Published in final edited form as:

Curr Opin Pharmacol. 2020 October ; 54: 82–90. doi:10.1016/j.coph.2020.08.015.

Disruption of energy utilization in diabetic cardiomyopathy; A mini review

Shinsuke Nirengi^{1,2}, Carmem Peres Valgas da Silva^{1,2}, Kristin I Stanford^{1,2}

¹Dorothy M. Davis Heart and Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA

²Department of Physiology and Cell Biology, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA

Abstract

Type 2 diabetes (T2D) substantially elevates the risk for heart failure, a major cause of death. In advanced T2D, energy metabolism in the heart is disrupted; glucose metabolism is decreased, fatty acids (FA) metabolism is enhanced to maintain ATP production, and cardiac function is impaired. This condition is termed diabetic cardiomyopathy (DCM). The exact cause of DCM is still unknown although altered metabolism is an important component. Although type 2 diabetes is characterized by insulin resistance, the traditional antidiabetic agents that improve insulin stimulation or sensitivity only partially improve DCM-induced cardiac dysfunction. Recently, sodium-glucose transporter-2 (SGLT2) inhibitors have been identified as potential pharmacological agents to treat DCM. This review highlights the molecular mechanisms underlying cardiac energy metabolism in DCM, and the potential effects of SGLT2 inhibitors.

Keywords

diabetic cardiomyopathy; substrate utilization; heart failure

Introduction

Type 2 diabetes (T2D) is increasing at alarming rates and its complications constitute a major worldwide problem [1]. T2D has many co-morbidities, including an increased risk of heart failure (HF), a major cause of death. The prevalence of HF in T2D patients is twice as high in men, and five times as high in women, compared with non-diabetic patients [2]. Diabetic cardiomyopathy (DCM) is characterized by cardiac hypertrophy (increased left

Corresponding author: Kristin I Stanford, Kristin.Stanford@osumc.edu; Tel.: +1-614-247-8287.

Author Contributions

S.N., C.P.V.S., and K.I.S. designed, wrote, and edited the manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interests Statement

There are no conflicts of interest

ventricular [LV] mass and wall thickness) accompanied by compromised systolic and diastolic function [3] independent of hypertension, valvular heart disease and coronary artery disease [4,5], and altered substrate utilization [6–10]. There are several mechanisms involved in the pathogenesis of DCM, including dysfunctional signaling and metabolism of the energy substrates in the heart [6, 7, 9–10]. Recent studies have focused on new therapeutic targets to correct the metabolic imbalance that occurs in the diabetic heart [11–13**]. In this review, we will describe the altered substrate metabolism in DCM and potential therapeutic targets, specifically the use of sodium-glucose transporter-2 (SGLT2) inhibitors.

Metabolism in the healthy heart.

The heart is the central organ of the circulatory system and is involved in the transport of oxygen and nutrients through the bloodstream and throughout the body. Due to a constant workload, the cardiac requirements for energy to fuel optimal function are immense [14]. The heart exhibits a high rate of ATP production and turnover, which is required to maintain continued cardiac contraction. At steady state, 90–95% of the ATP is supplied by the mitochondria through aerobic oxidative phosphorylation, whereas the remaining 5–10% is produced by the anaerobic glycolytic system [15].

The healthy heart uses a large amount of fatty acids (FA) (~70%) and glucose (~30%) as the principal fuels of energy providing substrates for ATP production. Myocardial ATP production is highly oxidative, as more than 90% of its energy comes from mitochondrial respiration [16]. Under normal physiological circumstances, the heart is metabolically flexible, and while glucose is not the predominant fuel for the heart at rest, the heart can switch substrate preference from FA to glucose in response to increased workload, changes in substrate supply and/or circulating hormone levels [19]. Myocardial glucose metabolism generates pyruvate, which is metabolized within the mitochondria to produce most of the carbohydrate-derived energy; meanwhile FA undergo β -oxidation. The remaining ATP is produced by the oxidation of small amounts of ketone bodies and certain amino acids [6,7,9]. In contrast to the healthy heart, the main metabolic characteristics of DCM are suppressed glucose metabolism and elevated FA metabolism in the heart. Alterations in the normal rates of glucose and FA availability and utilization impairs cardiac metabolism and plays a central role in DCM [9,17].

Glucose metabolism is altered in patients with DCM.

A hallmark of DCM is impaired cardiac glucose metabolism [18]. Derangements in cardiac glucose metabolism occur early in the deterioration of heart function in DCM [6,7,9]. Impaired glucose utilization in diabetic heart is mediated by reduced glucose uptake, reduced glycolytic activity, and reduced pyruvate oxidation [18].

Reduced insulin-dependent cardiac glucose uptake is an important characteristic of DCM [20]. The mechanism for reduced cardiac glucose uptake in DCM is attributed to impaired signaling of glucose transporter 4 (GLUT4) and GLUT1 [20]. Studies in rodents have shown decreased expression and translocation of GLUT4 in DCM hearts [25, 26*], concurrent with

reduced glucose uptake [20, 27]. The decrease in myocardial glucose uptake is related to impaired glucose oxidation and decreased ejection fraction in patients with T2D [28, 29*]. In the DCM hearts, the reduction in GLUT4 uptake and subsequent decrease in glucose utilization are in response to hyperglycemia [30], myocardial insulin resistance [31], and downregulation of the AMP-activated kinase (AMPK) [32, 33*], all of which represent potential therapeutic targets for DCM.

