energetics, oxygenation, and perfusion during increased workload in patients with type
649 2 diabetes mellitus. Eur Heart J 2016;37:3461-3469
650 59. Scheuermann-Freestone M, Madsen PL, Manners D, Blamire AM, Buckingham RE, Styles P,
651 Radda GK, Neubauer S, Clarke K: Abnormal cardiac and skeletal muscle energy metabolism in
652 patients with type 2 diabetes. Circulation 2003;107:3040-3046
653 60. Abdurrachim D, Nabben M, Hoerr V, Kuhlmann MT, Bovenkamp P, Ciapaite J, Geraets IME,
654 Coumans W, Luiken J, Glatz JFC, Schafers M, Nicolay K, Faber C, Hermann S, Prompers JJ:
655 Diabetic db/db mice do not develop heart failure upon pressure overload: a longitudinal in vivo

PET, MRI, and MRS study on cardiac metabolic, structural, and functional adaptations. Cardiovasc Res 2017;113:1148-1160
61. Kerr M, Miller JJ, Thapa D, Stiewe S, Timm KN, Aparicio CNM, Scott I, Tyler DJ, Heather LC: Rescue of myocardial energetic dysfunction in diabetes through the correction of mitochondrial hyperacetylation by honokiol. JCI Insight 2020;5
62. Boudina S, Sena S, Theobald H, Sheng X, Wright JJ, Hu XX, Aziz S, Johnson JI, Bugger H, Zaha VG, Abel ED: Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. Diabetes 2007;56:2457-2466
63. Tong M, Mukai R, Mareedu S, Zhai P, Oka SI, Huang CY, Hsu CP, Yousufzai FAK, Fritzky L, Mizushima W, Babu GJ, Sadoshima J: Distinct Roles of DRP1 in Conventional and Alternative Mitophagy in Obesity Cardiomyopathy. Circ Res 2023;133:6-21
64. Berthiaume JM, Kurdys JG, Muntean DM, Rosca MG: Mitochondrial NAD(+)/NADH Redox State and Diabetic Cardiomyopathy. Antioxid Redox Signal 2019;30:375-398
