DOI：10.6314/JIMT.202410_35(5).01 內科學誌 2024：35：317-338

Sodium-Glucose Cotransporter-2 Inhibitors and Euglycemic Ketosis: Friends or Foes

Kuo-Bin Tseng

Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital/I-Shou University, Kaohsiung, Taiwan

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are new antidiabetic drugs that were originally developed for the management of type 2 diabetes mellitus. SGLT2is exert glucosuric effects, leading to increased glucagon synthesis, enhanced fatty acid oxidation, and promoted adipose tissue mobilization, which modestly increase systemic ketone levels. For energy production under normal conditions, the healthy adult heart relies minimally on glucose but strongly on fatty acid oxidation, which contributes to between 60% and 90% of the cardiac adenosine triphosphate yield. Ketones play a minor role in adenosine triphosphate production under normal conditions. Notably, trends toward heart failure and cardiac hypertrophy can decelerate glucose metabolism, prompting a shift to ketones as alternative fuels. This transition is crucial for meeting the energy demands of cardiac cells. Furthermore, both exogenous and endogenous ketones confer protection against kidney damage and disease. Consequently, ketones are regarded as evolutionarily conserved fuels for cellular metabolism, designed to supply energy during periods of nutritional stress. In addition, ketones may improve myocardial and renal functions. The ketone β-hydroxybutyrate exerts intrinsic anti-inflammatory, antioxidative, and antifibrotic effects and can mitigate adverse left ventricular and renal remodeling or fibrosis. The cardiorenal benefits of SGLT2is are partially attributed to the occurrence of chronic low-grade hyperketonemia and a shift in myocardial and renal fuel metabolisms from relatively energy-inefficient fatty acid oxidation to energy-efficient ketone metabolism. However, SGLT2i-induced excessive ketogenesis is detrimental to certain patients, such as those with type 2 diabetes mellitus and severe acute illness and those with type 1 diabetes mellitus with substantial insulin dose reductions. This narrative review summarizes currently available evidence to provide potential mechanisms underlying the SGLT2i-induced positive and negative effects of ketones on the cardiorenal system.

Key Words: Sodium-glucose cotransporter 2 inhibitors; ketones; cardiorenal effects; mechanisms; diabetic ketoacidosis.

1. Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors (SGLT2is) are glucose-lowering drugs that inhibit glucose reabsorption in the renal proximal tubule by blocking SGLT2, thereby increasing the level of urinary glucose excretion and reducing

Reprint requests and correspondence：Kuo-Bin Tseng
Address：Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital/I-Shou University, Kaohsiung, Taiwan, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan, R.O.C.

that of glucose[1]. SGLT2is reduce the levels of fasting glucose, postprandial glucose, and glycated hemoglobin (HbA1c). In addition, these drugs confer substantial cardiovascular and renal benefits—for example, by reducing the risks of major adverse cardiovascular events, heart failure (HF), and chronic kidney disease (CKD; Table 1)[2-13]. In addition to their effects on glycemia, blood pressure, visceral adiposity, and body weight, SGLT2is confer cardiorenal benefits through several mechanisms, such as improving cardiac function, arterial stiffness, and cardiac oxygen demand and reducing uric acid levels, rates of albuminuria, and intraglomerular pressure[2]. However, the precise mechanisms underlying the beneficial effects of SGLT2is remain unclear. A potential mechanism mediating the effects of SGLT2is may involve a shift in myocardial and renal fuel metabolisms from an energy-inefficient process (e.g., fatty acid oxidation) to an energy-efficient process (e.g., ketone oxidation). SGLT2is alleviate ketonemia, promoting myocardial and renal metabolisms and improving cardiorenal energetics[14,15]. The present study explored the SGLT2i-induced positive and negative effects of ketones on the cardiorenal system.

