Cardiovascular Diabetology

REVIEW

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Impact of peroxisome proliferator-activated receptor-α on diabetic cardiomyopathy

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Abstract

The prevalence of cardiomyopathy is higher in diabetic patients than those without diabetes. Diabetic cardiomyopathy (DCM) is defined as a clinical condition of abnormal myocardial structure and performance in diabetic patients without other cardiac risk factors, such as coronary artery disease, hypertension, and significant valvular disease. Multiple molecular events contribute to the development of DCM, which include the alterations in energy metabolism (fatty acid, glucose, ketone and branched chain amino acids) and the abnormalities of subcellular components in the heart, such as impaired insulin signaling, increased oxidative stress, calcium mishandling and inflammation. There are no specific drugs in treating DCM despite of decades of basic and clinical investigations. This is, in part, due to the lack of our understanding as to how heart failure initiates and develops, especially in diabetic patients without an underlying ischemic cause. Some of the traditional anti-diabetic or lipid-lowering agents aimed at shifting the balance of cardiac metabolism from utilizing fat to glucose have been shown inadequately targeting multiple aspects of the conditions. Peroxisome proliferator-activated receptor α (PPARα), a transcription factor, plays an important role in mediating DCM-related molecular events. Pharmacological targeting of PPARα activation has been demonstrated to be one of the important strategies for patients with diabetes, metabolic syndrome, and atherosclerotic cardiovascular diseases. The aim of this review is to provide a contemporary view of PPARα in association with the underlying pathophysiological changes in DCM. We discuss the PPARα-related drugs in clinical applications and facts related to the drugs that may be considered as risky (such as fenofibrate, bezafibrate, clofibrate) or safe (pemafibrate, metformin and glucagon-like peptide 1-receptor agonists) or having the potential (sodium–glucose co-transporter 2 inhibitor) in treating DCM.

Keywords: Diabetic cardiomyopathy, PPARα modulator, Metformin, Glucagon-like peptide 1-receptor agonists, Sodium–glucose co-transporter type 2 inhibitors

Introduction

Diabetic cardiomyopathy (DCM) is defined as left ventricular (LV) dysfunction in diabetic patients without coronary artery disease and hypertension [1, 2]. It is usually asymptomatic in the early stages of its evolution [3]. Minimal diagnostic criteria of DCM include LV hypertrophy, interstitial fibrosis, LV diastolic dysfunction and reduced LV ejection fraction [1]. Although it remains unclear as to what initiates DCM on the molecular level, the major clinical and biochemical abnormalities in diabetes, such as hyperglycemia, systemic insulin resistance, and impaired cardiac insulin signaling, are the risk factors contributing to the pathogenesis of DCM [3, 4]. Emerging evidence highlight the importance of altered mitochondrial function as a major contributor to cardiac dysfunction in diabetes [5–7]. It has been demonstrated that in obese, insulin-resistant men, abnormal LV energy metabolism is evident prior to structural and functional pathological remodeling in the heart [8]. Clinical

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observations by using magnetic resonance (MR) imaging and phosphorus-31-nuclear MR spectroscopy have demonstrated that diastolic dysfunction and reduced myocardial high-energy phosphate metabolism is evident in asymptomatic normotensive male patients with well-controlled and uncomplicated type II diabetes (T2D) as compared with control subjects [9]. These findings were further demonstrated by Clarke et al. who showed that T2D patients with normal cardiac mass and function had impaired cardiac energy metabolism [10]. Mitochondrial dysfunction can occur through several mechanisms involving cardiac substrate metabolic changes, impaired cardiac insulin and glucose homeostasis [11–13], impaired cellular and mitochondrial calcium (Ca^{2+}) handling [14], oxidative stress [15–17], lipotoxicity [2] and cardiac collagen deposition [18].

Under physiological condition, fatty acid is a major energy supplier contributing about 70% of the ATP to the working heart whereas the remaining energy relies on glucose, ketone body and branched chain amino acids (BCAA) (Fig. 1). In diabetic hearts, however, increased fatty acid uptake and decreased glucose utilization have been observed in animal models and patients [19, 20]. Meanwhile, increased utilization of ketones as an energy source is also evident in the human diabetic heart [21]. A decrease in cardiac BCAA oxidation was observed in obese mouse induced by high fat diet [13] and in heart failure patients [12]. The switch of energy substrate preference in diabetic heart occurs in parallel with higher rates of oxygen consumption and impaired oxidative phosphorylation [19]. In addition, the results obtained by using electron microscopy have demonstrated that mitochondria from diabetic patients are smaller with a reduced capacity to retain Ca^{2+} and are associated with reduced expression of mitochondrial fission protein [22]. This suggests that changes of mitochondrial ultrastructure and dynamics contribute to the development of cardiomyopathy since the impairments in mitochondrial