65. Spallotta F, Cencioni C, Atlante S, Garella D, Cocco M, Mori M, Mastrocola R, Kuenne C, Guenther S, Nanni S, Azzimato V, Zukunft S, Kornberger A, Surun D, Schnutgen F, von Melchner H, Di Stilo A, Aragno M, Braspenning M, van Criekinge W, De Blasio MJ, Ritchie RH, Zaccagnini G, Martelli F, Farsetti A, Fleming I, Braun T, Beiras-Fernandez A, Botta B, Collino M, Bertinaria M, Zeiher AM, Gaetano C: Stable Oxidative Cytosine Modifications Accumulate in Cardiac Mesenchymal Cells From Type2 Diabetes Patients: Rescue by alpha-Ketoglutarate and TET-TDG Functional Reactivation. Circ Res 2018;122:31-46
66. Kronlage M, Dewenter M, Grosso J, Fleming T, Oehl U, Lehmann LH, Falcao-Pires I, Leite-Moreira AF, Volk N, Grone HJ, Muller OJ, Sickmann A, Katus HA, Backs J: O-GlcNAcylation of Histone Deacetylase 4 Protects the Diabetic Heart From Failure. Circulation 2019;140:580-594
67. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez-Neut M, Ding J, Czyz D, Hu R, Ye Z, He M, Zheng YG, Shuman HA, Dai L, Ren B, Roeder RG, Becker L, Zhao Y: Metabolic regulation of gene expression by histone lactylation. Nature 2019;574:575-580
68. Maschari D, Saxena G, Law TD, Walsh E, Campbell MC, Consitt LA: Lactate-induced lactylation in skeletal muscle is associated with insulin resistance in humans. Front Physiol 2022;13:951390
69. De Loof M, Renguet E, Ginion A, Bouzin C, Horman S, Beauloye C, Bertrand L, Bultot L: Enhanced protein acetylation initiates fatty acid-mediated inhibition of cardiac glucose transport. Am J Physiol Heart Circ Physiol 2023;324:H305-H317
70. Renguet E, De Loof M, Fourny N, Ginion A, Bouzin C, Pous C, Horman S, Beauloye C, Bultot L, Bertrand L: alpha-Tubulin acetylation on lysine 40 controls cardiac glucose uptake. Am J Physiol Heart Circ Physiol 2022;322:H1032-H1043
71. Alrob OA, Sankaralingam S, Ma C, Wagg CS, Fillmore N, Jaswal JS, Sack MN, Lehner R, Gupta MP, Michelakis ED, Padwal RS, Johnstone DE, Sharma AM, Lopaschuk GD: Obesity-induced lysine acetylation increases cardiac fatty acid oxidation and impairs insulin signalling. Cardiovasc Res 2014;103:485-497