In addition to reduced glucose uptake, reduced glucose utilization and oxidation are major causes of the loss in metabolic flexibility, leading to myocardial dysfunction in DCM. In the healthy heart, after glucose enters the cardiomyocyte, it is rapidly phosphorylated to glucose-6-phosphate (G6P) by hexokinase (HK), then subsequently enters different metabolic pathways [19]. Most glucose enters the glycolytic pathway and is eventually broken down into pyruvate. Pyruvate is then decarboxylated to form acetyl-CoA via pyruvate dehydrogenase (PDH), a multienzyme complex located in mitochondrial matrix. In DCM, cardiac glycolysis and pyruvate oxidation are both impaired, as evidenced from animal models [21]. The mechanisms involved in the decreased glucose oxidation in the DCM also include the reduced expression and activity of important glucose oxidation enzymes including G6P and PDH [22]. As a consequence of the reduced myocardial glycolysis and glucose oxidation in DCM, there is an accumulation of glycolytic intermediates. These glycolytic intermediates are associated with increased reactive oxygen species (ROS) production [23], reduced calcium ATPase 2a (SERCA2a) expression in the sarcoplasmic reticulum [24] and increased Ca^{2+} accumulation, all of which contribute to cardiac dysfunction.

Another mechanism related to the accumulation of glucose intermediates in T2D hearts is chronic activation of the hexosamine biosynthetic pathway (HBP) [18, 21]. The HBP pathway is a major branch of the glycolytic pathway. Under conditions of hyperglycemia and reduced glucose oxidation, such as those seen with T2D, flux through the HBP increases, leading to O-GlcNAcylation (O-GlcNAc) [34]. O-GlcNAc is a post-translational modification via the addition of the O-GlcNAc sugar moiety to serine and threonine residues of nuclear, cytosolic and mitochondrial proteins, which competes with their phosphorylation [35]. In normal physiology, transient O-GlcNAc is associated with cardioprotection and cell survival under stressful conditions, such as myocardial infarction [36], but sustained O-GlcNAc activation is detrimental, leading to increased insulin resistance and glucose toxicity [37]. Recent studies suggest that aberrant cardiac O-GlcNAc signaling contributes to the adverse effects of cardiac glucose metabolism in DCM [37]. Sustained O-GlcNAc-induced protein modification is associated with cardiac impairments including mitochondrial dysfunction [34], cardiac hypertrophy [35], and cardiomyocyte contractile dysfunction [35, 37, 38]. One recent study suggested that the O-GlcNAcylation is an important factor for mitochondrial oxidative phosphorylation in DCM [39**]. This study showed that diabetic hearts with impaired glucose oxidation have a higher O-GlcNAcylation of many-electron transport-chain subunits and other mitochondrial proteins. This results in lower mitochondrial oxidative phosphorylation (State I- IV) and reduced cardiac function [39**]. Thus, impaired glucose oxidation in DCM may be contributing to cardiac dysfunction. Together, these studies indicate that reduced cardiac glucose uptake, mitochondrial pyruvate

oxidation and hyperglycemia with increased O-GlcNAc activation are involved in the impaired cardiac function seen in diabetic cardiomyopathy.

Patients with DCM have an increased dependency on FA metabolism.

Increases in FA availability and utilization contribute to impaired cardiac metabolism and in DCM [40]. Patients with DCM have elevated plasma glucose and FA, however the insulin resistance that occurs with T2D results in reduced glucose uptake and oxidation in the diabetic heart [9, 17, 40]. This causes increased reliance on FA oxidation to maintain ATP production [6–9, 40], which reduces cardiac efficiency by increasing myocardial oxygen consumption [41]. This increased reliance on FA and impaired metabolic flexibility over time contributes to myocardial dysfunction in DCM [9].

There are several mechanisms through which FA overload contribute to the development of DCM. The systemic insulin resistance in T2D leads to increased lipolysis in white adipose tissue, resulting in elevated levels of FA into the circulation [42]. Chronic increases in both insulin and circulating FA are accompanied by increased expression and activation of proteins involved in FA uptake in the heart, such as the fatty acid translocase CD36 and fatty acid binding proteins (FABP) [7, 40]. In addition, overexpression of other proteins involved with FA uptake such as long-chain acyl-CoA synthetase and lipoprotein lipase contribute to excess accumulation of triglycerides and lipotoxicity in DCM [40, 43].

FA are endogenous ligands of the transcription factor peroxisome proliferator-activated receptors (PPARs) family (PPAR- α , PPAR β /PPAR- δ , and PPAR- γ) [11, 40, 44]. The PPAR isoforms differ in distribution, function, and ligand specificity. Studies in rodents have shown that persistent FA accumulation increases PPAR α and PPAR γ expression in T2D hearts [44, 45, 95]. Enhanced expression of PPAR α increases the expression of proteins involved in cellular fatty acid esterification (*GPAT*, glycerol-3-phosphate acyl-transferase; and *DGAT*, diacylglycerol acyl-transferase) and oxidation (*CPT-1*, Carnitine palmitoyltransferase-1; MCD, malonyl-CoA decarboxylase), with a concomitant reduction in the expression of genes involved in glucose utilization (*GLUT4* and PFK) [44–46]. PPAR- γ plays a crucial role in regulating lipid storage and adipogenesis. While the abundance of PPAR γ in the healthy heart is very low, studies in rodents have demonstrated that PPAR γ overexpression in diabetic hearts contributes to increased lipid accumulation with compromised cardiac function [47, 48]. These data suggest that PPARs play an important role in the metabolic reprogramming in diabetic hearts, contributing to increased cardiac lipid accumulation and altered glucose metabolism in DCM [12, 46, 49].

Mitochondrial dysfunction and impaired energy production are also observed in DCM [40]. In DCM hearts, β -oxidation is increased but cannot adequately metabolize the increased demand for FA. This results in reduced cardiomyocyte efficiency [41] and accumulation of intracellular lipids [10, 50]. The accumulation of intracellular lipids compromises the mitochondrial fatty acid β -oxidation and the respiratory chain, resulting in mitochondrial dysfunction, accumulation of ROS and toxic lipid metabolites, such as ceramides, diacylglycerols, long-chain acyl-CoAs, and acylcarnitines [51, 52]. Increased accumulation of ROS and lipotoxicity impairs cardiac insulin signaling, induces damage to the

cardiomyocytes, and modifies structural proteins, resulting in reduced autophagy and enhanced cell death [51–53]. Together, these effects promote a progressive proinflammatory and profibrotic response [10, 51, 54], contributing to the cardiac pathological hypertrophy and diastolic dysfunction in DCM [55**–57]. Thus, the impaired FA metabolism in the heart can directly contribute to the cardiac dysfunction observed in DCM (Fig 1).

