ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as powerful drugs that can be used to treat heart failure (HF) patients, both with preserved and reduced ejection fraction and in the presence or absence of type 2 diabetes. While the mechanisms underlying the salutary effects of SGLT2 inhibitors have not been fully elucidated, there is clear evidence for a beneficial metabolic effect of these drugs. In this review, we discuss the effects of SGLT2 inhibitors on cardiac energy provision secondary to ketone bodies, pathological ventricular remodeling, and inflammation in patients with HF. While the specific contribution of ketone bodies to the pleiotropic cardiovascular benefits of SGLT2 inhibitors requires further clarification, ketone bodies themselves may also be used as a therapy for HF.

Keywords: Sodium-glucose transporter 2 inhibitors; Ketone bodies; Heart failure; Inflammation; Ventricular remodeling

INTRODUCTION

Heart failure (HF) is a devastating condition that affects 40 million people worldwide. The prevalence of HF is reaching epidemic proportions, at least partially explained by the global burden of cardiovascular risk factors and population aging. In the past decades, advances in medical and device-based therapy have considerably improved outcomes for HF patients. Nevertheless, the mortality rates continue to be very high. For instance, a recent meta-analysis demonstrated that the 10-year survival rate of HF is only 34.9%, irrespective of the cause of HF.

Pharmacotherapy remains the cornerstone of HF treatment, and several powerful new therapeutic opportunities have recently emerged, such as angiotensin-neprilysin receptor inhibitors (ARNI), sodium-glucose cotransporter-2 (SGLT2) inhibitors, omecamtiv mecarbil (INN), and vericiguat. Of these, SGLT2 inhibitors have arguably provided the most impressive and consistent benefits across the HF spectrum, coupled with an exceptional safety profile. This feature is all the more remarkable because SGLT2 inhibitors were initially designed as antidiabetic drugs, and recent antidiabetic drugs have paradoxically increased the incidence of cardiovascular events.
Despite taking the HF world by storm, the mechanism responsible for the beneficial effects on HF outcomes is not fully understood and is often debated. Multiple mechanisms have been proposed, including metabolic, diuretic, and pleiotropic off-target effects. The current review will discuss a prevailing theory in which SGLT2 inhibitors provide the failing heart with an additional energy source, secondary to an increase in circulating ketone bodies.

**SGLT2 INHIBITORS**

The first SGLT inhibitor was isolated from the bark of apple trees, evoking the aphorism “an apple a day keeps the doctor away.” Nevertheless, the connection between the benefit of SGLT2 inhibitors and HF is a serendipitous story. SGLT2 inhibitors were designed as antidiabetic drugs because they block glucose reabsorption in the proximal renal tubules, resulting in renal excretion of glucose; promoting glycosuria, they cause a mild insulin-independent reduction in serum glucose levels.

Phlorizin, the first-discovered unselective SGLT1/SGLT2 inhibitor, was discovered in 1835 and was used to treat malaria, nephritis, and sarcoma. It was also noted that phlorizin promoted glucosuria and decreased plasma glucose levels. However, high doses were required to achieve glucosuria, often offset by severe diarrhea. More recently, the stability, specificity, and selectivity of SGLT2 inhibitors have been considerably improved, resulting in modern SGLT2 inhibitors with favorable safety characteristics such as dapagliflozin, canagliflozin, ertugliflozin, sotagliflozin, and empagliflozin. The main differences lie in their selectivity. For example, while canagliflozin is 250-fold more selective for SGLT2 than SGLT1, empagliflozin is the most selective, exceeding 2,500-fold.

These compounds are all registered antidiabetic agents that were approved by the United States Food and Drug Administration (FDA) to manage type 2 diabetes mellitus (T2DM) in 2008 and by the European Medicines Agency (EMA) in 2012.