72. Fulop N, Mason MM, Dutta K, Wang P, Davidoff AJ, Marchase RB, Chatham JC: Impact of Type 2 diabetes and aging on cardiomyocyte function and O-linked N-acetylglucosamine levels in the heart. Am J Physiol Cell Physiol 2007;292:C1370-1378
73. Prakoso D, Lim SY, Erickson JR, Wallace RS, Lees JG, Tate M, Kiriazis H, Donner DG, Henstridge DC, Davey JR, Qian H, Deo M, Parry LJ, Davidoff AJ, Gregorevic P, Chatham JC, De Blasio MJ, Ritchie RH: Fine-tuning the cardiac O-GlcNAcylation regulatory enzymes governs the functional and structural phenotype of the diabetic heart. Cardiovasc Res 2022;118:212-225
74. Dodd MS, Sousa Fialho MDL, Montes Aparicio CN, Kerr M, Timm KN, Griffin JL, Luiken J, Glatz JFC, Tyler DJ, Heather LC: Fatty Acids Prevent Hypoxia-Inducible Factor-1alpha Signaling Through Decreased Succinate in Diabetes. JACC Basic Transl Sci 2018;3:485-498

75. Kim HS, Woo JS, Joo HJ, Moon WK: Cardiac transcription factor Nkx2.5 is downregulated under excessive O-GlcNAcylation condition. PLoS One 2012;7:e38053
76. Yang J, Sambandam N, Han X, Gross RW, Courtois M, Kovacs A, Febbraio M, Finck BN, Kelly DP: CD36 deficiency rescues lipotoxic cardiomyopathy. Circ Res 2007;100:1208-1217
77. Ussher JR, Fillmore N, Keung W, Mori J, Beker DL, Wagg CS, Jaswal JS, Lopaschuk GD: Trimetazidine therapy prevents obesity-induced cardiomyopathy in mice. Can J Cardiol 2014;30:940-944
78. Zhao P, Zhang J, Yin XG, Maharaj P, Narraindoo S, Cui LQ, Tang YS: The effect of trimetazidine on cardiac function in diabetic patients with idiopathic dilated cardiomyopathy. Life Sci 2013;92:633-638
79. Yan D, Cai Y, Luo J, Liu J, Li X, Ying F, Xie X, Xu A, Ma X, Xia Z: FOXO1 contributes to diabetic cardiomyopathy via inducing imbalanced oxidative metabolism in type 1 diabetes. J Cell Mol Med 2020;