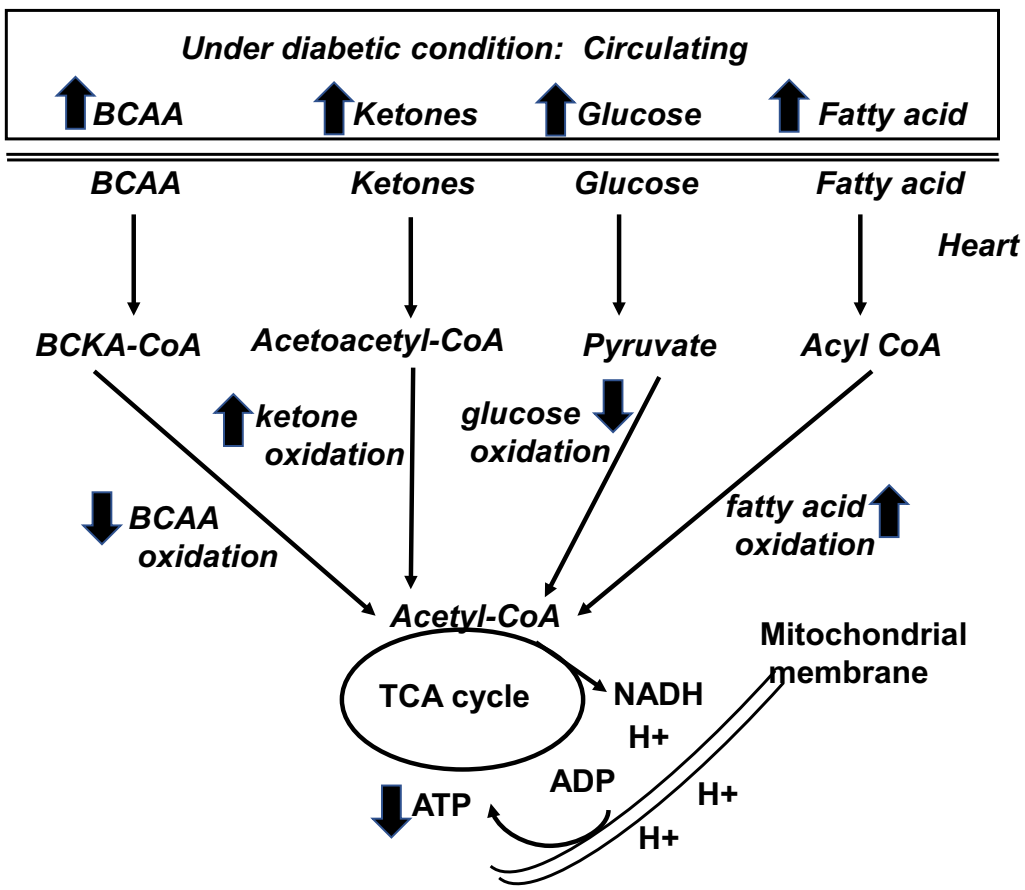

Fig. 1 Alteration of cardiac metabolism under diabetic condition. Although circulating levels of branched chain amino acids (BCAA), ketones, glucose and fatty acids are increased under diabetic condition, their oxidation rates are not increased accordingly. Reduced BCAA and glucose oxidation, while increased ketone and fatty acid oxidation are evident in diabetic subject. Thus, reduced ATP production contributes to cardiac dysfunction

function is associated with impaired cardiac contractility [22].

Although patients with diabetes may not all develop heart failure, clinical trials have shown that the incidence of heart failure was increased in both male and female diabetic patients when compared with age-matched individuals [23–27]. During the last decade, considerable progress has been made in DCM management by pharmacological interventions mainly through lipid-lowering therapies [28] and glycemic control strategies for the prevention of heart failure targeted at the diabetic population [29]. Peroxisome proliferator-activated receptor α (PPARα), a transcription factor which can present in a high concentration in the heart, is involved not only in regulating lipid metabolism and glucose homeostasis [30, 31], but also in Ca^{2+} handling, inflammation and oxidative stress in heart [32]. Mice with cardiac specific PPARα over-expression exhibited a similar phenotype of DCM, with LV hypertrophy, systolic dysfunction and reduced uptake of Ca^{2+} into sarcoplasmic reticulum [33]. Conversely, increases in fatty acid oxidation and uptake in diabetic hearts were significantly reduced in PPARα deficiency mice in parallel with an increase in glucose metabolism [31, 34]. Thus, modulating cardiac PPARα to prevent metabolic alterations may be a promising therapeutic strategy in DCM management.

Diastolic dysfunction, as an early sign of DCM [1], is detected in 40–75% of patients with type 1 diabetes (T1D) or T2D [35, 36] patients and in rodent diabetic models [16] in the absence of overt vascular dysfunction or atherosclerosis, suggesting a cardiac-specific response to diabetes. Excess adiposity and altered fat distribution have been shown to contribute to DCM in T1D similar to T2D [37]. However, the deleterious effects of diabetes on myocardial parameters are not all the same in patients with T1D versus T2D. For example, T1D is mostly associated with hyperglycemia, oxidative stress, myocardial fibrosis [37]. In contrast, T2D is more linked to hyperinsulinemia, insulin resistance, obesity, and cardiomyocyte hypertrophy [38]. Glycemia is a powerful promoter of heart failure in diabetic patients [39, 40], as each 1% rise in glycated hemoglobin A1C level is linked to a 30% increase in the risk of heart failure in T1D mellitus [39] and an 8% increase in risk in T2D mellitus, independent of other risk factors such as obesity, smoking, hypertension, dyslipidemia, and coronary heart disease [1, 40]. In contrast, a 1% reduction in hemoglobin A1C in T2D patients was associated with a 16% risk reduction for the development of heart failure [40]. Clearly, more studies are required to understand the differences in phenotype and underlying mechanisms for DCM in T1D and T2D.