Table 1. Cardiorenal Protective Effects of SGLT2is in Dedicated Cardiovascular, HF, and CKD Outcome Trials

Clinical tria[1]	Intervention (enrollment)	Trial type	Main inclusion criteria	Median follow-up duration (years)	Primary outcomes (HR [95% CI]; *P* value)
CV outcome trials					
EMPA-REG OUTCOME[2]	Empagliflozin (N = 7020)	Double-blind, placebo-controlled RCT	T2DM (%): 100 ASCVD; eGFR ≥ 30 mL/min/1.73 m^2 BMI ≤ 45 kg/m^2 HbA1c: 7.0% to 9.0% without GLD or 7.0% to 10.0% with stable GLD	3.3	Composite MACEs: 0.86 (0.74 to 0.99); *P* = 0.04 Cardiovascular death: 0.62 (0.49 to 0.77); *P* < 0.001 HHF: 0.65 (0.50 to 0.85); *P* = 0.002 All-cause mortality: 0.68 (0.57 to 0.82); *P* < 0.001 Nonfatal MI: 0.87 (0.70 to 1.09) Nonfatal stoke: 1.24 (0.92 to 1.67)
CANVAS[3]	Canagliflozin (N = 10 142)	Double-blind, placebo-controlled RCT	T2DM (%): 100 ASCVD or age ≥ 50 years with ≥2 risk factors for CVD	3.6	Composite MACEs: 0.86 (0.75 to 0.97); *P* = 0.02 Cardiovascular death: 0.87 (0.72 to 1.06) HHF: 0.67 (0.52 to 0.87) All-cause mortality: 0.87 (0.74 to 1.01) Nonfatal MI: 0.85 (0.69 to 1.05) Nonfatal stoke: 0.90 (0.71 to 1.15)
DECLARE-TIMI-58[4]	Dapagliflozin (N = 17 160)	Double-blind, placebo-controlled RCT	T2DM (%): 100 ASCVD or multiple risk factors for ASCVD eGFR ≥ 60 mL/min/1.73 m^2	4.2	Composite MACEs: 0.83 (0.73 to 0.95); *P* = 0.005 Cardiovascular death: 0.98 (0.82 to 1.17) HHF: 0.73 (0.61 to 0.88) All-cause mortality: 0.93 (0.82 to 1.04) Nonfatal MI: 0.89 (0.77 to 1.01) Nonfatal stoke: 1.01 (0.84 to 1.21)
VERTIS-CV[5]	Ertugliflozin (N = 8246)	Double-blind, placebo-controlled RCT	T2DM (%): 100 CVD Age ≥ 40 years eGFR ≥ 30 mL/min/1.73 m^2	3.5	Composite MACEs: 0.97 (0.85 to 1.11); *P* = 0.001 for noninferiority) Cardiovascular death: 0.92 (0.77 to 1.11) HHF: 0.70 (0.54 to 0.90) All-cause mortality: 0.93 (0.80 to 1.08) Nonfatal MI: 1.04 (0.86 to 1.27) Nonfatal stoke: 1.00 (0.76 to 1.32)