Ketone bodies as an alternative energy metabolism in the heart

Glucose and FA are the major energy substrates for the healthy heart [7, 8, 10] while ketone bodies provide only a modest contribution to cardiac energy metabolism [58, 59]. In relation to oxygen consumption, ketone bodies are the most efficient substrate for ATP production and thus are an important fuel source under conditions of disrupted energy metabolism, such as advanced DCM [60]. Most ketone bodies, including β -hydroxybutyric acid (β -OHB), are produced by the metabolism of FA in the liver and converted from acetoacetate (AcAc) by β -hydroxybutyrate dehydrogenase 1 (BDH1) and then released by solute carrier 16A (SLC16A) [61]. FA mobilized from adipose tissue are converted to acetyl-CoA and undergo β -oxidation in the liver, where they are converted to HMG-CoA by the mitochondrial enzyme hydroxymethyl glutaryl (HMG)-CoA synthase 2, and β -OHB is produced through acetoacetic acid metabolism [60]. The β -OHB is taken up into heart cells through monocarboxylate transporter (MCT) 1,2, then converted to acetoacetyl-CoA by 3-oxoacid CoA-transferase1 and used for ATP production [58] (Fig 2).

The circulating levels of ketone bodies are increased with heart failure and DCM, due to increased cardiac FA overload [41, 62]. In uncontrolled diabetes, insulin deficiency promotes ketone body formation in liver [63]. It has also been shown that serum ketone concentrations and genes related to ketone oxidation were increased in the heart of HF patients, while myocardial ketone levels were decreased, suggesting that ketone body utilization in the myocardium is increased in HF patients [60]. The increase in ketone bodies may improve glucose and FA metabolism, [64] and the increase in glucose availability may attenuate utilization of myocardial ketone bodies [65]. Interestingly, recent studies have shown that ketone bodies may have a protective effect in HF, likely by reducing inflammation and maintaining energy homeostasis [66, 67]. A recent study showed that β -OHB perfusion increased energy production in the heart in mice with aortic constriction, without improving ejection fraction [68]. These data indicate that increasing ketone utilization is a potential therapeutic to improve energy metabolism and, could potentially improve cardiac function in the hearts of patients with DCM.

The effect of ketone oxidation in cardiac metabolism in DCM, however, is not clear. It has been postulated that β -OHB is easily oxidized by the heart in preference to glucose and FA, and that ketones improves both cardiac function and mechanical efficiency in the failing heart [69]. However, it is not clear if the increase in ketone oxidation in DCM is beneficial or harmful. The increase in ketone body oxidation likely creates a fuel supply for oxidative metabolism, but it may also have a detrimental effect on mitochondrial protein acetylation, thus impairing cardiac energetics [70] and decreasing mitochondrial oxidative phosphorylation [71]. It has also been proposed that ketones can act as insulin mimetics, compensating for defects in mitochondrial function associated with insulin resistance [72];

however increased acetyl-CoA production from ketones can decrease insulin-stimulated glucose oxidation [72]. In addition, increased β -OHB oxidation decreases histone deacetylase (HDAC) inhibitor which can inhibit hypertrophic transcription [73], thus decreasing HDAC activity and decreasing hypertrophic signaling. Thus, while ketone bodies are increased in DCM, it has not yet been determined whether this is beneficial or detrimental response [69], and if it is a potential therapeutic target.

SGLT2 inhibitors improve cardiac metabolism in DCM.

SGLT2 inhibitors such as empagliflozin and sotagliflozin (a SGLT1/SGLT2 dual inhibitor) are the newest class of oral hypoglycemic agents approved by the Food and Drug Administration [74] and commercially available for T2D treatment. SGLT2 inhibitors have a unique antidiabetic mechanism that inhibits renal tubular glucose reabsorption, thereby reducing the level of blood glucose [75]. The SGLTs are transporters involved in glucose reabsorption and are mainly expressed in the intestines (SGLT1) and kidneys (SGLT2). SGLT1 can also be found in the heart sarcolemma, colocalized with GLUT1, a cardiac glucose transporter [76], while SGLT2 is not expressed in the heart [74]. SGLT1 and SGLT2 are involved in glucose reabsorption and up-regulated in patients with type 2 diabetes. Importantly, current clinical studies of SGLT2 inhibitors have identified a significant protective effects for this compound in DCM patients, including reduced risk of death from cardiovascular disease and reduced rates of hospitalization from heart failure [77, 78]; however the mechanisms for this improvement are still unknown. This beneficial effect is unlikely to be explained by improved glycemic control, since glycemic control only partially improves cardiac dysfunction [79–81]. In fact, a recent clinical study showed that only a small difference in HbA1c was observed between SGLT2 inhibitors group and placebo group after 206 weeks of intervention [82]. To date, numerous studies have showed SGLT2 inhibitors have favorable effects including improved SGLT1 expression in the heart, sympathetic nervous system function, blood pressure, arterial stiffness, insulin sensitivity, body weight (visceral adiposity), inflammation, oxidative stress and Na⁺/H⁺ exchanger activity [77, 83–85]. These effects are proposed pathways by which SGLT2 inhibitors protect against heart dysfunction in T2D [77]. However, other studies have suggested that SGLT2 inhibitors have a more direct effect on cardiac function by improving altering cardiac ketone body oxidation and mitochondrial function in the heart [13**, 86*, 87*]. These two specific mechanisms will be discussed in more detail.