Owing to the inherent limitations of performing mechanistic studies in humans, many of the insights into the underlying mechanisms of DCM have come from investigating rodent models. However, many of the observations in rodent models of obesity, insulin resistance, and diabetes mimic what has been seen in humans with these same pathologies. In addition, although the initial cause of impaired glucose utilization is different between T1D and T2D diabetes, ultimately they share similar downstream metabolic consequences as a result of increasing cardiomyocyte fatty acid utilization and decreased glucose utilization [1, 7]. Considering that T2D is by far the most common type of diabetes, in this review, we focus on evidence behind DCM in T2D to discuss the roles of PPARα not only in energy metabolism but also in insulin resistance, oxidative stress, inflammation, and Ca^{2+} handling regulation. We discuss the PPARα-related drugs in clinical applications. Based on the new breakthrough that some anti-diabetic drugs are associated with a lower risk of heart failure hospitalization in patients with cardiovascular disease, we also discuss PPARα-related drugs that may be risky (such as fenofibrate, bezafibrate, clofibrate) or relatively safer (pemafibrate, metformin and glucagon-like peptide 1-receptor (GLP-1R) agonists) or drugs that may have the potential (sodium–glucose co-transpoter 2 inhibitors:SGLT2i) in treating DCM.

PPARα related mechanisms in the pathogenesis of diabetic cardiomyopathy

Alterations of PPARα expression in DCM

A major physiological role of PPARα in the heart is to regulate the expression of target genes involved in energy metabolism *via* transactivation or transrepression through distinct mechanisms. However, abnormally increased cardiac PPARα expression has been suggested to be an important player in the development of DCM. This notion is supported by the experimental data that over-expression of PPARα resulted in the development of severe cardiomyopathy in mice [33], whereas inhibition of PPARα prevented the development of DCM [41, 42]. Likewise, mice with over-expression of PPARα on a low-fat diet also develop DCM [43]. However, clinical studies have demonstrated that the expression of PPARα is not significantly altered in the hearts of type II diabetic patients [44]. As a transcription factor, the functional expression of PPARα as reflected by its transcriptional activity is more important than its gene or protein expression. However, neither the expression profile of PPARα in relation to its activity in the context of DCM in patients, nor the co-relation of PPARα activity with cardiac function has been specifically studied.

PPARα and mitochondrial biosynthesis in DCM

Peroxisome-proliferator-activated receptor gamma-coactivator-1α (PGC1α) has been widely accepted as

a master regulator of fatty acid oxidation by modulating gene expression in the failing heart [45], and mitochondrial biogenesis in DCM [46]. Signaling of PGC1-α through activation of PPARs has been shown to control the molecules involved in mitochondrial citric acid cycle and electron transport chain [47]. On the other hand, PGC1β, which shares significant sequence homology with PGC1α [48], is also upregulated in the T2D db/db mouse heart [49], and the PGC1β/PPARα pathway has been shown to be involved in DCM through regulating cardiac metabolism [49]. This notion is further supported by the observation that knockdown of PGC1β reduced the transcriptional activity of PPARα, in parallel with an improved cardiac metabolism and cardiac dysfunction [49]. Collectively, mitochondrial dysfunction plays a pivotal role in the development of DCM, while modulating PPARα activity *via* PGC1 is a promising approach to attenuate mitochondrial dysfunction.

PPARα and mitochondrial energy metabolism in DCM

Effect of PPARα on mitochondrial fatty acid and glucose oxidation in DCM

Under normal circumstances, fatty acids are the predominant energetic substrate for the heart, providing 50–70% of myocardial ATP [50]. After transport into cardiomyocytes, the majority of fatty acids are imported into mitochondria for β-oxidation, and the remaining are re-esterified into triglycerides as energy storage [50]. Cardiac PPARα is such a regulator mediating fatty acid oxidation in both neonatal heart and adult heart. The cardiac PPARα expression increases in the postnatal period [51, 52] and is responsible for regulating the expression of genes involved in fatty acid metabolism [53]. Gene expression of PPARα was decreased, in concert with reduced fatty acid oxidation in the hypertrophied newborn rabbit heart [54], while chronic stimulation of PPARα has been shown to lead to elevated fatty acid oxidation and improved cardiac function [55]. Similarly, PPARα gene expression is downregulated in the failing heart of adult mice induced by pressure overload, in parallel with a reduced fatty acid oxidation but an accumulation of triglyceride and diacylglycerol [30].

The expression of PPARα is increased in pathological conditions that accompanied with insulin resistance and in diabetes mellitus where metabolisms are impaired, suggesting its potential role in enhancing fatty acid transport and oxidation observed in diabetic hearts [33, 55]. Indeed, in diabetes, increased circulating concentrations of fatty acids activate PPARα [6], that, in turn, modulates the expression of genes involved in fatty acid uptake (such as CD36, which facilitates a major fraction of fatty acid uptake), mitochondrial transport (such as carnitine palmitoyl transferase 1), and oxidation [45]. This notion is further supported by a recent finding which shows that the abundance of the carnitine transporter OCTN2, a downstream target of PPARα, is decreased in patients with DCM [56]. There is a strong evidence from PPARα agonist and PPARα deficiency mouse models which shows that carnitine transporter OCTN2 expression contributes to tissue levels of carnitine, including that in the cardiac tissue [57]. Deficiency of carnitine, due to mutations in the carnitine transporter OCTN2 gene, is known to be associated with heart failure [58]. Of interest, the reduced expression of carnitine transporter OCTN2 is evident in patients with chronic DCM [59]. Furthermore, hearts from PPARα transgenic mice are characterized by increased fatty acid oxidation and a metabolic phenotype similar to that found in DCM [33, 60]. Taken together, these findings provide strong evidence that increased PPARα facilitates mitochondrial fatty acid metabolism in DCM.