Clinical tria[1]	Intervention (enrollment)	Trial type	Main inclusion criteria	Median follow-up duration (years)	Primary outcomes (HR [95% CI]; *P* value)
HF outcome trials					
DAPA-HF[6]	Dapagliflozin (N = 4744)	Double-blind, placebo-controlled RCT	T2DM (%): 45 EF ≤ 40% NYHA class II, III, or IV NT-proBNP level ≥ 600 pg/mL eGFR ≥ 30 mL/min/1.73 m^2	1.8	Composite of cardiovascular death or HF exacerbation: 0.74 (0.65 to 0.85); $P < 0.001$ Cardiovascular death: 0.82 (0.69 to 0.98) HHF: 0.70 (0.59 to 0.83) All-cause mortality: 0.83 (0.71 to 0.97)
EMPEROR-Preserved[8]	Empagliflozin (N = 5988)	Double-blind, placebo-controlled RCT	T2DM (%): 49.1 EF ≥ 40% NYHA class II, III, or IV	2.2	Composite of cardiovascular death or HF exacerbation: 0.79 (0.69 to 0.90); $P < 0.001$ Cardiovascular death: 0.91 (0.76 to 1.09) HHF: 0.71 (0.60 to 0.83) All-cause mortality: 1.00 (0.87 to 1.15)
EMPEROR-Reduced[7]	Empagliflozin (N = 3730)	Double-blind, placebo-controlled RCT	T2DM (%): 49.8 EF ≤ 40% NYHA class II, III, or IV	1.3	Composite of cardiovascular death or HF exacerbation: 0.75 (0.65 to 0.86); $P < 0.001$ Cardiovascular death: 0.92 (0.75 to 1.12) HHF: 0.69 (0.59 to 0.81) All-cause mortality: 0.91 (0.77 to 1.10)
SOLOIST-WHF[12]	Sotagliflozin (N = 1222 [20% with LVEF >50%])	Double-blind, placebo-controlled RCT	T2DM (%): 100 Age ≥18 years Recent HHF	0.75	Composite of cardiovascular death, HHF, or urgent visits for HF: 0.67 (0.52 to 0.85); $P < 0.001$) Cardiovascular death: 0.84 (0.58 to 1.22) HHF (total number, including urgent visits for HF): 0.64 (0.49 to 0.83) All-cause mortality: 0.82 (0.59 to 1.14)
SCORED[13]	Sotagliflozin (N = 10584)	Double-blind, placebo-controlled RCT	T2DM (%): 100 eGFR: 25 to 60 mL/min/1.73 m^2 CVD risks	1.3	Composite of cardiovascular death, HHF, or urgent visits for HF: 0.74 (0.63 to 0.88); $P < 0.001$ Cardiovascular death: 0.90 (0.73 to 1.12) HHF (total number, including urgent visits for HF): 0.67 (0.55 to 0.82) All-cause mortality: 0.99 (0.83 to 1.18)
CKD outcome trials					
CREDENCE[9]	Canagliflozin (N = 4401)	Double-blind, placebo-controlled RCT	T2DM (%): 100 Age ≥ 30 years eGFR ≥30 to <90 mL/min/1.73 m^2 UACR > 300 to 5000 mg/g HbA1c: 6.5% to 12.0% Requirement for a stable dose of an ACE inhibitor or ARB	2.6	Composite of ESRD (dialysis, transplantation, or sustained eGFR at <15 mL/min/1.73 m^2), sCr doubling, or renal or cardiovascular death: 0.70 (0.59 to 0.82); $P = 0.00001$ Composite of cardiovascular death or HHF: 0.69 (0.57 to0.83); $P < 0.001$ Doubling of sCr or 50% reduction in eGFR: 0.60 (0.48 to 0.76); $P < 0.001$ Dialysis initiation/transplantation/renal death: 0.72 (0.54 to 0.97); P = NA Cardiovascular death: 0.78 (0.61 to 1.00); $P = 0.05$ All-cause mortality: 0.83 (0.68 to 1.02)

Clinical tria[1]	Intervention (enrollment)	Trial type	Main inclusion criteria	Median follow-up duration (years)	Primary outcomes (HR [95% CI]; *P* value)
DAPA-CKD[10]	Dapagliflozin (N = 4304)	Double-blind, placebo-controlled RCT	T2DM (%): 67.5 eGFR: 25 to 75 mL/min/1.73 m^2 UACR: 200 to 5000 mg/g Required stable dose of ACE inhibitor or ARB	2.4	Composite of a sustained decrease in eGFR to ≥50% (confirmed after ≥28 days), ESRD (dialysis for ≥28 days, transplantation, or eGFR < 15 mL/min/1.73 m^2 confirmed after ≥28 days), or renal or cardiovascular death: 0.61 (0.51 to 0.72); $P < 0.001$ Composite of cardiovascular death or HHF: 0.71 (0.55 to 0.92); $P = 0.009$ Doubling of sCr or 50% reduction in eGFR: >50% reduction in eGFR, 0.53 (0.42 to 0.67); P = NA Dialysis initiation/transplantation/renal death: 0.64 (0.50 to 0.82); P = NA Cardiovascular death: 0.81 (0.58 to 1.12); P = NA All-cause mortality: 0.69 (0.53 to 0.88); $P = 0.004$
EMPA-KIDNEY[11]	Empagliflozin (N = 6609)	Double-blind, placebo-controlled RCT	T2DM (%): 44 eGFR ≥20 to <45 or ≥45 to <90 mL/min/1.73 m^2 UACR ≥ 200 mg/g Use of ACE inhibitor or ARB	2.0	Composite of kidney disease (ESRD; a sustained decrease in eGFR to <10 mL/min/1.73 m^2, a sustained decrease in eGFR to ≥40% from baseline, or renal death) progression or death from cardiovascular causes: 0.72 (0.64 to 0.82); $P < 0.001$ Composite of cardiovascular death or HHF: 0.84 (0.67 to 1.07); $P = 0.15$ Cardiovascular death: 0.84 (0.60 to 1.19) ESRD or death from cardiovascular causes: 0.73 (0.59 to 0.89) All-cause mortality: 0.87 (0.70 to 1.08); $P = 0.21$