SGLT2 affect ketone body metabolism and oxidation

SGLT2 inhibitors are thought to improve DCM by increasing ketone bodies, since ketone bodies are the most efficient substrate for ATP production [88]. It has been hypothesized that the SGLT2 inhibitors promote utilization of ketone bodies, including β -OHB, in the heart [63,65], which may improve metabolism in DCM hearts [60,64,67]. For instance, SGLT2 inhibitors increase serum ketone body level and improve cardiac function change in ob/ob mouse [89*]. Furthermore, SGLT2 inhibitors increase blood ketone body concentration levels in patients with DCM [88,90], likely due to an increase in α -cell induced glucagon or lipolysis [90,91] which can stimulate ketone body production [92,93]. However, the effect of SGLT2 inhibitors to improve ketone body oxidation in DCM has not been investigated

[13**]. This suggests that SGLT2-induced ketone bodies may indirectly improve cardiac function.

SGLT2 inhibitors improve mitochondrial function

Increased presence of ketone bodies increases mitochondrial oxidative phosphorylation [94,95]. Therefore, several studies have investigated whether SGLT2 inhibitors improve mitochondrial function [13**,86*,87*]. A previous study showed that SGLT2 inhibitors dramatically increase ATP production in the heart by increasing glucose and palmitate oxidation [13**]. This increase in ATP production was also observed with ketone perfusion in diabetic mouse hearts [13**]. Similarly, other studies have shown that SGLT2 inhibitors directly improve mitochondrial oxidative phosphorylation [86*] and expression of mitochondrial proteins [87*], thus decreasing the accumulation of metabolites of incomplete FA oxidation in DCM [86]. Together these studies indicate SGLT2 inhibitors may improve DCM by altering mitochondrial oxidative phosphorylation (Fig. 2). Although the exact mechanism through which mitochondrial improvement through SGLT2 ketone bodies has not been defined, the pyrin domain-containing 3 (NLRP3) inflammasome has been identified as a potential pathway [96**]. This NLRP3 induces mitochondrial damage [97] and is suggested as a pro-inflammatory factor [96**]. A study has suggested that SGLT2 inhibitors attenuate NLRP3 inflammasome activation and secretion of interleukin (IL)-1 β via ketone bodies in DCM, and decreases macrophage expression of NLRP3 *ex vivo* [96**]. Thus, the SGLT2 inhibitor might improve mitochondrial function by attenuating activation of the NLRP3 inflammasome. Further investigation of SGLT2 inhibitors studies may be indicate that mitochondrial oxidative phosphorylation is the primary target or mechanism of DCM.

Conclusion

DCM is a serious complication of T2D that results in altered heart fuel utilization and impaired cardiac function. Impaired metabolic flexibility in DCM is an important mechanism contributing to impaired cardiac function. While traditional antidiabetic agents only partially improve the cardiac function in DCM, SGLT2 inhibitors are a new class or pharmacological agents that improve the DCM phenotype independent of glycemic control, likely through adaptations to mitochondria or ketone body metabolism. More investigations, particularly in humans, need to be completed to fully elucidate the role for SGLT2 inhibitors to improve cardiac function and metabolism in patients with DCM.

Acknowledgements

This work was supported by the National Institutes of Health R01-HL138738 and R01-AG060542 to KIS and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (17J11622) to SN.

References

1. World Health Organization, Global report on diabetes. Geneva, Switzerland; 2016.
2. Peterson Linda R, Saeed Ibrahim M, McGill Janet B, Herrero Pilar, Schechtman Kenneth B, Gunawardena Ratnasiri, Recklein Carol L, Coggan Andrew R, DeMoss Amanda J, Dence Carmen

- S, Gropler Robert J. Sex and type 2 diabetes: obesity-independent effects on left ventricular substrate metabolism and relaxation in humans. *Obesity* (Silver Spring) 2012; 20: 802–810. [PubMed: 21818149]
3. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation* 2000; 101: 2271–2276. [PubMed: 10811594]
 4. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 2003; 46: 760–765. [PubMed: 12774166]
 5. Wu Yanling, Ding Yanping, Tanaka Yoshimasa, Zhang Wen. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int J Med Sci* 2014; 11: 1185–1200. [PubMed: 25249787]
 6. Doenst T, Nguyen TD, and Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. *Circ Res* 2013; 113: 709–724. [PubMed: 23989714]
 7. Ormazabal Valeska, Nair Soumyalekshmi, Elfeky Omar, Aguayo Claudio, Salomon Carlos, Zuñiga Felipe A. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* 2018; 17: 122. [PubMed: 30170598]
 8. Sakamoto J, Barr RL, Kavanagh KM, Lopaschuk GD. Contribution of malonyl-CoA decarboxylase to the high fatty acid oxidation rates seen in the diabetic heart. *Am J Physiol Heart Circ Physiol* 2000; 278: H1196–H1204. [PubMed: 10749714]
 9. Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. *Cardiovasc Res* 1997; 34:25–33 [PubMed: 9217869]
 10. Varma U, Koutsifeli P, Benson VL, Mellor KM, Delbridge LMD. Molecular mechanisms of cardiac pathology in diabetes - Experimental insights. *Biochim Biophys Acta Mol Basis Dis* 2018; 1864: 1949–1959. [PubMed: 29109032]
 11. Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. *Proc Natl Acad Sci U S A* 2003; 100:1226–1231. [PubMed: 12552126]
 12. Dyck Jason R B, Cheng Jie-Fei, Stanley William C, Barr Rick, Chandler Margaret P, Brown Steven, Wallace David, Arrhenius Thomas, Harmon Charles, Yang Guang., et al. Malonyl coenzyme a decarboxylase inhibition protects the ischemic heart by inhibiting fatty acid oxidation and stimulating glucose oxidation. *Circ Res* 2004; 94: e78–e84. [PubMed: 15105298]
 13. Verma Subodh, Rawat Sonia, Ho Kim L, Wagg Cory S, Zhang Liyan, Teoh Hwee, Dyck John E, Uddin Golam M, Oudit Gavin Y, Mayoux Eric et al. 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. [PubMed: 30456329] ** This study is the first study to demonstrate the effect of SGLT2 inhibitors on ATP production in DCM.
 14. Gibbs CL and Chapman JB, Cardiac heat production. *Annu Rev Physiol* 1979; 41: 507–519. [PubMed: 219764]
 15. Ventura-Clapier R, Garnier A, and Veksler V, Energy metabolism in heart failure. *J Physiol* 2004; 555: 1–13. [PubMed: 14660709]
 16. Mootha VK, Arai AE, and Balaban RS Maximum oxidative phosphorylation capacity of the mammalian heart. *Am J Physiol* 1997; 272: H769–H775. [PubMed: 9124437]
 17. Randle PJ, Garland PB, Hales CN Newsholme EA The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963; 1: 785–799. [PubMed: 13990765]
 18. Brahma MK, Pepin ME, and Wende AR, My Sweetheart Is Broken: Role of Glucose in Diabetic Cardiomyopathy. *Diabetes Metab J* 2011, 41: 1–9.
 19. Shao D and Tian R, Glucose Transporters in Cardiac Metabolism and Hypertrophy. *Compr Physiol* 2015; 6: 331–351. [PubMed: 26756635]
 20. Kainulainen H, Breiner M, Schürmann A, Martinen A, Virjo A, Joost HG,. In vivo glucose uptake and glucose transporter proteins GLUT1 and GLUT4 in heart and various types of skeletal muscle from streptozotocin-diabetic rats. *Biochim Biophys Acta* 1994; 1225: 275–82. [PubMed: 8312374]