80. Gopal K, Karwi QG, Tabatabaei Dakhili SA, Wagg CS, Zhang L, Sun Q, Saed CT, Panidarapu S, Perfetti R, Ramasamy R, Ussher JR, Lopaschuk GD: Aldose reductase inhibition alleviates diabetic cardiomyopathy and is associated with a decrease in myocardial fatty acid oxidation. Cardiovasc Diabetol 2023;22:73
81. Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, Hovingh GK, Kitzman DW, Lindegaard ML, Moller DV, Shah SJ, Treppendahl MB, Verma S, Abhayaratna W, Ahmed FZ, Chopra V, Ezekowitz J, Fu M, Ito H, Lelonek M, Melenovsky V, Merkely B, Nunez J, Perna E, Schou M, Senni M, Sharma K, Van der Meer P, von Lewinski D, Wolf D, Petrie MC, Committees ST-HT, Investigators: Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med 2023;389:1069-1084
82. Wang S, Schianchi F, Neumann D, Wong LY, Sun A, van Nieuwenhoven FA, Zeegers MP, Strzelecka A, Col U, Glatz JFC, Nabben M, Luiken J: Specific amino acid supplementation rescues the heart from lipid overload-induced insulin resistance and contractile dysfunction by targeting the endosomal mTOR-v-ATPase axis. Mol Metab 2021;53:101293
83. Thai PN, Miller CV, King MT, Schaefer S, Veech RL, Chiamvimonvat N, Bers DM, Dedkova EN: Ketone Ester D-beta-Hydroxybutyrate-(R)-1,3 Butanediol Prevents Decline in Cardiac Function in Type 2 Diabetic Mice. J Am Heart Assoc 2021;10:e020729
84. Sun X, Han F, Lu Q, Li X, Ren D, Zhang J, Han Y, Xiang YK, Li J: Empagliflozin Ameliorates Obesity-Related Cardiac Dysfunction by Regulating Sestrin2-Mediated AMPK-mTOR Signaling and Redox Homeostasis in High-Fat Diet-Induced Obese Mice. Diabetes 2020;69:1292-1305
85. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, Dyck JE, Uddin GM, Oudit GY, Mayoux E, Lehrke M, Marx N, Lopaschuk GD: Empagliflozin Increases Cardiac Energy Production in Diabetes: Novel Translational Insights Into the Heart Failure Benefits of SGLT2 Inhibitors. JACC Basic Transl Sci 2018;3:575-587
86. Pouleur H: Diastolic dysfunction and myocardial energetics. Eur Heart J 1990;11 Suppl C:30-34
87. Burrage MK, Hundertmark M, Valkovic L, Watson WD, Rayner J, Sabharwal N, Ferreira VM, Neubauer S, Miller JJ, Rider OJ, Lewis AJM: Energetic Basis for Exercise-Induced Pulmonary Congestion in Heart Failure With Preserved Ejection Fraction. Circulation 2021;144:1664-1678
88. Ussher JR, Greenwell AA, Nguyen MA, Mulvihill EE: Cardiovascular Effects of Incretin-Based Therapies: Integrating Mechanisms With Cardiovascular Outcome Trials. Diabetes 2022;71:173-183
89. Wright AK, Carr MJ, Kontopantelis E, Leelarathna L, Thabit H, Emsley R, Buchan I, Mamas MA, van Staa TP, Sattar N, Ashcroft DM, Rutter MK: Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes. Diabetes Care 2022;45:909-918

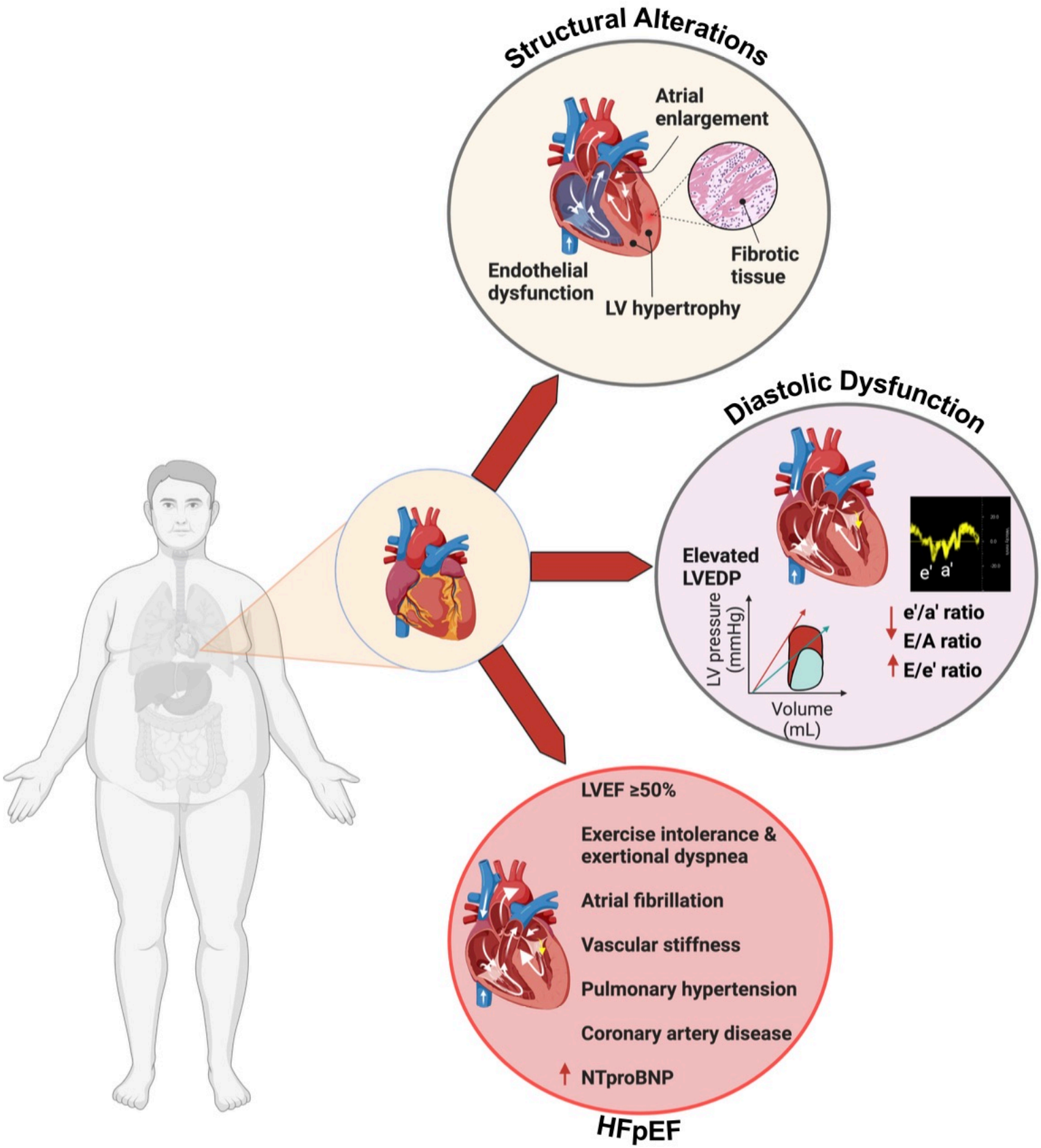
Figure Legends

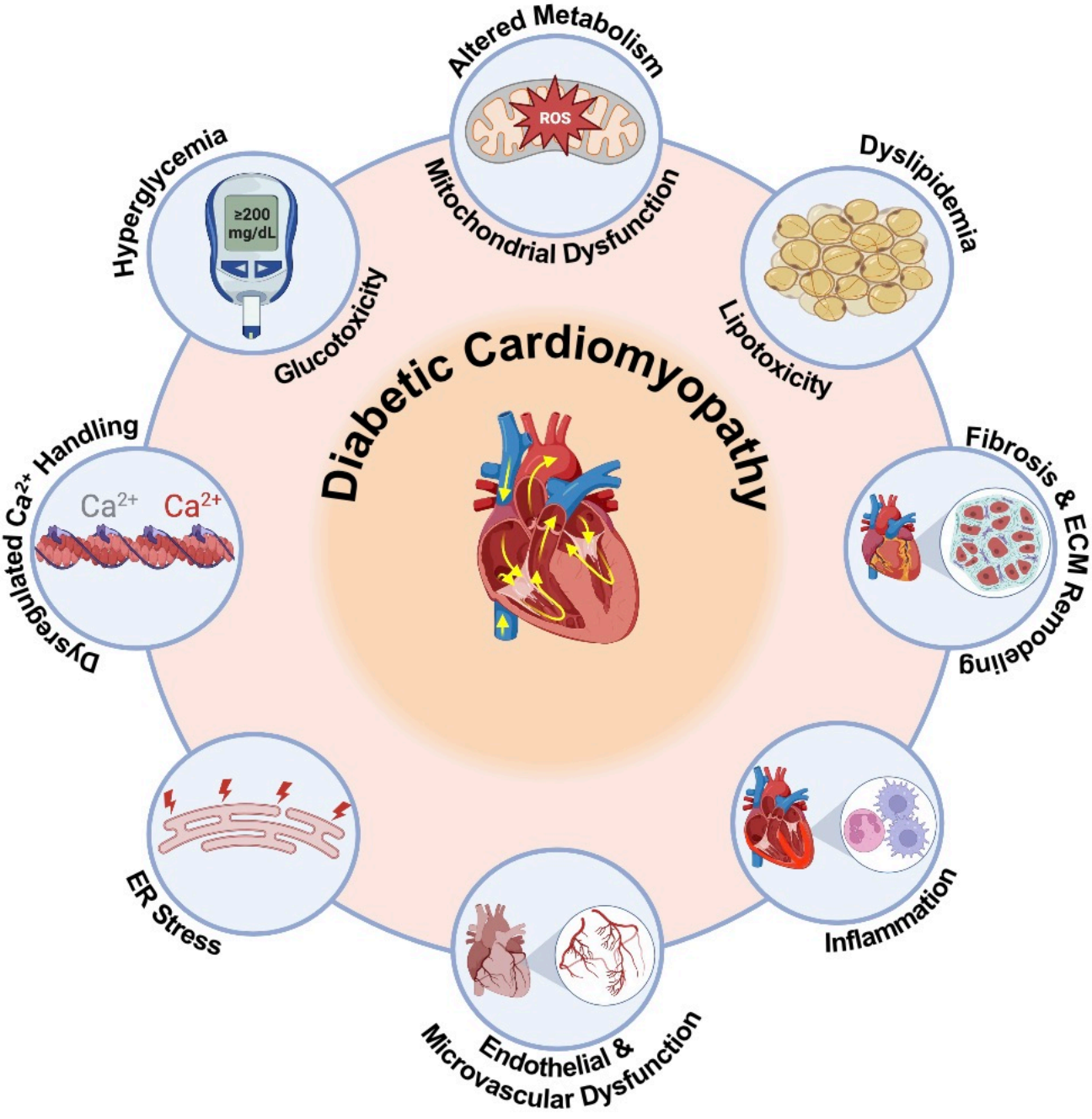
Figure 1. Clinical features of diabetic cardiomyopathy. People with DbCM often exhibit cardiac structural alterations, diastolic dysfunction, or can even present with HFpEF. Nonetheless, there is no clear distinction explaining which cardiac phenotype an individual will present with, and an individual may present with several features of these various phenotypes that characterize DbCM. DbCM; diabetic cardiomyopathy, e'/a'; ratio of myocardial tissue velocity during the early (e') and late (a') phase of diastole, E/A; ratio of peak blood flow velocity during the early (E) and late (A) phase of diastole, HFpEF; heart failure with preserved ejection fraction. LV; Left ventricular, LVEDP; LV end-diastolic pressure, NTproBNP; BNP fragment of natriuretic peptide.