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EF, ejection fraction; ESRD, end-stage renal disease; GLD, glucose-lowering drug; HF, heart failure; HHF, hospitalization for heart failure; HbA1c, glycated hemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RCT, randomized controlled trial; sCr, serum creatinine; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

2. Role of Ketones in Fuel Metabolism

Ketones, vital evolutionarily conserved fuel sources for cellular metabolism, are synthesized primarily in the liver from acetyl-CoA units, which are derived from fatty acid oxidation through a process related to the activation of lipolysis. After synthesis, ketones are transported to extrahepatic mitochondria, where they are catalyzed by a series of enzymes. Finally, ketones enter the Kreb cycle to produce adenosine triphosphate (ATP) under glucose-deficient and prolonged starvation conditons[16]. Ketogenesis is influenced by several hormones, predominately insulin, that are released under physiologic and pathologic stress conditions. Insulin inhibits lipolysis and reduces ketogenetic flux in the liver. By contrast, catecholamines promote lipolysis and thus ketogenesis[17].

Fuel efficiency is measured in terms of the P:O ratio, which indicates the number of ATP molecules (P) generated per oxygen atom (O) consumed by the mitochondrial electron transport chain. The P:O ratio is 2.50 for ketones, 2.58 for glucose, and 2.33 for pal-

mitate; therefore, the efficiency of ATP generation per oxygen atom is lower and higher for ketones than for glucose and fatty acids, respectively (Table 2)[14]. Therefore, ketones can serve as efficient fuel sources for tissues with high metabolic demands, particularly those with high oxygen demands—for example, the heart and kidney. Ketones resulting from SGLT2i use are regarded as excellent or super fuels because they are energy-dense (similar to free fatty acids [FFAs]), water soluble, readily available, and fuel-efficient[18]. Ketone metabolism is integral to mammalian cell metabolism, homeostasis, and signaling under both physiologic and pathologic conditions[16].

3. SGLT2Is Increase Ketones Levels

During fasting, glucose levels decrease with decreasing insulin secretion, leading to increased lipolysis, FFA release, and fatty acid oxidation. These changes constitute the physiologic starvation response. Under starvation conditions, the heart, liver, muscle, and kidneys use fatty acids as major fuels; glucose is spared for use by tissues that preferentially rely on glucose—for example, the brain, red blood cells, and renal medulla. The glucose demands of these tissues are met through increased glycogenolysis and gluconeogenesis. During a prolonged fasting period, glycogen stores are depleted. To prevent excessive breakdown of proteins (sources of the precursors [amino acid] of gluconeogenesis) during this period, the liver produces the ketones *β*-hydroxybutyrate (BHOB) and acetoacetate as alternative fuels[19,20]. An increase is noted in the synthesis of ketones from acetyl-CoA units because the Kreb cycle cannot oxidize all acetyl-CoA units resulting from increased FFA degradation. This is because acetyl-CoA, which requires oxaloacetate to enter the Kreb cycle, is redirected toward gluconeogenesis[20]. Consequently, the liver produces large quantities of ketones, which are then released into the bloodstream as glucose-sparing fuels.