**CARDIOVASCULAR EFFECTS OF SGLT2 INHIBITORS**

Following the discovery that dipeptidyl peptidase-4 increases ischemic cardiovascular risk, the monitoring of HF outcomes is currently mandatory in the USA during the clinical development of new antidiabetic therapies. Surprisingly, the safety analysis of the EMPA-REG OUTCOME trial published in 2015 demonstrated that empagliflozin resulted in a significant reduction in HF hospitalizations. Furthermore, a similar reduction in HF hospitalizations in patients with T2DM was observed with canagliflozin and dapagliflozin in the DECLARE-TIMI 58 trial, suggesting a class effect.

A possible beneficial effect of these drugs in patients with HF was quickly hypothesized. Subsequently, this benefit in cardiovascular events was confirmed in HF patients with or without diabetes through clinical trials, such as DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF. More recently, systematic reviews with meta-analyses revealed that the beneficial effects of SGLT2 inhibitors in HF are comparable in patients with and without diabetes (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.71–0.83 and HR, 0.75; 95% CI, 0.65–0.87, respectively).
Within a decade since the first clinical trial in diabetes, SGLT2 inhibitors are now recommended as the first-line therapy for patients with HF with reduced ejection fraction (HFrEF). Furthermore, SGLT2 inhibitors have been shown to reduce HF hospitalization and mortality in patients with HF with preserved ejection fraction (HFpEF).

**KETOGENESIS**

Ketogenesis is a metabolic pathway that generates ketone bodies, predominantly in the liver. First, free fatty acids (FFA) are converted to acetyl-coenzyme A (CoA) via mitochondrial β-oxidation. Acetyl-CoA is condensed with acetoacetyl-CoA via 3-methylglutaryl-CoA synthase 2 (HMGCSS2) to generate 3-hydroxy 3-methylglutaryl-CoA (HMGC), and later converted by HMGC lyase to acetoacetate (AcAc). AcAc is then reduced by D-b-hydroxybutyrate dehydrogenase (BDH1) to generate 3-hydroxybutyrate (β-OHB), which is released into the circulation by the solute carrier 16A family on hepatocytes. β-OHB consequently enters the myocyte mitochondria via monocarboxylic acid transporter 1/2 (MCT1/2) and is converted back to AcAc by BDH1, subsequently transformed into acetoacetyl-CoA by succinyl-CoA, 3-ketoacid-CoA transferase/3-oxoacid CoA-transferase 1 (SCOT/OXCT1), and finally by conversion of mitochondrial acetoacetyl-CoA thiolase into two acetyl-CoA molecules that enter the tricarboxylic acid (TCA) cycle to produce ATP (Fig. 1).

**REGULATION OF KETOGENESIS**

Ketone bodies are considered evolutionarily conserved fuels for cellular metabolism designed to provide energy during periods of nutritional stress, such as starvation. Ketone bodies are mainly generated in the liver, with minor if any production of ketone bodies in the kidney and the retinal pigment epithelium. Ketogenesis is sensitive to multiple hormonal stimuli released during physiological and pathological stress conditions, the most important of which is insulin. In the presence of insulin, lipolysis is reduced, and the ketogenetic flux in the liver is diminished. Conversely, catecholamines (norepinephrine and epinephrine) stimulate lipolysis and, subsequently, ketogenesis. Natriuretic peptides (NPs) also stimulate lipolysis.

Type B natriuretic peptide (BNP), a central peptide in the diagnosis and treatment of HF, has been shown to correlate with circulating total ketone body levels. This suggests that BNP is secreted from the heart under stress to promote lipolysis and ketogenesis and provide an endogenous fuel surge during hemodynamic stress.

Atrial natriuretic peptide (ANP) activates hormone-sensitive lipase (HSL) in adipocytes; as a result, it increases lipolysis and mobilizes FFA from adipose tissue deposits to the liver. ANP is now increasingly recognized as a metabolic hormone that controls lipid metabolism and energy expenditure. However, whether its lipolytic effects also translate into a ketogenic effect has not been well described.