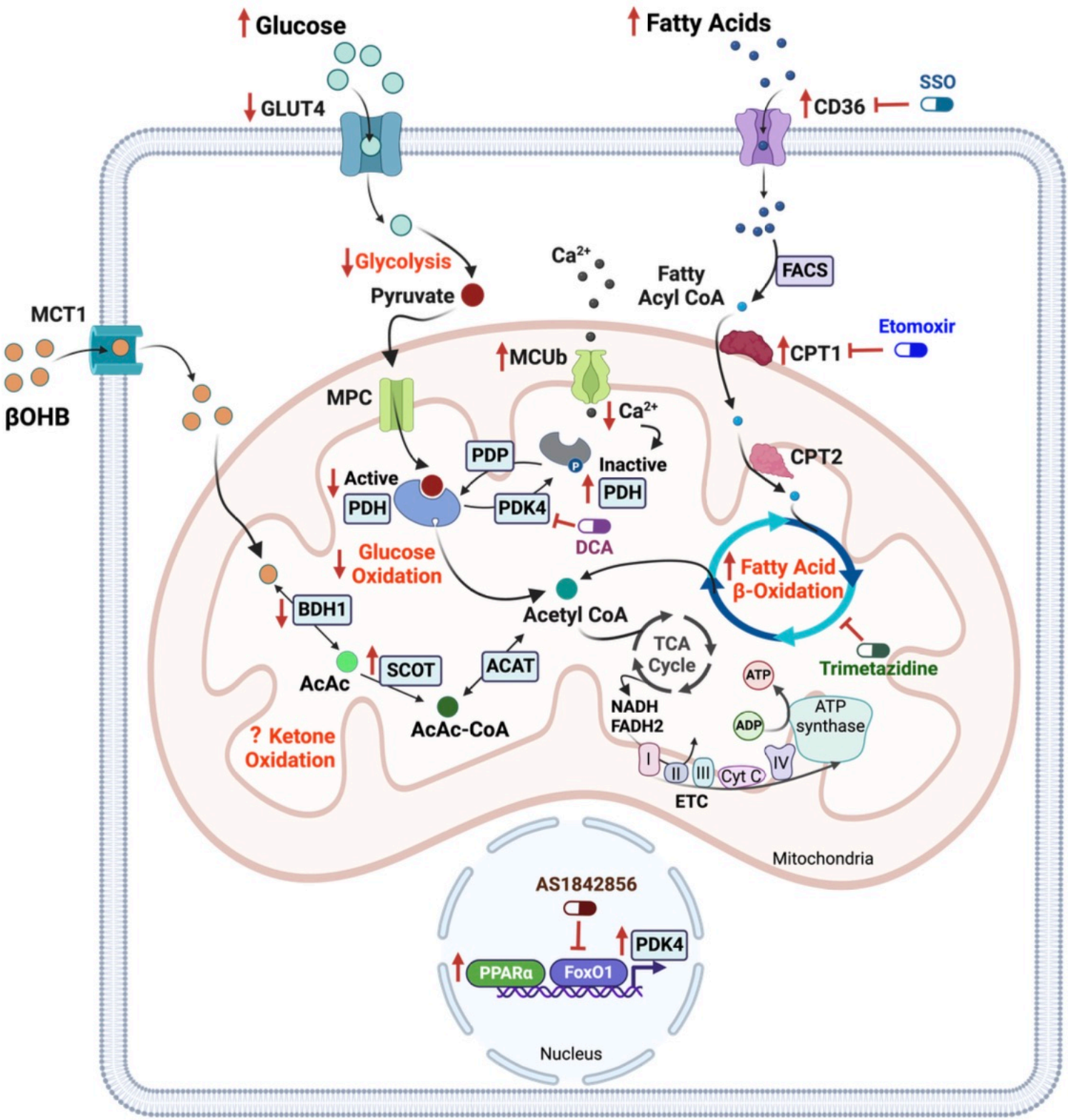
Figure 2. Key mediators of diabetic cardiomyopathy. Schematic representing several key mediators proposed to contribute to the myocardial pathology present in people with DbCM. DbCM; diabetic cardiomyopathy, ECM; Extracellular matrix, ER; endoplasmic reticulum, ROS; reactive oxygen species.