The precise mechanism of ketogenesis by SGLT2is is not fully elucidated. It is hypothesized that this effect is facilitated by a decline in blood glucose levels due to improved insulin sensitivity in muscle tissue and endothelial cells. This reduction in glucose levels leads to an increase in glucagon levels, subsequently lowering the insulin/glucagon ratio. This shift triggers the mobilization of fat reserves towards the liver by activating hormone-sensitive lipase. In the liver, FFAs are metabolized to acetyl-CoA for energy production. However, under conditions of increased gluconeogenesis and reduced glucose levels, acetyl-CoA is diverted from the tricarboxylic acid cycle to generate ketone bodies. This metabolic switch from glucose to fat oxidation results in a decreased insulin-to-glucagon ratio, which in turn promotes gluconeogenesis, stimulates lipolysis, and facilitates ketogenesis (Figure 1)[17].

Table 2. Energy Generated From Various Fuels

Substrate, complete oxidation of a molecule	ATP generated	Oxygen atoms consumed	P:O ratio*	Energy liberated (kcal/mol of 2-carbon units)
Palmitate	105	46	2.33	297.99
β-hydroxybutyrate	23	9	2.50	243.59
Glucose	31	12	2.58	223.58
Pyruvate	15	6	2.50	185.68

*P:O ratio is the number of ATP molecules generated per oxygen atom consumed by the mitochondrial electron transport chain.
Abbreviations: ATP, adenosine triphosphate.

SGLT2is also induce a state of accelerated starvation (characterized by ketogenesis) in the liver due to continuous glucosuria[21]. These inhibitors lead to an approximately 2-fold increase in ketone levels compared with baseline fasting levels[22]. These drugs induce low-grade hyperketonemia, which may persist for >52 weeks[22,23]. Notably, changes in serum ketones could not be fully explained by changes in plasma fatty acids, indicating the ketogenesis-inducing effects of SGLT2is on hepatic metabolism[2,3]. The presence of certain carbohydrates in meals influences SGLT2i-induced hepatic ketogenesis. In a Japanese study, fasting ketone levels were significantly higher in participants who received luseogliflozin and a low-carbohydrate diet (carbohydrates constituting 40% the total energy content) than in those who received only a high-carbohydrate diet (55% of the total energy) for 2 weeks (115.3 to 752.4 vs 139.1 to 502.9 μmol/L, respectively)[24]. Furthermore, recent evidence suggests that dapagliflozin-induced ketogenesis is driven by the accelerated release of FFAs from adipose tissue reserves and the diversion of hepatic FFAs toward *β*-oxidation[25].

4. Cardiac Benefits of SGLT2is May be Mediated Through Altered Ketone Metabolism and Improved Myocardial Fuel Energetics

The healthy adult heart consumes approximately 60% to 90% of the fatty acid oxidation–derived myo-