The myocardium is the largest consumer of ketone bodies per unit mass and follows a pattern of circadian oscillations. In overnight-fasted adults, total ketone body concentrations are approximately 0.1–0.4 mM and tend to increase 1–8 mM during prolonged fasting, extreme physical activity, and insulin deprivation. Ketosis is defined as a β-OHB concentration above 0.5 mM. Chu et al. recently proposed that the ideal therapeutic β-OHB concentration is 1–3 mM, which may be achieved with treatment with...
SGLT2 inhibitors. However, the available clinical evidence suggests that the ketogenic effects of SGLT2 inhibitors are less pronounced. 

**THE PHYSIOLOGICAL ROLE OF KETONE BODIES IN THE HEART**

The heart requires tremendous amounts of ATP, for which it primarily depends on the oxidation of fatty acids (60%–90%), followed by glucose at 10%–30%. Finally, ketone bodies contribute up to 5% of total ATP under normal conditions. The most abundant systemic ketone body is β-OHB. The amount of cardiac ketone body oxidation is strongly correlated with its circulating concentrations, and a dramatic spare capacity for ketone body oxidation

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**Fig. 1.** Energy production through SGLT2 inhibitors and ketone bodies. By reducing plasma glucose levels due to increased insulin sensitivity and enhanced gluconeogenesis, the mobilization of deposits of FFA to the liver increases secondary to HSL stimulation. In the liver, FFA are oxidized, generating acetyl-CoA. Two acetyl-CoA derived from FFA are used to produce acetoacetyl-CoA by a thiolase reaction; another acetyl-CoA is condensed into acetoacetyl-CoA by HMGCS2 (this synthase is inhibited by insulin and stimulated by glucagon). After HMGCS, it is lysed by HMGCL, generating AcAc, which is oxidized by BDH1 to generate β-OHB. The latter two substances are probably released into circulation through SCL16. Myocytes take up ketone bodies through MCT. β-OHB is converted to AcAc again to be metabolized to acetoacetyl-CoA by SCOT; subsequently, through ACAT, acetyl-CoA is generated to enter the TCA cycle and produce ATP. The image was created with BioRender.com.

ACAT, acetoacetyl-CoA thiolase; AcAc, acetoacetate; ATP, adenosine triphosphate; BDH1, β-hydroxybutyrate dehydrogenase-1; CPT-I, carnitine palmitoyltransferase 1; ECT, electron transport chain; FA, fatty acid; FFA, free fatty acids; HMGCS2, 3-methylglutaryl-CoA synthase 2; HMGIC, 3-hydroxy-3-methylglutaryl-CoA; HMGCL, 3-hydroxy 3-methylglutaryl-CoA lyase; HSL, hormone-sensitive lipase; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier; PDH, pyruvate dehydrogenase; SCL16, solute carrier 16A family members; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SCOT, succinyl-CoA: 3-ketoacid coenzyme A transferase; TCA, tricarboxylic acid; TG, triglyceride; β-OHB, β-hydroxybutyrate; β-Oxid, β-oxidation.
exists. Of note, when concentrations reach 2.0 mM in *ex vivo* perfused hearts, ketone bodies become the primary source of fuel.

**Ketone bodies in HF**

In HF, ketone body concentrations are increased in the circulation of patients with acute and chronic HF, both with reduced and preserved ejection fraction, and also in animal models. Furthermore, it has been postulated that the increase in ketone body production reflects an autonomous response to cardiac stress in HF that is mediated by NPs and other neurohormones.

A myocardial energy deficit has been well described in patients with HF, and it is attributed to a progressive diminution of FFA and glucose oxidation, the "energy-starved heart" theory. ATP production in advanced HF is reduced by approximately 30%–40%, associated with losses of high-energy phosphates and creatine kinase activity that reduce the delivery of ATP to the myofibrils. In this context, the HF-induced increase in ketone body levels is considered to be adaptive for several reasons:

1. Ketone body oxidation does not influence the oxidation rates of fatty acids (FA) or glucose; thus, ketone bodies provide an additional source of fuel.
2. Because the failing heart is considered to be oxygen-deprived and ketone bodies are more oxygen-efficient than FA, multiple authors have referred to ketones as super-fuels, although their oxygen efficiency is lower than glucose.
3. There is a linear relationship between circulating ketone body concentrations and extraction by the heart muscle, suggesting that there is an impressive spare capacity for ketone body oxidation that can be used to refuel the failing heart.