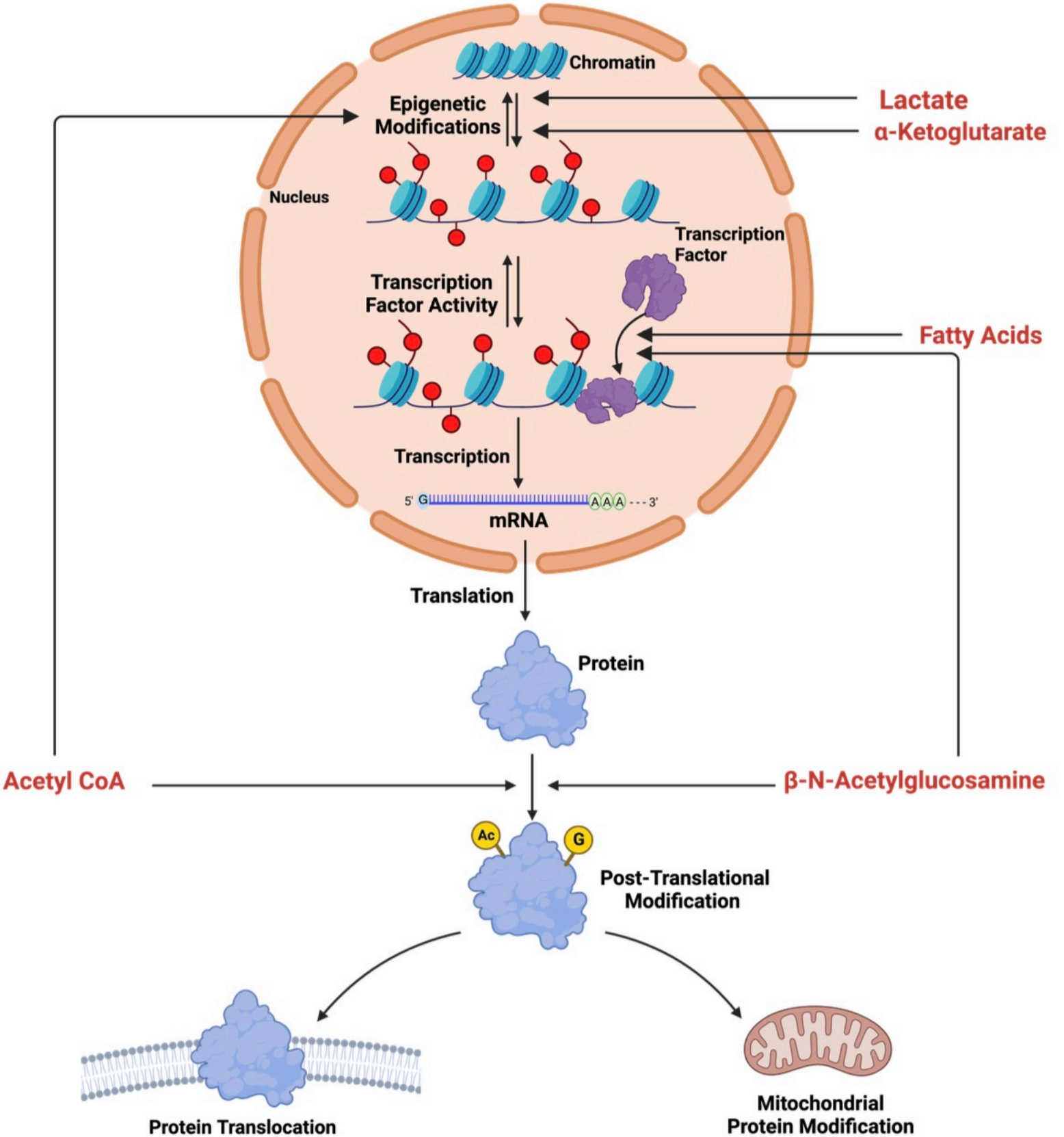
Figure 3. Perturbations in cardiac substrate metabolism in diabetic cardiomyopathy. Illustration depicts the primary perturbations in cardiac substrate metabolism reported in preclinical and clinical studies of DbCM, as well as pharmacological agents that can target these perturbations and the enzymes they modify. AcAc; acetoacetate, ACAT; acetoacetyl CoA thiolase, BDH1; β-hydroxybutyrate dehydrogenase 1, βOHB; β-hydroxybutyrate, CD36; cluster of differentiation 36, CPT; carnitine palmitoyltransferase, DbCM; diabetic cardiomyopathy, ETC; electron transport chain, FACS; fatty acyl CoA synthetase, FoxO1; forkhead box protein O1, GLUT4; glucose transporter 4, MCT1; monocarboxylate transporter 1, MCUb; mitochondrial calcium uniporter subunit b, MPC; mitochondrial pyruvate carrier, PDH; pyruvate dehydrogenase, PDK4; PDH kinase 4, PDP; PDH phosphatase, PPARα; peroxisome proliferator-activated receptor alpha, SCOT; succinyl-CoA:3-ketoacid CoA transferase, TCA; tricarboxylic acid.

Figure 4. Key features of metabolites beyond the traditional role as fuel sources for ATP production. Illustration depicts several key roles by which metabolic intermediates (i.e. acetyl CoA, lactate) can modify cellular protein function by regulating epigenetics, gene transcription, post-translational modifications, and trafficking.