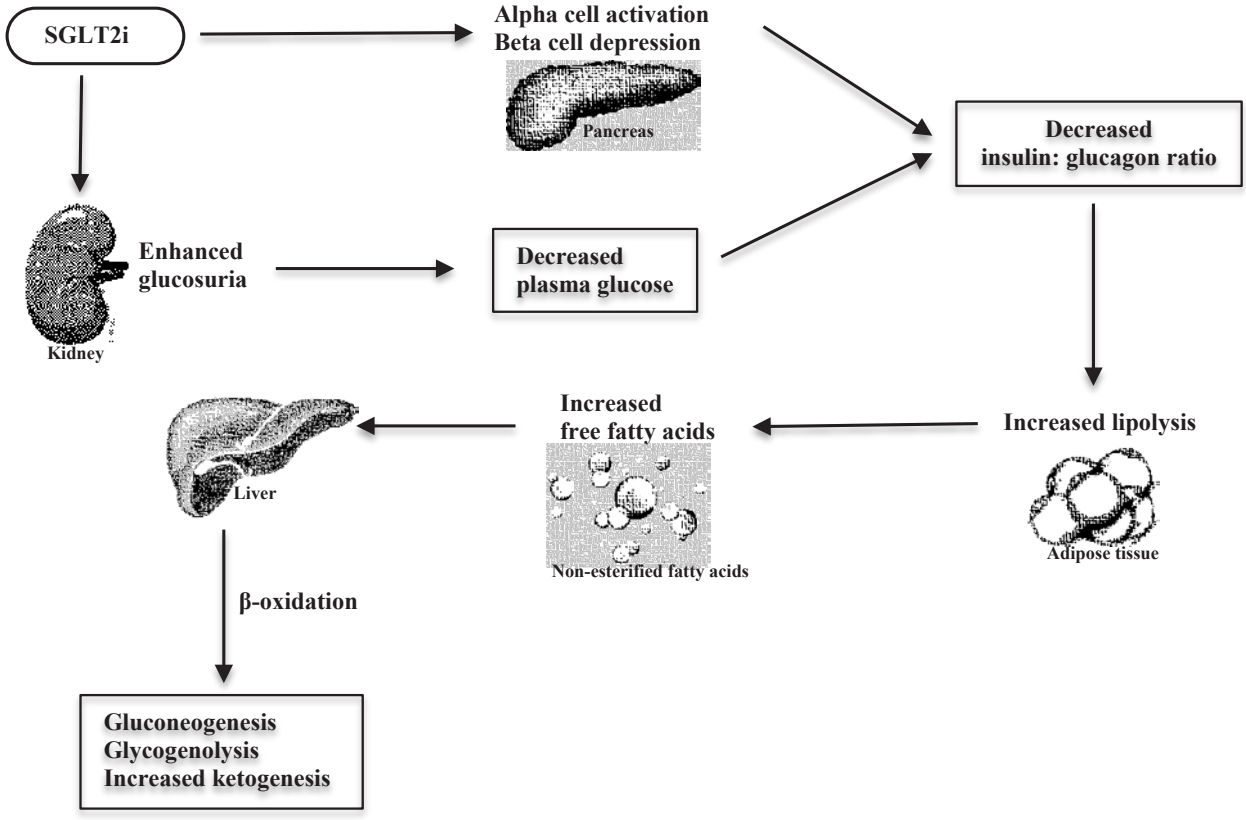

Figure 1. Schematic diagram depicting mechanism of ketogenesis by SGLT2i.
SGLT2is work by enhancing the excretion of glucose in the kidneys, thereby reducing blood glucose levels. This reduction in plasma glucose concentrations results in a decrease in insulin levels and an increase in glucagon levels, leading to a shift in the insulin/glucagon ratio. Consequently, this alteration promotes the breakdown of fats (lipolysis), causing an increased release of free fatty acids to the liver. In the liver, these free fatty acids undergo oxidation to form acetyl-CoA, a compound typically utilized for energy production. However, under conditions of low plasma glucose levels and increased gluconeogenesis, acetyl-CoA is redirected towards the process of ketogenesis.

cardial ATP. The remaining energy originates from the oxidation of ketones, amino acids, and glucose[26]. To maintain its contractility, the heart rapidly switches fuels depending on work demands and fuel availability. Glucose is the predominant fuel in the postprandial state, whereas FFAs are preferred in the fasting state. In addition, ketones serve as key sources of cardiac ATP, accounting for 5% to 10% of the total myocardial fuel in healthy individuals[27]. The levels of ketones circulating in the healthy heart range from 0.2 to 0.6 mM; however, SGLT2is increase the serum levels of ketones to approximately twice their baseline fasting levels and <1 mM[22].

A trend toward HF can markedly affect myocardial fuel metabolism. Several factors mediate the alterations in fuel energetics—for example, HF severity or stage, HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF), and comorbidities (e.g., hypertension, obesity, and diabetes)[22].