Besides the altered fatty acid metabolism, the decrease in glucose metabolism is also evident in diabetic heart [61–63]. PPARα induces the expression of pyruvate dehydrogenase kinase 4, thereby decreasing pyruvate dehydrogenase activity leading to further suppression of glucose oxidation [55, 64]. PPARα overexpression in the mouse myocardium attenuates glucose transporter gene expression and glucose uptake [65] as well as enzymes key for glycolysis such as phosphofructokinase [66]. Thus, abnormal alteration of PPARα in response to pathological situations like diabetes and the subsequent PPAR mediated increase in fatty acid oxidation and decrease in glucose metabolism contribute to the cardiac dysfunction observed in DCM [67, 68].

PPARα in relation to BCAA metabolism in DCM

Elevated circulating level of BCAA correlates with an increasing risk of insulin resistance and T2D in human and in rodent models [69]. Reduced cardiac BCAA oxidation was observed in obese mice induced by high fat diet [13] and in heart failure patients [12]. BCAAs consist of valine, leucine and isoleucine. The metabolic homeostasis of BCAAs is controlled by a series of BCAA catabolic enzymes (Fig. 2), including branched chain aminotransferase (BCAT) and branched chain α-keto acid dehydrogenase (BCKDH) [70]. As the rate-limiting enzyme of BCAAs degradation, BCKDH is regulated by phosphorylation/inactivation via BCKDH-kinase (BCKDK), while dephosphorylated and activated by a mitochondrion-localized protein phosphatase-2Cm (PP2Cm) [70].

Although BCAAs can be highly oxidized in the heart, their contribution to cardiac ATP production only counts about 1–2% [13]. Thus, one of the important roles of BCAAs in the heart is to modulate glucose and fatty acid metabolism [71, 72]. This notion is further supported by

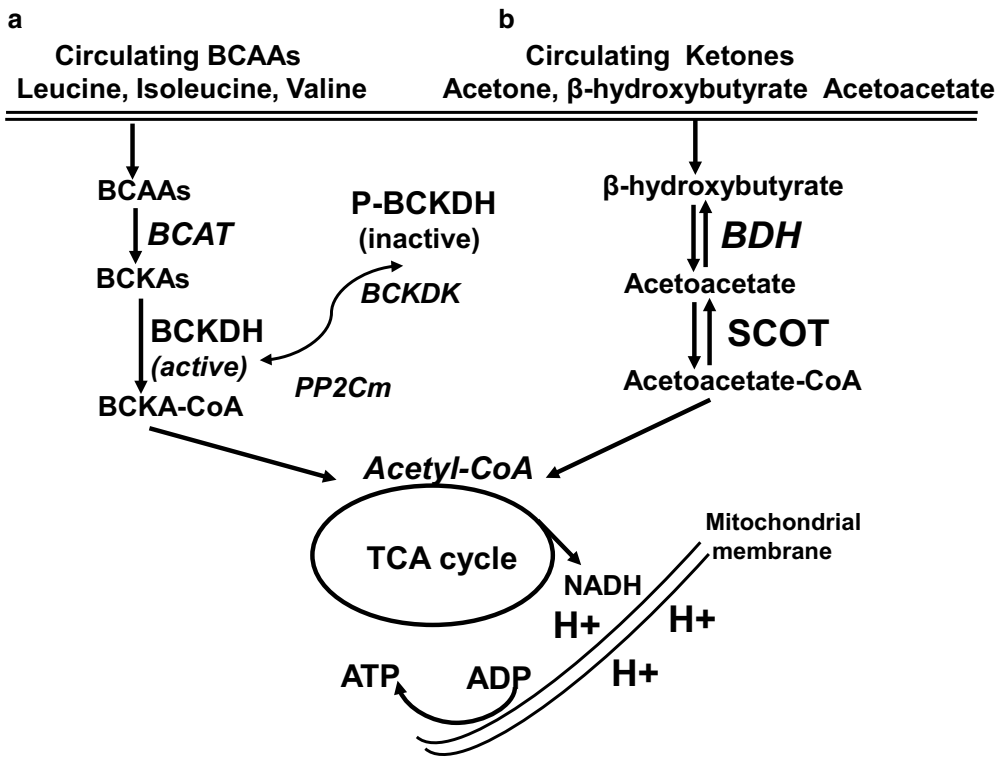

Fig. 2 Metabolism of branched chain amino acids (BCAAs) and ketones. **a** BCAAs consist of valine, leucine and isoleucine. The metabolic homeostasis of BCAAs is controlled by a series of BCAA catabolic including branched chain aminotransferase (BCAT) and branched chain α-keto acid dehydrogenase (BCKDH). As the rate-limiting enzyme of BCAA degradation, activity of BCKDH is regulated by phosphorylation/inactivation via BCKDH-kinase (BCKD), while dephosphorylated and activated by a mitochondrion-localized protein phosphatase-2C. BCAAs are converted to acetyl CoA, which enters the tricarboxylic acid cycle (TCA) and electron transport chain (ETC) to generate ATP. **b** Ketone bodies are produced predominantly in the liver through ketogenesis, as the form of acetone, β-hydroxybutyrate and acetoacetate. The later two are the the main ketones circulating in the blood and transported to heart for oxidation. Once ketones enter the cardiomyocytes and be transported to the mitochondrial matrix, β-hydroxybutyrate and acetoacetate is oxidized into acetyl-CoA by β-hydroxybutyrate-dehydrogenase (BDH) and succinyl-CoA:3-oxoacid-C oA-transferase (SCOT). Acetyl CoA enters TCA and ETC to generate ATP

the observation that chronic accumulation of BCAAs reduced glucose oxidation by inactivating mitochondrial pyruvate dehydrogenase [73]. Increasing cardiac BCAAs by dietary BCAA intake or genetic knockout of PP2Cm, directly contributes to the pathogenesis of a variety of cardiometabolic diseases, including heart failure [72]. Importantly, impaired BCAA oxidation as reflected by the decreased expression of BCAA metabolic enzymes has been demonstrated in patients with DCM [12].