21. Le Page Lydia M, Rider Oliver J, Lewis Andrew J, Ball Vicky, Clarke Kieran, Johansson Edvin, Carr Carolyn A, Heather Lisa C, Tyler Damian J. Increasing Pyruvate Dehydrogenase Flux as a Treatment for Diabetic Cardiomyopathy: A Combined ¹³C Hyperpolarized Magnetic Resonance and Echocardiography Study. *Diabetes* 2015; 64: 2735–2743. [PubMed: 25795215]
22. Heather LC and Clarke K. Metabolism, hypoxia and the diabetic heart. *J Mol Cell Cardiol* 2011; 50: 598–605. [PubMed: 21262230]
23. Jine-Yuan Hsieh Dennis, Shang-Chuan Ng, Zeng Ren-You, Vijaya Padma Viswanadha, Huang Chih-Yang, Kuo Wei-Wen. Diallyl Trisulfide (DATS) Suppresses AGE-Induced Cardiomyocyte Apoptosis by Targeting ROS-Mediated PKC δ Activation. *Int J Mol Sci* 2020; 21.
24. Pereira Laetitia, Matthes Jan, Schuster Iris, Valdivia Héctor H, Herzig Stefan, Richard Sylvain, Gómez Ana M. Mechanisms of [Ca²⁺]_i transient decrease in cardiomyopathy of db/db type 2 diabetic mice. *Diabetes* 2006; 55: 608–615. [PubMed: 16505222]
25. Faramoushi Mahdi, Sasan Ramin Amir, Sarraf Vahid Sari, Karimi Pouran. Cardiac fibrosis and down regulation of GLUT4 in experimental diabetic cardiomyopathy are ameliorated by chronic exposures to intermittent altitude. *J Cardiovasc Thorac Res* 2016; 8: 26–33. [PubMed: 27069564]
26. Hou Ning, Mai Yunpei, Qiu Xiaoxia, Yuan Wenchang, Li Yilang, Luo Chengfeng, Liu Yun, Zhang Guiping, Zhao Ganjiang, Luo Jian-Dong. Carvacrol Attenuates Diabetic Cardiomyopathy by Modulating the PI3K/AKT/GLUT4 Pathway in Diabetic Mice. *Front Pharmacol* 2019; 10: 998. [PubMed: 31572181] * The authors investigated the effects of carvacrol in the cardiac remodeling in both streptozotocin-induced and db/db mouse model of T1DM and T2DM. Carvacrol significantly improved cardiac function by restoring PI3K/AKT signaling and promoting GLUT4 membrane translocation, which were impaired in mice with T1DM and T2DM. This study demonstrated that restoring PI3K/AKT signaling-mediated GLUT4 membrane translocation is a potential treatment of DCM.
27. Maria Z, Campolo AR, and Lacombe VA. Diabetes Alters the Expression and Translocation of the Insulin-Sensitive Glucose Transporters 4 and 8 in the Atria. *PLoS One* 2015; 10: e0146033. [PubMed: 26720696]
28. Iozzo Patricia, Chareonthaitawee Panithaya, Dutka David, Betteridge D John, Ferrannini Ele, Camici Paolo G. Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. *Diabetes* 2002; 51: 3020–3024. [PubMed: 12351442]
29. Nielsen Roni, Jorsal Anders, Iversen Peter, Tolbod Lars, Bouchelouche Kirsten, Sørensen Jens, Harms Hendrik Johannes, Flyvbjerg Allan, Bøtker Hans Erik, Wiggers Henrik. Heart failure patients with prediabetes and newly diagnosed diabetes display abnormalities in myocardial metabolism. *J Nucl Cardiol* 2018; 25: 169–176. [PubMed: 27473218] * This study demonstrated that diabetic patients with chronic heart failure have reduced cardiac glucose uptake compared with nondiabetic chronic heart failure patients.
30. Montaine David, Marechal Xavier, Coisne Augustin, Debry Nicolas, Modine Thomas, Fayad Georges, Potelle Charlotte, El Arid Jean-Marc, Mouton Stéphanie, Sebti Yasmine, et al. Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circulation* 2014; 130: 554–564. [PubMed: 24928681]
31. Gray S and Kim JK. New insights into insulin resistance in the diabetic heart. *Trends Endocrinol Metab* 2011; 22: 394–403. [PubMed: 21680199]
32. Lu Qingguo, Liu Jia, Li Xuan, Sun Xiaodong, Zhang Jingwen, Ren Di, Tong Nanwei, Li Ji. Empagliflozin attenuates ischemia and reperfusion injury through LKB1/AMPK signaling pathway. *Mol Cell Endocrinol* 2020; 501: 110642. [PubMed: 31759100]
33. Koyani Chintan N, Plastira Ioanna, Sourij Harald, Hallström Seth, Schmidt Albrecht, Rainer Peter P, Bugger Heiko, Frank Saša, Malle Ernst, Lewinski Dirk von. Empagliflozin protects heart from inflammation and energy depletion via AMPK activation. *Pharmacol Res* 2020; 158: 104870. [PubMed: 32434052] *The study identified a novel cardio protective mechanism of SGLT2 inhibitor, empagliflozin, suggesting that AMPK activation-mediated energy repletion and reduced inflammation contribute to the observed cardiovascular benefits of the drug in HF.
34. Hu Yong, Suarez Jorge, Fricovsky Eduardo, Wang Hong, Scott Brian T, Trauger Sunia A, Han Wenlong, Hu Ying, Oyeleye Mary O, Dillmann Wolfgang H. Increased enzymatic O-