A retrospective study involving 1030 consecutive patients who had undergone cardiac catheterization reported a positive correlation between the level of ketone bodies and that of B-type natriuretic peptide ($P = 0.003$) but not hemodynamic indices such as left ventricular (LV) end-diastolic pressure or volume[28]. The researchers suggested that natriuretic peptides secreted from the failing heart induce the utilization of ketones as alternative fuels. In a recent population-based cohort study comprising 6134 individuals who were followed for a median of 8.2 years, 227 individuals had HF (HFrEF, 137; HFpEF, 90)[29]. Cox regression revealed a significant association between high BHOB levels and incident HF (hazard ratio [HR] per 1 standard deviation [SD] increase, 1.40; $P < 0.001$), which was largely attributable to HFrEF. Multivariate models were adjusted for various covariates, including age, body mass index, type 2 diabetes mellitus (T2DM), hypertension, myocardial infarction, smoking habit, alcohol consumption, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, glucose, and renal function. Sex-stratified multivariate analyses revealed that the HR for HFrEF per 1 SD increase in BHOB level was 1.73 ($P = 0.005$) in women and 1.14 ($P = 0.36$) in men ($P < 0.01$ for sex interaction). Furthermore, age-adjusted analyses revealed a significant and positive association between HF and the level of N-terminal pro-brain natriuretic peptide in women ($P = 0.008$). The researchers suggested a positive correlation between high plasma BHOB levels and the risk of HFrEF, particularly in women[29]. Together, these findings indicate that ketones can serve as alternative sources of fuel in the body.

Augmented delivery of ketones to the failing heart may promote ketone oxidation, thereby increasing its contribution to cardiac ATP yield to approximately 30%[26]. Elevated ketone levels may offer an extra source of energy to the falling heart. However, several animal experiments have demonstrated that the promotion of cardiac ketone oxidation did not translate into enhanced cardiac efficiency[26]. Such findings were also reported by a study involving patients with HF, where ketone infusion to enhance the delivery of ketones to the heart did not increase cardiac efficiency[30]. Notably, some of the benefits conferred by elevated levels of circulating ketones in patients with HF may result from the anti-inflammatory effects of ketones; however, this hypothesis has been challenged[26]. A major metabolic change in the failing heart involves the development of insulin resistance; consequently, glucose metabolism is impaired, and the heart's reliance on fatty acid oxidation is increased[26]. Myocardial insulin resistance may be mitigated by improving insulin sensitivity and reducing glucose levels through SGLT2is[22]. Moreover, the SGLT2i-induced increase in ketone availability may benefit the failing heart by improving fuel efficiency, enhancing myocardial function, reducing production of reactive oxygen species, and decelerating HF progression[31].

In preclinical animal studies, the effects of

SGLT2is on myocardial metabolism and function have been evaluated in terms of ketone levels. In a rodent model of HF, the establishment of ketone ester diet–induced ketonemia as an HF prevention or treatment strategy decelerated the development of LV dysfunction, suppressed the pathologic remodeling of cardiac tissues, reprogrammed the expression of genes involved in myocardial ketone uptake and oxidation, and facilitated the restoration of myocardial ATP production[32]. In a nondiabetic porcine model of HF, empagliflozin treatment resulted in a switch in myocardial fuel utilization from glucose to ketones and, to a lesser extent, FFAs, thereby improving myocardial energetics, ameliorating adverse LV remodeling, and enhancing LV systolic function[33]. In db/db mice, empagliflozin treatment enriched the pool of cardiac energy (by increasing overall cardiac ATP yield by approximately 30%) and prevented the development of HF without increasing the overall cardiac work efficiency; these effects were ascribed to increased rates of glucose and fatty acid oxidation without any changes in the rate of ketone oxidation or glycolysis[34]. In a murine model of cardiac hypertrophy, ertugliflozin treatment induced the expression of ketolytic genes, CD36, and adenosine monophosphate–activated protein kinase (AMPK) but reduced the levels of mammalian target of rapamycin (mTOR), insulin signaling, cardiac fibrosis risk, and hypertrophy risk[35].