The increase in ketone body oxidation is accompanied by a parallel increase in the cardiac expression of the ketolytic enzymes BDH1 and SCOT. Furthermore, in models with cardio-specific deletion of BDH1 and SCOT, the severity of HF increases. In contrast, transgenic animal models with BDH1 overexpression and increased afterload revealed increased ketone oxidation, decreased oxidative stress, and consequent protection against adverse cardiac remodeling.

**Mechanism of ketogenesis by SGLT2 inhibitors**

The mechanism by which SGLT2 inhibitors increase ketone body concentrations is not entirely understood. By decreasing plasma glucose levels secondary to increased insulin sensitivity in muscle tissue and endothelium, glucagon levels increase (thereby decreasing the insulin/glucagon ratio), mobilizing fat deposits towards the liver through the stimulation of HSL. In the liver, FFA are oxidized to acetyl-CoA to generate energy. However, when gluconeogenesis increases and glucose levels are low, acetyl-CoA is redirected from the TCA cycle to produce ketone bodies (AcAc or $\beta$-OHB).

This shift in fuel consumption from glucose to fat oxidation leads to a decreased insulin-to-glucagon ratio, which enhances gluconeogenesis, promotes lipolysis, and facilitates ketogenesis (Fig. 2).

**Ketone body levels with SGLT2 administration**

Since improvements in cardiac energetic efficiency have been attributed to ketone bodies, they have been called a "super-fuel" and "thrifty substrate." Thus, it is attractive to hypothesize that the increased bioavailability of ketones and the use of ketone bodies by the myocardium observed during SGLT2 inhibitor therapy could explain the cardiovascular
benefits observed in HFrEF and HFpEF in clinical trials (Table 1). However, it should be noted that experimental and clinical evidence comparing the ketogenic effects of different SGLT2 inhibitors currently remains sparse.

In an animal HF model, Yurista et al. demonstrated an increase in \(\beta\)-OHB levels, associated with a significant increase in the expression of BDH1 and SCOT. Santos-Gallego et al. \(^{21}\) also showed increased levels of total ketone bodies in a non-diabetic HF animal model treated with empagliflozin. Moreover, using a non-selective SGLT1/SGLT2 inhibitor, it has been demonstrated that there is an increase in tubular reabsorption of ketone bodies, which contributes to the sustained increment in circulating ketone body levels. \(^{110-112}\)

The possible mechanism behind the increase in circulating ketone body levels is that treatment with SGLT2 inhibitors produce a metabolic state that resembles the accelerated starvation response (a quicker shift from glucose to FFA oxidation). \(^{113}\) As a consequence of a reduction in glucose oxidation, the mobilization of FA from adipocytes increases and, consequently, the levels of \(\beta\)-OHB and acetoacetate rise significantly. \(^{25,95}\) With long-term SGLT2 inhibitor treatment, ketone body levels double; for \(\beta\)-OHB, the median percent increase is 78\% compared to baseline, \(^{103}\) suggesting downstream effects of SGLT2 inhibitors on hepatic metabolism. \(^{114}\)

In patients with T2DM, Ferrannini et al. \(^{87}\) identified an increase in fasting \(\beta\)-OHB of up to 0.56 mmol/L 4 weeks after starting treatment with empagliflozin. Furthermore, Al Jobori et al. \(^{90}\) demonstrated a significant increase in ketone body concentrations and a strong correlation between plasma FFA levels and plasma ketone concentrations in patients with T2DM. Moreover, it has been observed that in patients with a low-carbohydrate diet
EMPA treatment is associated with an increase in circulating levels of total ketone body, increase ATP production and improves LVEF and cardiac remodelling

EMPA switches myocardial fuel to ketone bodies, FFA and BCAA. It also ameliorates adverse cardiac remodelling and improves LV systolic function

EMPA improves diastolic function regardless of changes in cardiac ketone body metabolism

β-OHB does not differ in EMPA compared to the control group but improves LV mass and improves diastolic dysfunction

Combining this with SGLT2 inhibitors, the increase in ketone bodies is more pronounced than in those consuming high-carbohydrate diets. It should be noted that the association between SGLT2-induced ketonemia and the salutary effects observed are descriptive in nature. Future studies—for instance research employing cardiomyocyte-specific knockdown of the BDH1 receptor—are required to define the exact contribution of ketones to the salutary effects of SGLT2 inhibitors.