- GlcNAcylation of mitochondrial proteins impairs mitochondrial function in cardiac myocytes exposed to high glucose. *J Biol Chem* 2009; 284: 547–555. [PubMed: 19004814]
35. Marsh SA, Dell'Italia LJ, and Chatham JC. Activation of the hexosamine biosynthesis pathway and protein O-GlcNAcylation modulate hypertrophic and cell signaling pathways in cardiomyocytes from diabetic mice. *Amino Acids* 2011; 40: 819–828. [PubMed: 20676904]
 36. Zachara NE and Hart GW. O-GlcNAc a sensor of cellular state: the role of nucleocytoplasmic glycosylation in modulating cellular function in response to nutrition and stress. *Biochim Biophys Acta* 2004; 1673: 13–28. [PubMed: 15238246]
 37. Qin Cheng Xue, Sleaby Rochelle, Davidoff Amy J, Bell James R, De Blasio Miles J, Delbridge Leanne M, Chatham John C, Ritchie Rebecca H. Insights into the role of maladaptive hexosamine biosynthesis and O-GlcNAcylation in development of diabetic cardiac complications. *Pharmacol Res* 2017; 116: 45–56. [PubMed: 27988387]
 38. Yokoe S, Asahi M, Takeda T, et al. Inhibition of phospholamban phosphorylation by O-GlcNAcylation: implications for diabetic cardiomyopathy. *Glycobiology* 2010; 20: 1217–1226. [PubMed: 20484118]
 39. Wende AR, Schell JC, CM Ha, Pepin ME, Khalimonchuk O, Schwartz H, Pereira RO, Brahma MK, Tuinei J, Contreras-Ferrat A: Maintaining Myocardial Glucose Utilization in Diabetic Cardiomyopathy Accelerates Mitochondrial Dysfunction. *Diabetes* 2020.** This study showed that the largest changes, driven by glucose and diabetes, were in genes involved in mitochondrial function using transcriptomic analysis.
 40. Fillmore N, Mori J, and Lopaschuk GD. Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy. *Br J Pharmacol* 2014; 171: 2080–2090. [PubMed: 24147975]
 41. How Ole-Jakob, Aasum Ellen, Severson David L, Chan W Y Anna, Essop M Faadiel, Larsen Terje S. Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice. *Diabetes* 2006; 55: 466–473. [PubMed: 16443782]
 42. Hue L and Taegtmeyer H, The Randle cycle revisited: a new head for an old hat. *Am J Physiol Endocrinol Metab* 2009 297: E578–E591. [PubMed: 19531645]
 43. Kim MS, Wang Y, Rodrigues B. Lipoprotein lipase mediated fatty acid delivery and its impact in diabetic cardiomyopathy. *Biochim Biophys Acta* 2012; 1821: 800–808. [PubMed: 22024251]
 44. Finck Brian N, Lehman John J, Leone Teresa C, Welch Michael J, Bennett Michael J, Kovacs Attila, Han Xianlin, Gross Richard W, Kozak Ray, Lopaschuk Gary D, Kelly Daniel P. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *J Clin Invest* 2002 109: 121–130. [PubMed: 11781357]
 45. Huang TH, Yang Q, Harada M, et al. Salacia oblonga root improves cardiac lipid metabolism in Zucker diabetic fatty rats: modulation of cardiac PPAR-alpha-mediated transcription of fatty acid metabolic genes. *Toxicol Appl Pharmacol* 2006; 210: 78–85. [PubMed: 16129467]
 46. Banke Natasha H, Wende Adam R, Leone Teresa C, O'Donnell J Michael, Abel E Dale, Kelly Daniel P, Lewandowski E Douglas. Preferential oxidation of triacylglyceride-derived fatty acids in heart is augmented by the nuclear receptor PPARalpha. *Circ Res* 2010; 107: 233–241. [PubMed: 20522803]
 47. Lee TI, Kao YH, Chen YC, Pan NH, Chen YJ. Oxidative stress and inflammation modulate peroxisome proliferator-activated receptors with regional discrepancy in diabetic heart. *Eur J Clin Invest* 2010; 40: 692–699. [PubMed: 20561028]
 48. Lee TW, Bai KJ, Lee TI, Chao TF, Kao YH, Chen YJ. PPARs modulate cardiac metabolism and mitochondrial function in diabetes. *J Biomed Sci* 2017; 24: 5. [PubMed: 28069019]
 49. Wang W, Zhang L, Battiprolu PK, et al. Malonyl CoA Decarboxylase Inhibition Improves Cardiac Function Post-Myocardial Infarction. *JACC Basic Transl Sci*. 2019; 4: 385–400. [PubMed: 31312761]
 50. Marfella R, Di Filippo C, Portoghese M, et al. Myocardial lipid accumulation in patients with pressure-overloaded heart and metabolic syndrome. *J Lipid Res* 2009; 50: 2314–2323. [PubMed: 19470430]