Structural Alterations
Atrial enlargement
Fibrotic tissue
Endothelial dysfunction
LV hypertrophy
Diastolic Dysfunction
Elevated LVEDP
e' a'
LV pressure (mmHg)
Volume (mL)
e'/a' ratio
E/A ratio
E/e' ratio
LVEF ≥50%
Exercise intolerance & exertional dyspnea
Atrial fibrillation
Vascular stiffness
Pulmonary hypertension
Coronary artery disease
NTproBNP
HFpEF


Diabetic Cardiomyopathy
Altered Metabolism
ROS
Mitochondrial Dysfunction
Hyperglycemia
≥200 mg/dL
Glucotoxicity
Dyslipidemia
Lipotoxicity
Dysregulated Ca2+ Handling
Ca2+ Ca2+
Fibrosis & ECM Remodeling
ER Stress
Inflammation
Endothelial & Microvascular Dysfunction


Glucose
GLUT4
Fatty Acids
CD36
SSO
Glycolysis
Pyruvate
Ca2+
Fatty
Acyl CoA
FACS
MCT1
βOHB
MCUb
CPT1
Etomoxir
MPC
Ca2+
PDP
Inactive
Active
PDH
PDK4
DCA
CPT2
Glucose
Oxidation
Fatty Acid
β-Oxidation
BDH1
Acetyl CoA
TCA
Cycle
Trimetazidine
AcAc
SCOT
ACAT
AcAc-CoA
NADH
FADH2
ATP
ADP
ATP
synthase
? Ketone
Oxidation
I
II
III
Cyt C
IV
ETC
Mitochondria
AS1842856
PDK4
PPARα
FoxO1
Nucleus


Chromatin
Epigenetic Modifications
Lactate
α-Ketoglutarate
Nucleus
Transcription Factor
Transcription Factor Activity
Fatty Acids
Transcription
5' G
A A A
3'
mRNA
Translation
Protein
Acetyl CoA
β-N-Acetylglucosamine
Ac
G
Post-Translational Modification
Protein Translocation
Mitochondrial Protein Modification