Of interest, a most recent study shows that BCAAs accumulation due to its catabolic defects sensitizes the cardiomyocytes to ischemia/reperfusion injury through enhancing PPARα-mediated fatty acid oxidation and lipid peroxidation [74], and that chronic accumulation of BCAAs in PP2Cm global knockout mouse heart exacerbates ischemia/reperfusion-induced injury [74]. This occurs in conjunction with an enhanced glycolysis and reduced glucose oxidation *via* enhancing PPARα dependent fatty acid oxidation [74]. The molecular signaling is that BCAA or its ketone form inactivates the general control nonderepresible-2 (GCN2) and upregulates the activating transcription factor-6 (ATF6), thereby promoting PPARα transcription [74]. This is further supported by other findings showing that amino acid starvation leads to phosphorylation and activation of GCN2 [75], while ATF6 is a transcription factor essential for PPARα transcription [76]. Importantly, the ischemia/reperfusion-induced injury was attenuated in conjunction with a reduced fatty acid oxidation [74], by adenovirus-mediated PPARα silencing and by pharmacological inhibition of PPARα [74]. These results have put one step forward for understanding the association of BCAA metabolism with PPARα.

PPARα in relation to ketone metabolism in DCM

Ketones have long been knowing as an energy substrate to be oxidized in the heart [77]. Elevated ketone body

levels have been observed in individuals with diabetes and heart failure [78]. Meanwhile, cardiac ketone oxidation can increase significantly in response to changes in the arterial concentration of ketones [79] by mass action of ketone flux [80]. Increase in ketone oxidation has been observed in the failing hearts from mouse [81, 82], rat [83], and patients [56, 84].

Ketone bodies are produced predominantly in the liver through ketogenesis, during the period of fasting, in the form of acetone, β-hydroxybutyrate (β-OHB) and acetoacetate. The later two are the the main ketones circulating in the blood [80] and being transported to extrahepatic tissues for oxidation due to very low activity of β-OHB dehydrogenase in liver [85]. Once circulating ketones enter the cardiomyocytes and be transported to the mitochondrial matrix, β-OHB is oxidized into acetoacetate by β-OHB dehydrogenase (BDH) [86], after which acetoacetate together with succinyl-CoA and be converted to acetoacetyl-CoA via succinyl-CoA:3-oxoacid-CoA-transferase (SCOT), the rate limiting enzyme that is encoded by the gene *Oxct1*. Lastly, acetoacetyl-CoA is catalyzed by acetyl-CoA acetyltransferase to become acetyl-CoA, which then enter the tricarboxylic acid cycle and electron transport chain to generate ATP (Fig. 2).

Diabetes causes an elevation of circulating ketones [87]. Dysfunction of insulin coupled with glucagon release increases hepatic gluconeogenesis and ketogenesis [88]. Buildup of circulating ketones potentially results in a drop of blood pH levels that can lead to ketoacidosis, a devastating complication [88]. The increase in the level of circulating β-OHB has been observed in patients with advanced heart failure in the absence of a history of diabetes [89]. Elevation in the expression of BDH and SCOT is evident in the myocardium of patients with DCM [56], implicating an increased cardiac ketone oxidation. Mice with cardiac specific SCOT deficiency exhibit accelerated pathological ventricular remodelling in response to surgically induced pressure overload injury [90]. Thus, ketones, certainly, are the vital alternative metabolic fuel, but whether the increased utilization in the failing heart is adaptive or maladaptive remains unclear [56].

Relevant to PPARα, which is recognized as a master transcriptional regulator of ketogenesis [91], a decrease in hepatic expression of genes related to ketogenesis was observed in PPARα-deficient mice that was accompanied with aggravated steatohepatitis in mice fed a high saturated-fat diet and with the inability to maintain ketone body levels during fasting [34, 91, 92]. B-OHB may play a key role in maintaining bio-energetic homeostasis in DCM where cardiac glucose utilization is reduced [93]. To this point, treatment with empagliflozin, a sodium-glucose co-transporter-2 antagonist, increased ketone levels, which could be a more efficient energy source in the failing myocardium of diabetic patients with heart failure [78] to compensate for the decreased myocardial glucose utilization [78]. However, the direct role of PPARα in the diabetic heart needs further studies to define.

PPARα and abnormalities of subcellular components in DCM

An important feature of PPARα transgenic mice is the lipid accumulation in the heart [94], in which, diacylglycerol is closely associated with cardiac insulin resistance [95], while elevation of ceramide is related to cardiac dysfunction [96]. Accumulation of toxic lipids in heart is a hallmark of DCM distinct from atherosclerotic cardiovascular diseases [2], and precede the onset of diabetes and contractile dysfunction in T2D patient [97]. The increase in the level of ceramide [98] and diaceylglycerol [99] is evident in human failure heart.

PPARα confers anti-inflammatory effects mainly through inhibiting the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) [100]. NFκB has been observed in myocardial tissues from patients with heart failure as reflected by the overexpression of NFκB-regulated genes [101]. Importantly, NFκB can be activated by excessive circulating low density lipoprotein or glucose during the pathological courses of DCM [102, 103].