51. Tan Yi, Zhang Zhiguo, Zheng Chao, Wintergerst Kupper A, Keller Bradley B, Cai Lu. Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence. *Nat Rev Cardiol* 2020.
52. Lou PH, Lucchinetti E, Scott KY, et al. Alterations in fatty acid metabolism and sirtuin signaling characterize early type-2 diabetic hearts of fructose-fed rats. *Physiol Rep* 2017; 5: e13388. [PubMed: 28830979]
53. Kobayashi S, Liang Q. Autophagy and mitophagy in diabetic cardiomyopathy. *Biochim Biophys Acta* 2015; 1852: 252–261. [PubMed: 24882754]
54. Aragno M, Mastrocola R, Alloati G, et al. Oxidative stress triggers cardiac fibrosis in the heart of diabetic rats. *Endocrinology* 2008; 149: 380–388. [PubMed: 17901230]
55. Alex Linda, Russo Ilaria, Holoborodko Volodymir, Frangogiannis Nikolaos G. Characterization of a mouse model of obesity-related fibrotic cardiomyopathy that recapitulates features of human heart failure with preserved ejection fraction. *Am J Physiol Heart Circ Physiol* 2018; 315: H934–H949. [PubMed: 30004258] **The study investigated the functional and structural myocardial alterations in db/db mice. Obese diabetic C57BL6J db/db mice exhibit diastolic dysfunction with preserved ejection fraction, associated with cardiomyocyte hypertrophy, interstitial/perivascular fibrosis, and microvascular rarefaction, thus recapitulating aspects of human obesity-related heart failure with preserved ejection fraction.
56. Nishikawa T and Araki E, Impact of mitochondrial ROS production in the pathogenesis of diabetes mellitus and its complications. *Antioxid Redox Signal* 2007; 9: 343–353. [PubMed: 17184177]
57. Heerebeek Loek van, Hamdani Nazha, Handoko M Louis, Falcao-Pires Ines, Musters René J, Kupreishvili Koba, Ijsselmuiden Alexander J J, Schalkwijk Casper G, Bronzwaer Jean G F, Diamant Michaela, et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 2008; 117: 43–51. [PubMed: 18071071]
58. Nagao M, Toh R, Irino Y, Mori T, Nakajima H, Hara T, Honjo T, Satomi-Kobayashi S, Shinke T, Tanaka H, et al. β -Hydroxybutyrate elevation as a compensatory response against oxidative stress in cardiomyocytes. *Biochem Biophys Res Commun* 2016; 475: 322–328 [PubMed: 27216458]
59. Ho KL, Zhang L, Wagg C, Al Batran R, Gopal K, Levasseur J, Leone T, Dyck JRB, Ussher JR, Muoio DM, et al. Increased ketone body oxidation provides additional energy for the failing heart without improving cardiac efficiency. *Cardiovasc Res* 2019; 115:1606–1616 [PubMed: 30778524]
60. Newman JC, Verdin E. Ketone bodies as signaling metabolites. *Trends Endocrinol Metab* 2014; 25: 42–52 [PubMed: 24140022]
61. Garcia-Ropero A, Santos-Gallego CG, Zafar MU, Badimon JJ. Metabolism of the failing heart and the impact of SGLT2 inhibitors. *Expert Opin Drug Metab Toxicol* 2019; 15: 275–285. [PubMed: 30822172]
62. Bedi KC Jr, Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, Wang LL, Javaheri A, Blair IA, Margulies KB, Rame JE. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. *Circulation* 2016; 133: 706–716. [PubMed: 26819374]
63. McGarry JD, Foster DW. Regulation of hepatic fatty acid oxidation and ketone body production. *Annu Rev Biochem* 1980; 49: 395–420. [PubMed: 6157353]
64. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME Study? A unifying hypothesis. *Diabetes Care* 2016; 39: 1115–1122. [PubMed: 27289124]
65. Brahma Manoj K, Ha Chae-Myeong, Pepin Mark E, Mia Sobuj, Sun Zhihuan, Chatham John C, Habegger Kirk M, Abel Evan Dale, Paterson Andrew J, Young Martin E, Wende Adam R. Increased Glucose Availability Attenuates Myocardial Ketone Body Utilization. *J Am Heart* 2020; 9: e013039.
66. Kim DH, Park MH, Ha S, Bang EJ, Lee Y, Lee AK, Lee J, Yu BP, Chung HY. Anti-inflammatory action of β -hydroxybutyrate via modulation of PGC-1 α and FoxO1, mimicking calorie restriction. *Aging (Albany NY)* 2019; 11: 1283–1304. [PubMed: 30811347]
67. Rojas-Morales P, Tapia E, Pedraza-Chaverri J. β -Hydroxybutyrate: A signaling metabolite in starvation response? *Cell Signal* 2016; 28: 917–923 [PubMed: 27083590]