**Ketone bodies as a metabolic biomarker in heart failure**

The increase of ketone body levels in HF suggests that they could serve as a prognostic metabolic biomarker. Moreover, a strong correlation has been found between the concentration of ketone bodies and that of BNP. Many methods are used to detect elevated ketone body levels, such as blood, urine, and exhaled acetone concentrations in the breath of HF patients.

Yokokawa et al. found elevated exhaled acetone concentrations in patients with acute HF and observed a decrease in concentrations after treatment and clinical improvement. Furthermore, exhaled acetone concentrations have shown a good correlation with hemodynamic severity (pulmonary capillary wedge pressure ≥18 mmHg) in non-ischemic HF. A similar observation is a higher exhaled acetone concentration in stage C of HF than in early stages.

**Table 1. Relationship of the use of SGLT2 inhibitors and ketone bodies in pre-clinical and clinical studies**

| Reference | SGLT2 inhibitor | Model | HF | Diabetes | Ketone body measured | Outcome |
|-----------|-----------------|-------|----|----------|----------------------|---------|
| Al Jobori et al. | EMPA | Human | No | T2DM | β-OHB (µmol/L) | Significant increase in glucagon, FFA and β-OHB in T2DM vs. non-diabetic |
| Polidori et al. | CANA | Human | No | T2DM | β-OHB and acetoacetate (µmol/L) | Increases in ketone bodies that were greater than other metabolic measures in patients with T2DM |
| Ferranini et al. | EMPA | Human | No | T2DM | β-OHB (µmol/L) | Lower insulin to glucagon ratio favours ketogenesis. T2DM patients doubled fasting β-OHB levels |
| Daniele et al. | DAPA | Human | No | T2DM | β-OHB and acetoacetate (µmol/L) | DAPA caused a shift from glucose to lipid oxidation and increased plasma ketone bodies concentration |
| Inagaki et al. | CANA | Human | No | T2DM | Total ketone body (µmol/L) | EMPA increases circulating levels of total ketone bodies |
| Oldgren et al. | DAPA | Human | No | T2DM | β-OHB (µmol/L) | No differences in plasma levels of β-OHB between DAPA vs the placebo group. DAPA reduced heart work but limited effects on myocardial function |
| Yabe et al. | LUSEO | Human | No | T2DM | Ketone bodies (µmol/L) | Ketone bodies were significantly higher in the low carbohydrate and high glycaemic index diet |
| Verma et al. | EMPA | C57BL/6J and db/db mice | No | Mouse surrogates for diabetes (db/db mice) | Total ketone body (µmol/L) | EMPA treatment is associated with an increase in ATP production but did not increase cardiac efficiency |
| Yurista et al. | EMPA | Sprague-Dawley rats | Yes (M1) | Non-diabetic | Total ketone body (µmol/L) | EMPA increases circulating levels of total ketone body, increase ATP production and improves LVEF and cardiac remodelling |
| Santos-Gallego et al. | EMPA | Yorkshire pigs | Yes (M1) | Non-diabetic | Total ketone bodies myocardial uptake (ng/g/min) | EMPA switches myocardial fuel to ketone bodies, FFA and BCAA. It also ameliorates adverse cardiac remodelling and improves LV systolic function |
| Moellmann et al. | EMPA | Male db/db mice | Yes (DD) | Mouse surrogates for diabetes (db/db mice) | β-OHB and acetoacetate (µmol/L) | EMPA improves diastolic function regardless of changes in cardiac ketone body metabolism |
| Connelly et al. | EMPA | Sprague-Dawley rats | Yes (DD) | Non-diabetic | β-OHB (µmol/d) | β-OHB does not differ in EMPA compared to the control group but improves LV mass and improves diastolic dysfunction |