The association of oxidative stress with DCM has been demonstrated by elevated levels of O-linked N-acetylglucosamine (O-GlcNAc) in DCM and heart failure [1] and in animal models of diabetes [104, 105]. Excessive glucose can increase O-GlcNAcylation event, which in turn upregulates posttranslational modification of proteins in the diabetic heart to reduce mitochondrial function and ATP production [106]. This ultimately leads to cardiac dysfunction and heart failure [106]. In supporting, mice with overexpression of antioxidant protein metallothionein are protected from developing DCM [107]. Inhibition of NFκB with pyrrolidine dithiocarbamate improved mitochondrial structural integrity in parallel with a reduced oxidative stress but increased ATP synthesis and nitric oxide bioavailability thereby restoring cardiac function in T2D [108].

Lastly, over-expression of cardiomyocyte-specific PPARα causes decreased uptake of Ca^{2+}, LV hypertrophy and systolic dysfunction in the mouse heart [33]. Ca^{2+} handling is mainly controlled by the Ca^{2+} transporters, including voltage sensitive L-type Ca^{2+} channels, troponin C, Na^{+}/Ca^{2+} exchanger, sarcoplasmic reticulum $Ca^{2+}\alpha$ ATPase (SERCA2a) and the plasma membrane Ca^{2+} pump [109, 110]. Ca^{2+} mishandling has been observed not only in animal models with T1D [111, 112]

or T2D [113, 114] with DCM, but also in patients with both ischemic and non-ischemic cardiomyopathy [115].

Current therapeutic options related to PPARα for treating DCM

To date, the DCM treatment is not specifically tailored for diabetic patients with cardiac dysfunction, neither are the clinical trials [116]. The most common co-existing conditions that cause heart failure in patients with T2D are cardiovascular disease and hypertension. Therefore, antidiabetic drugs and anti-heart failure drugs have been considered in treating heart failure patients with T2D.

The most prescribed medications for diabetic patients were metformin, sulfonylureas, insulin, thiazolidinediones (Pioglitazone, Rosiglitazone). The new class of antidiabetic medications include the dipeptidyl peptidase-4 (DPP4) inhibitors (such as saxagliptin, sitagliptin, liraglutide, and alogliptin), GLP-1R agonists and SGLT2i [117]. The anti-heart failure drugs, such as angiotensin-converting enzyme inhibitors [117], angiotensin receptor blockers [118], beta-blockers [119] and mineralocorticoid receptor antagonists [120] have been tried in heart failure patients with T2D. However, over the years it has been found that some of the anti-diabetic drugs, such as Liraglutide [121, 122] and saxagliptin [123, 124] increase the risk for heart failure. Meanwhile, the prescribed drugs for treatment of heart failure, such as rosiglitazone [124–129] and pioglitazone [130] either showed similar effect between heart failure patients with or without diabetes [131] or increased the hospitalization risk for heart failure patients in clinical trials. In contrast, a significant breakthrough in cardiology is the finding that some antidiabetic drugs are associated with a lower risk of heart failure hospitalization in patients with cardiovascular disease. Among which, some are PPARα-related as listed below.

Ligands for activation of PPARα The endogenous ligands of PPARα include fatty acids (saturated or unsaturated fatty acids [132] and its metabolites [133, 134], while the exogenous ligands are synthetic pharmaceutical agents. Current therapeutic options related to PPARα agonists include synthetic lipid-lowering drugs and glucose-lowering drugs. Of which, the former includes the conventional fibrates [135, 136] and pemafibrate, a selective PPARα modulator [41], while the later include metformin, SGLT2i and GLP-1R agonists [1].

PPARα-related drugs that might be risky in treating DCM The conventional fibrates, such as fenofibrate, bezafibrate, and clofibrate, are mainly excreted from the kidney [137, 138]. Their effect on antidiabetic microvascular disorders has been demonstrated in a number of large-scale clinical studies [139–141]. However, various off-target effects, such as, deterioration in liver and kidney function were evident [142, 143], indicating that their clinical efficacy is not reliable. Administration of gemfibrozil significantly reduced cardiovascular event rate (the primary endpoints of the trials), but significant drug-drug interactions between gemfibrozil and cerivastatin resulted in a very high incidence of rhabdomyolysis in patients [144]. On the other hand, the meta-analysis showed that treatment with fibrates did not significantly reduce the total mortality rate [145–147]. Thus, it was confirmed that bezafibrate [148] and fenofibrate [140] have a significant inhibitory effect on cardiovascular events. The lack of a significant mortality benefit by fibrates has led many doctors to consider them as second line drugs [143, 149].

PPARα-related drugs that might be safe in treating DCM Different from conventional fibrates, pemafibrate (K-877, Parmodia™), a novel selective PPARα modulator, is mainly metabolized by the liver [150, 151], and is 2500 times effective in activating PPARα than the conventional fibrates [41, 150] and having a better triglyceride-lowering activity. One of the mechanisms for lowering triglyceride is that, pemafibrate, through PPARα (Fig. 3), up-regulates not only hepatic fibroblast growth factor 21(FGF21) [152], but also lipoprotein lipase (LPL) in mice [152]. FGF21 is known to reduce secretion of very low-density lipoprotein (VLDL) [153], while LPL is known to catalyze the hydrolysis of triglyceride in VLDL and chylomicrons [154]. Its higher efficacy over fenofibrate has been confirmed by several clinical trials in Japan [155–158]. The safety profile of pemafibrate has shown no clinically adverse effects on renal or hepatic function [157, 159], and it is well tolerated over 52 weeks in T2D patients with hypertriglyceridemia [159], and in patients with impaired kidney function [160]. Importantly, pemafibrate does not show any drug interactions with various statins as demonstrated in two clinical studies [161].