68. Janardhan A, Chen J, Crawford PA. Altered systemic ketone body metabolism in advanced heart failure. *Tex Heart Inst J* 2011; 38: 533–538. [PubMed: 22163128]
69. Lopaschuk Gary D, Verma Subodh. Empagliflozin's Fuel Hypothesis: Not so Soon. *Cell Metab* 2016; 24: 200–202. [PubMed: 27508868]
70. Horton JL, Martin OJ, Lai L, Riley NM, Richards AL, Vega RB, Leone TC, Pagliarini DJ, Muoio DM, Bedi KC Jr. Mitochondrial protein hyperacetylation in the failing heart. *JCI Insight* 2016; 2: e84897. [PubMed: 26998524]
71. Russell RR 3rd, Taegtmeyer H. Changes in citric acid cycle flux and anaplerosis antedate the functional decline in isolated rat hearts utilizing acetoacetate. *J Clin Invest* 1991; 87: 384–390. [PubMed: 1671390]
72. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A “Thrifty Substrate” Hypothesis. *Diabetes Care* 2016; 39: 1108–1114 [PubMed: 27289126]
73. Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, Le Moan N, Grueter CA, Lim H, Saunders LR, Stevens RD et al. Suppression of oxidative stress by β -hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science* 2013; 339: 211–214. [PubMed: 23223453]
74. Rieg Timo, Vallon Volker. Development of SGLT1 and SGLT2 inhibitors. *Diabetologia* 2018; 61: 2079–2086. [PubMed: 30132033]
75. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2017; 24: 73–79. [PubMed: 27898586]
76. Banejee SK, McGaffin KR, Pastor-Soler NM, Ahmad F. SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. *Cardiovasc Res* 2009; 84: 111–118. [PubMed: 19509029]
77. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. EMPA-REG OUTCOME investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
78. Edwards JL. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 Diabetes. *N Engl J Med* 2016; 374: 1093.
79. Beljic T, Miric M. Improved metabolic control does not reverse LV filling abnormalities in newly diagnosed NIDDM patients. *Acta Diabetol* 1994, 31: 147–150. [PubMed: 7827353]
80. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; 373: 1765–1772. [PubMed: 19465231]
81. Lathief S, Inzucchi SE Approach to diabetes management in patients with CVD. *Trends in cardiovascular medicine* 2016; 26: 165–179.
82. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC Jr, Probstfield JL, Cushman WC, Ginsberg HN et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011; 364: 818–828. [PubMed: 21366473]
83. Yaribeygi H, Sathyapalan T, Maleki M, Jamialahmadi T, Sahebkar A. Molecular mechanisms by which SGLT2 inhibitors can induce insulin sensitivity in diabetic milieu: A mechanistic review. *Life Sci* 2020; 240: 117090. [PubMed: 31765648]
84. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle HJ, von Eynatten M, Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol* 2014; 13: 28. [PubMed: 24475922]
85. Lopaschuk Gary D, Verma Subodh. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. *JACC basic Transl Sci* 2020; 5: 632–644. [PubMed: 32613148]
86. Makrecka-Kuka Marina, Korzh Stanislava, Videja Melita, Vilks Karlis, Cirule Helena, Kuka Janis, Dambrova Maija, Liepinsh Edgars. Empagliflozin Protects Cardiac Mitochondrial Fatty Acid Metabolism in a Mouse Model of Diet-Induced Lipid Overload. *Cardiovasc Drugs Ther* 2020.*This study suggested that SGLT2 inhibitors preserve mitochondrial fatty acid oxidation in the heart.

87. Shao Q, Meng L, Lee S, Tse G, Gong M, Zhang Z, Zhao J, Zhao Y, Li G, Liu T. Empagliflozin, a sodium glucose co-transporter-2 inhibitor, alleviates atrial remodeling and improves mitochondrial function in high-fat diet/streptozotocin-induced diabetic rats. *Cardiovasc Diabetol* 2019; 18: 165. . [PubMed: 31779619] *This study indicated that SGLT2 inhibitors improve mitochondrial function acid mitochondrial biogenesis in T2DM.
88. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A “Thrifty Substrate” Hypothesis. *Diabetes Care* 2016; 39: 1108–1114. [PubMed: 27289126]
89. Adingupu DD, Göpel SO, Grönros J, Behrendt M, Sotak M, Miliotis T, Dahlqvist U, Gan LM, Jönsson-Rylander AC. SGLT2 inhibition with empagliflozin improves coronary microvascular function and cardiac contractility in prediabetic ob/ob–/– mice. *Cardiovasc Diabetol* 2019; 18: 16. [PubMed: 30732594] *This study demonstrated that SGLT2 inhibitors improves cardiac function in diabetic mice.
90. AI Jobori H, Daniele G, Adams J, Cersosimo E, Solis-Herrera C, Triplitt C, DeFronzo RA, Abdul-Ghani M. Determinants of the increase in ketone concentration during SGLT2 inhibition in NGT, IFG and T2DM patients. *Diabetes Obes Metab* 2017; 19: 809–813. [PubMed: 28128510]
91. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, Broedl UC, Woerle HJ. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014; 124: 499–508. [PubMed: 24463454]
92. Ceriello A, Genovese S, Mannucci E, Gronda E. Glucagon and heart in type 2 diabetes: new perspectives. *Cardiovasc Diabetol* 2016; 15: 123. [PubMed: 27568179]
93. Taylor SI, Blau JE, Rother KI. SGLT2 Inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab* 2015; 100: 2849–2852. [PubMed: 26086329]
94. Baliotti Marta, Fattoretti Patrizia, Giorgetti Belinda, Casoli Tiziana, Di Stefano Giuseppina, Solazzi Moreno, Platano Daniela, Aicardi Giorgio, Bertoni-Freddari Carlo. A ketogenic diet increases succinic dehydrogenase activity in aging cardiomyocytes. *Ann N Y Acad Sci* 2009; 1171: 377–384. [PubMed: 19723079]
95. Cotter DG, Schugar RC, Crawford PA. Ketone body metabolism and cardiovascular disease. *Am J Physiol Heart Circ Physiol* 2013; 304: H1060–H1076. [PubMed: 23396451]
96. Kim SR, Lee SG, Kim SH, Kim JH, Choi E, Cho W, Rim JH, Hwang I, Lee CJ, Lee M et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nat Commun* 2020; 11:2127. [PubMed: 32358544] ** This study suggested that SGLT2 inhibitors attenuates NLRP3 inflammasome activation, which might help to explain its cardioprotective effects.
97. Poznyak Anastasia V, Melnichenko Alexandra A, Wetzker Reinhard, Gerasimova Elena V, Orekho Alexander Nv. NLRP3 Inflammasomes and Their Significance for Atherosclerosis. *Biomedicines* 2020; 8: E205. [PubMed: 32664349]

Fig 1.
Molecular mechanisms of energy shift in diabetic heart.
FA, Fatty acids.

Fig 2.

Expected molecular mechanisms of the effect of SGLT2 inhibitors on cardiomyocyte dysfunction protection.

FA, Fatty acids; TCA cycle, tricarboxylic acid cycle; AcAc, acetoacetate; BDH1, β-hydroxybutyrate dehydrogenase-1; β-OHB, β-hydroxybutyric acid; SLC16A, solute carrier 16A; GLUT, glucose transporter; MCT, Monocarboxylate transporter.