**References**

- Al Jobori et al. 2010
- Polidori et al. 2010
- Ferranini et al. 2017
- Daniele et al. 2010
- Inagaki et al. 2014
- Oldgren et al. 2016
- Yabe et al. 2016
- Verma et al. 2017
- Yurista et al. 2010
- Santos-Gallego et al. 2018
- Moellmann et al. 2019
- Connelly et al. 2010

**Note:** ATP, Adenosine triphosphate; BCAA, branched-chain amino acids; BMI, body mass index; CANA, canagliflozin; DAPA, dapagliflozin; DD, diastolic dysfunction; EMPA, empagliflozin; FFA, free fatty acids; HF, heart failure; LUSEO, luseogliflozin; LV, left ventricle; LVEF, left ventricle ejection fraction; MI, myocardial infarction; SGLT2, sodium/glucose cotransporter-2; T2DM, type 2 diabetes mellitus; β-OHB, β-hydroxybutyrate.
Other methods have also found a correlation between ketone bodies and HF. For example, in animal models with HF due to cardiotoxicity, using positron emission tomography of the myocardium, [11C]-acetoacetate has been proposed as a possible early marker of damage. Moreover, elevated levels of β-OHB in patients with acute HF have been associated with increased mortality using nuclear magnetic resonance spectroscopy, suggesting its prognostic value.

**POTENTIAL BENEFITS SECONDARY TO THE ELEVATION OF KETONE BODIES BY SGLT2 INHIBITORS**

**Increased cardiac energetics**

In HF, roadblocks in cardiac substrate metabolism result in impediments in the cardiac capacity to oxidize glucose and FA, so that the falling heart begins to rely more on ketone bodies and other substrates. Indeed, ketone bodies can account for up to 20% of cardiac metabolism in HF. β-OHB has been debated as a “thrifty substrate” because the heart takes it up freely, and it is oxidized in preference to FFA. In addition, Ferrannini et al. hypothesized that β-OHB improves work efficiency at the mitochondrial level.

It has been postulated that ketone body oxidation is an additional fuel source that is energy-efficient and has a very high extraction by the heart. Moreover, patients without T2DM who received a continuous infusion of β-OHB showed increases in cardiac output, left ventricular ejection fraction (LVEF), and myocardial oxygen consumption, without altering the myocardial external energy efficiency. Furthermore, animal models of myocardial infarction treated with empagliflozin or a ketone ester diet increased circulating ketone body levels and improved left ventricular function. Notwithstanding, different studies have not shown an improvement in cardiac efficiency.

Increasing ketone body levels could be a valuable strategy for treating metabolic dysfunction in HF, and it is reasonable to assume that the low ketonemia level induced by SGLT2 inhibitors could improve myocardial energetics and contractile function. Recently, the EMPA-TROPISM trial demonstrated improvement in left ventricular systolic function in patients with HFrEF without T2DM who received empagliflozin. Nevertheless, more evidence is required to determine the degree of the contribution of ketone bodies to energy metabolism and cardiac contractility.

**Reversing cardiac remodeling**

Adverse cardiac remodeling manifests as changes in sphericity, enlargement, and decreased left ventricular function after cardiac injury. In addition, inflammation, fibrosis, type I collagen levels, and cardiomyocyte cell death are involved in this process and can occur in HFrEF and HFP EF, worsening the prognosis. However, it has been shown that reversing cardiac remodeling can reduce mortality and the risk of cardiovascular events. Moreover, Kramer et al. have shown a proportional relationship between the effects of drugs or devices on short-term ventricular remodeling and long-term mortality.