With respect to cardiovascular event, pemafibrate has more potent anti-atherosclerotic effect [155–157] and glucose-lowering effect [162, 163] than the conventional fibrates in dyslipidaemic patients or hypertriglyceridemic patients with T2D. The decrease in fibrinogen expression has been demonstrated to be a predictor of reduced mortality [164], while a superior fibrinogen reducing effect of pemafibrate has been demonstrated when compared to fenofibrate in a 12-week clinical trial with dyslipidaemic patients [165]. In addition, postprandial hypertriglyceridemia is a known risk factor for cardiovascular disease due to increases in atherogenic chylomicron remnants. Pemafibrate significantly reduced postprandial triglycerides in dyslipidemic patients [163] and in diabetic patients [159, 162]. Furthermore, fasting blood glucose and insulin levels were significantly reduced by pemafibrate in hypertriglyceridemic patients with T2D relative

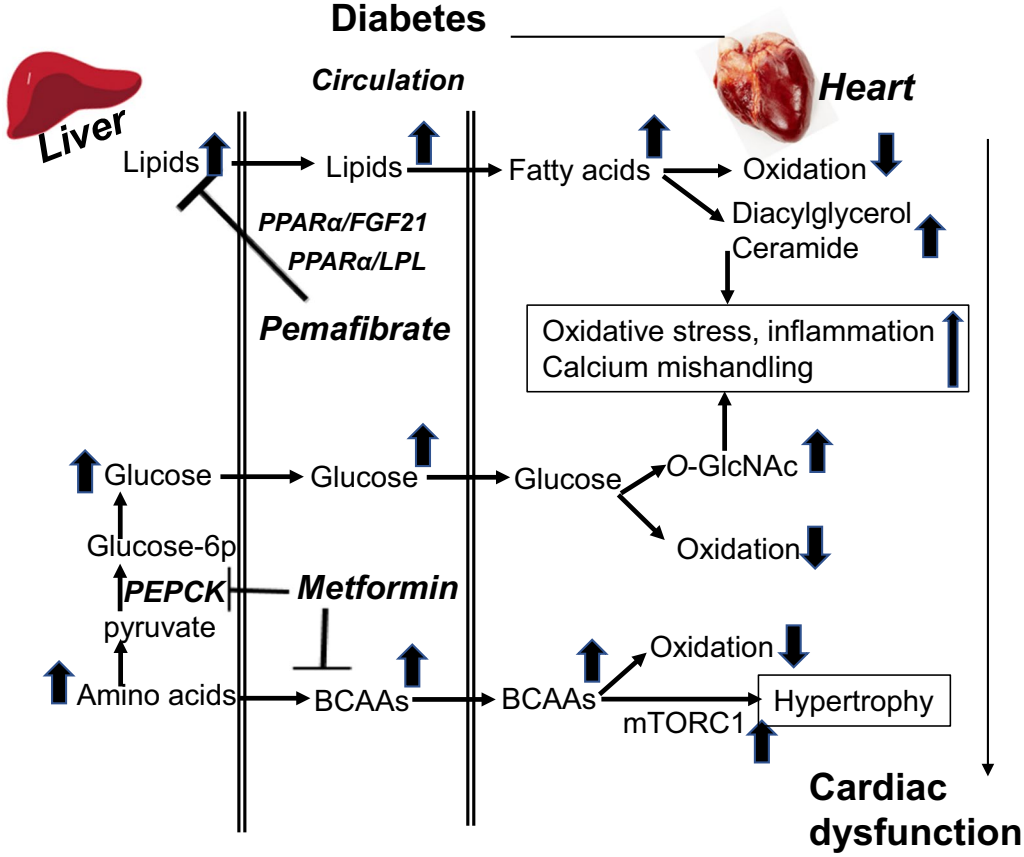

Fig. 3 PPARα, pemafibrate, metformin and cellular abnormalities in diabetic cardiomyopathy (DCM). In diabetes, enhanced hepatic lipids, glucose and BCAA output are enhanced, resulting in lipids accumulation, increased O-GlcNAcylation and mTORC1 activation in heart. Along with the altered mitochondrial energy metabolism, these intracellular abnormalities contribute to the formation of cardiac hypertrophy and cardiac dysfunction. Pemafibrate, a novel selective PPARα modulator, is highly effective in activating PPARα than the conventional fibrates and having a better triglyceride-lowering activity through up-regulating not only hepatic fibroblast growth factor 21 (FGF21), but also lipoprotein lipase (LPL) in mice. Metformin is used in treating DCM due to its effect on reduces hepatic gluconeogenesis by inhibiting phosphoenolpyruvate carboxykinase (PEPCK). In addition, an effect of metformin in reducing circulating branched chain amino acids (BCAA) is observed in insulin-resistant mice. Further studies need to clarify if metformin may reduce cardiac hypertrophy through down-regulating BCAA-mediated mTORC1 pathway

to placebo [166]. To date, a clinical study to investigate the effect of pemafibrate on reducing cardiovascular events is on going with large-scale of T2D patients and involving multiple countries [167]. Thus, pemafibrate is expected to have a superior benefit-risk balance, and offer the potential for ameliorating diabetic microvascular complication.

Metformin Clinical studies have shown that metformin reduces gluconeogenesis in T2D in association with decreasing plasma dipeptidyl peptidase-4 activity [168] and increasing circulating levels of GLP-1 [169]. The molecular mechanisms mediating the actions of metformin is PPARα-dependent [170]. Of interest, transcription factor Kruppel-like factor 15 (KLF15) has been demonstrated as a molecular target in coordination with PGC1α for the glucoregulatory actions of metformin [171]. KLF15 has recently emerged as a critical transcriptional regulator of BCAA metabolism [72]. Given metformin is known to activate PGC-1α, which is a positive regulator of BCAA catabolic gene expression [172, 173], one might expect metformin to affect circulating BCAA levels. Indeed, metformin reduces circulating BCAA in insulin-resistant mice [174] via a mechanism to favour serotonergic neurotransmission in the hippocampus and promote antidepressant-like effects in mice fed a high fat diet [174].