Clinical trials such as DAPA-HF, EMPEROR-Reduced, and EMPA-TROPISM have repeatedly shown that SGLT2 inhibitors reverse and improve adverse cardiac remodeling in patients with HFrEF and HFP EF, which could explain the observed cardiovascular benefits. However, since SGLT2 receptors are not expressed in the heart, the effect of
SGLT2 inhibitors on left ventricular mass is likely indirect and mediated by hemodynamic, anti-inflammatory, and metabolic effects.\textsuperscript{19,31,129}

Various hypotheses have been proposed. The diuretic and natriuretic hypotheses suggest that the sustained reduction in intravascular volume leads to a reduction in preload with consequent improvement in left ventricular systolic and diastolic function.\textsuperscript{141} This finding was also seen in the EMPA-TROPISM trial, which proved a significant reduction in end-systolic and diastolic volumes and a significant increase in LVEF compared to placebo (6% vs. −0.1%). Furthermore, this hypothesis was also supported by the findings of Mullens et al.,\textsuperscript{142} who demonstrated a significant decrease in mean pulmonary artery pressure after the initiation of SGLT2 inhibitors.

Another hypothesis suggests that ketone bodies may mitigate pathological remodeling. β-OHB has previously been shown to inhibit class I histone deacetylases, which can inhibit pro-hypertrophic transcription in HF.\textsuperscript{143} In addition, overexpression of key enzymes in ketone body oxidation, such as BDH1, protects against cardiac remodeling in models with ischemia or increased afterload.\textsuperscript{77} Moreover, in the SCOT knockout models, greater pathological remodeling is evidenced,\textsuperscript{89} suggesting some benefits of ketone bodies in cardiac remodeling. Thus, it is plausible to assume that the increase in levels of ketone bodies following SGLT2 inhibitors can ameliorate pathological remodeling. However, the mechanism is still unknown and requires further elucidation.

Attenuation of the inflammatory profile

Inflammation is central to HF syndrome, and the levels of several circulating inflammatory biomarkers correlate with the prognosis and severity of HF with a reduced or preserved ejection fraction.\textsuperscript{146-148} In particular, the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome has recently been recognized as contributing to inflammation in the myocardium of patients with chronic HF and has recently emerged as a new promising target in HF.\textsuperscript{149,150}

In patients with T2DM,\textsuperscript{151} SGLT2 inhibitors attenuate the activation of the NLRP3 inflammasome and the secretion of interleukin-1β through an increase in β-OHB levels and decreases in insulin and glucose levels, which could improve cardiovascular outcomes.\textsuperscript{152,154} In addition, by decreasing glucose levels, SGLT2 inhibitors minimize the inflammatory response of macrophages.\textsuperscript{155,156}

In HfPEF animal models, it was shown that the increase in β-OHB levels secondary to the use of empagliflozin attenuated the formation of the NLPR3 inflammasome, fibrosis, and mitochondrial dysfunction. As a mechanism, the authors proposed that mitochondrial protein acetylation was diminished due to the decrease in the acetyl-CoA pool through activation of citrate synthase and suppression of fatty acid uptake.\textsuperscript{157} Thus, this finding suggests that the SGLT2 inhibitor-mediated increase in β-OHB levels may serve as a therapeutic target to mitigate mitochondrial hyperacetylation and inflammation involved in the pathogenesis of HfPEF. Of note, in the EMPEROR-Preserved trial, a significant risk reduction was described with empagliflozin for the combination of cardiovascular death or hospitalization for HF in patients with HfPEF.\textsuperscript{41}

CONCLUSION

SGLT2 inhibitor therapy improves cardiac function and outcomes in patients with HF with or without T2DM, through multiple pleiotropic effects including increased ketone body levels.
The increase in ketone body levels appears to reflect an adaptive process that optimizes cardiac energy metabolism and could explain the improvement in overall cardiac function in patients treated with SGLT2 inhibitors.

Moreover, the reduction of adverse cardiac remodeling and fibrosis associated with ketone bodies could improve ventricular diastolic function and may also translate into benefits for patients with HFpEF. The exact contribution of ketone bodies to the cardiovascular benefits of SGLT2 inhibitors is not entirely clear and requires further clarification. Nevertheless, this mechanism of ketone bodies suggests that ketone bodies themselves could represent a new therapeutic option for HF.

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