Given that individuals with T2D have higher levels of circulating BCAA [175] and a strong link exists between dysregulated BCAA and cardiac function, one would propose that metformin treatment for diabetic patients may decrease circulating BCAA levels, thereby preventing cardiac hypertrophy via BCAA-mediated mTORC1 pathway (Fig. 3). Further investigation of the mechanisms by which KLF15 or BCAA is dysregulated in cells/tissues

would provide additional insight into metformin action for the development of new antidiabetic drugs. Based on the observational studies, it has been proposed that metformin is associated with lower mortality and heart failure hospitalization rates than insulin and sulphonylureas [176]. Metformin has been suggested as first-line treatment for patients with T2D and heart failure who have preserved or moderately reduced renal function [176]. However, the effect of metformin has not been assessed in clinical trials in diabetic patients with heart failure. Thus, the statement that metformin is efficacious and safe for T2D patients with hear failure is inconclusive.

GLP-1 receptor agonists In the past decade, GLP-1 and its analogs have been introduced as a new class of antidiabetic medications [177]. Most recent study has demonstrated that GLP-1 agonist exendin-4 ameliorated cardiac cardiac lipotoxicity in DCM via PPARα pathway in diabetic mice [42]. GLP-1 agonists attenuate apoptosis in rat cardiomyocytes [178], while enhance nitric oxide-induced vasodilation, and facilitate glucose use in the myocardium [179, 180]. In addition, GLP-1R is highly expressed in the heart, and prominent in the therapeutics of T2D due to their efficacy in glycemia, safety, low risk of hypoglycemia and multilevel pathophysiological superiority [181] and benefits in cardiovascular disease reduction [182]. Several large placebo-controlled trials in patients with T2D and cardiovascular disease have shown that GLP-1R agonists, such as semaglutide, have a neutral effect on reducing risk for heart failure hospitalization [183–186].

SGLT2 inhibitors The mechanism of SGLT2 action is through inhibiting the SGLT2 in the kidney proximal tubule leading to excretion of glucose in urea with consequent improvement in glucose control, weight reduction and decrease in blood pressure [187]. As the representative SGLT2i, empagliflozin and canagliflozin have been assessed in two randomized clinical trials for cardiovascular [188–190]. Both of which have shown a significant reduction in heart failure hospitalization [188, 190].

Recently reported evidence in cardiomyocytes have shown that SGLT2i can inhibit Na^+/H^+ exchanger, resulting in lowering intracellular Na^+ and Ca^{2+} while increasing mitochondrial Ca^{2+} concentrations, ultimately improving cardiac mitochondrial function and energetics [191]. This off-target effect of SGLT2i may explain, in part, the beneficial effect of SGLT2i on heart failure [187] in relevant to the role of cardiac Na^+/H^+ exchanger in the pathophysiology of heart failure [192].

To date, it is unknown whether a relationship between PPARα and SGL2 inhibitor exists. A systematic review and trial-level meta-analysis using the PubMed and EMBASE databases have indicated that GLP1-R agonist and SGLT2i reduce atherosclerotic myocardial infarction, stroke, and cardiovascular death to a similar degree in patients with established atherosclerotic cardiovascular disease [193].

Conclusions

The molecular mechanisms underlying the progression of diabetes and heart failure are closely intertwined, and the degree of clinical acceleration is greatly enhanced when the two conditions coexist as DCM. Pemafibrate, metformin and GLP-1 agonists are PPARα-related drugs that have demonstrated their efficacy and safety in reducing lipid and glucose in diabetic patients during the clinical studies. One theme common to rodent and human studies is the lack of data specific to sex differences and treatment options specific to females. Future clinical trials of heart failure treatment with these drugs that include both male and female patients with T2D would be helpful to clarify whether they can be specifically tailored for DCM patients. It is reasonable to expect that they would have a superior benefit-risk balance and offer potential for ameliorating DCM.

Abbreviations

ATF6: Activating transcription factor-6; BCAA: Branched chain amino acid; BCAT: Branched chain aminotransferase; BCKDH: Branched chain α-keto acid dehydrogenase; BCKDK: BCKDH-kinase; BDH: βOHB dehydrogenase; DCM: Diabetic cardiomyopathy; DPP4: Dipeptidyl peptidase-4; FGF21: Fibroblast growth factor 21; GCN2: General control nonderepresible-2; β-OHB: β-Hydroxybutyrate; GLP-1R: Glucagon-like peptide 1-receptor; KLF15: Kruppel-like factor 15; LPL: Lipoprotein lipase; LV: Left ventricular; MR: Magnetic resonance; NFκB: Nuclear factor kappa-light-chain-enhancer of activated B cells; *O*-GlcNAc: *O*-Linked N-acetylglucosamine; PGC1α: Peroxisome-proliferator-activated receptor gamma -coactivator-1α; PP2Cm: Protein phosphatase-2Cm; PPARα: Peroxisome proliferator-activated receptor α; SCOT: Succinyl-CoA:3-oxoacid-CoA-transferase; SERCA2a: Sarcoplasmic reticulum Ca^{2+}α ATPase; SGLT2i: Sodium-glucose co-transpoter 2 inhibitors; T1D: Type 1 diabetes; T2D: Type II diabetes; VLDL: Very low-density lipoprotein.

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Competing interests
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