In humans, the cardiovascular effects of ketones were first demonstrated in a randomized crossover study involving 16 patients with chronic HFrEF (LV ejection fraction [LVEF], 37% ± 3%) without T2DM[30]. The patients in the aforementioned study underwent a single 3-h session of BHOB or placebo infusion. Compared with placebo infusion, BHOB infusion improved cardiac output by 2.0 L/min ($P < 0.001$) and LVEF by 8% ($P < 0.001$) but reduced systemic vascular resistance by 30% ($P < 0.001$). In addition, BHOB infusion increased myocardial oxygen consumption without altering myocardial energy efficiency, which suggests improved myocardial work efficiency. The researchers concluded that BHOB holds promise as a new therapeutic agent for patients with HFrEF[30]. Similar results were reported by another study involving 11 patients with HFrEF and 6 control individuals[36]. A 12.9-fold increase was noted in BHOB levels 80 min after the oral administration of 25 g of ketone ester (through a drink). Furthermore, the degree of ketone utilization was higher in patients with HFrEF than in control individuals (fractional extraction, FE: 52% vs 39%, respectively; P=0.035). BHOB FE was found to be directly correlated with BHOB myocardial delivery, LV mass, and LV diameter but inversely correlated with LVEF (all P<0.05). According to the researchers, because subclinical metabolic remodeling occurs early during HF progression, exogenous ketones might be used to improve cardiac structure, function, clinical outcomes, and HF prognosis[36]. SGLT2i-induced increases in BHOB levels and reductions in serum insulin levels partially alleviated inflammation by reducing the activity of nod-like receptor family protein-3 (NLRP3) within macrophages in patients with T2DM who had a high risk of cardiovascular disease (CVD)[37]. These mechanisms may explain the cardiovascular effects of SGLT2is in humans.

Increasing the serum levels of ketones may mitigate metabolic dysfunction in patients with HF[23,24,34,38]. Therefore, SGLT2i-induced low-grade ketonemia may improve myocardial contractility and energy function. SGLT2is reduce the risks of cardiovascular death and hospitalization for HF in patients with HFrEF[6,7] or HFpEF[8], confirming the benefits of these drugs against HF. In the CANVAS trial, canagliflozin treatment significantly increased the plasma levels of FFAs and BHOB, regardless of background antihyperglycemic therapy[39]. A constitutive metabolic setup featuring elevated lipolysis may delay or prevent hospitalization for HF; further activation of lipolysis by canagliflozin may reinforce these effects[39]. In a study investigating the

effects of dapagliflozin on cardiac substrate uptake, myocardial efficiency, and myocardial contractility, 27 patients with T2DM and 26 control individuals with an LVEF of >50% were randomized to receive either dapagliflozin or a placebo. After the 6-week intervention, dapagliflozin significantly reduced LV global radial strain and improved left atrial volume compared with the effects of the placebo[40]. In addition, dapagliflozin significantly reduced external LV work and LV oxygen consumption, thereby reducing oxygen demands; however, these changes did not differ significantly between the treatment and placebo groups[40]. In a recent study involving patients with HFrEF without T2DM, empagliflozin treatment significantly improved LV volume, LV mass, LV systolic function, functional capacity, and quality of life compared with the effects of a placebo[41]. However, the observed benefits cannot be ascribed to SGLT2i-induced low-grade ketonemia because ketone levels were not measured in these studies. Nonetheless, the BHOB studies have reported substantial myocardial benefits; therefore, SGLT2i-induced low-grade ketonemia might have mediated some of the anti-HF benefits observed in the aforementioned studies[6-8,40,41]. A recent study investigating the effects of dapagliflozin on the biomarkers, symptoms, and functional effects of HFrEF revealed that dapagliflozin affected the principal metabolic pathways; this finding provides evidence for SGLT2i-induced alterations in ketone and fatty acid metabolisms in patients with HFrEF[42]. In the aforementioned study, the observed levels of ketosis were within the expected ranges. Among 234 patients (mean age, 62.0 ± 11.1 yr; women, 25%; Black patients, 38%; mean LVEF, 27% ± 8%), dapagliflozin increased the numbers of principal component analysis–defined metabolite clusters related to ketones and short-chain and medium-chain acylcarnitines (nominal $P = 0.01$; false discovery rate–adjusted $P = 0.08$ for both clusters). However, ketosis (BHOB levels > 500 μmol/L) rarely occurred in the treatment or placebo control group. Moreover, the levels of ketones did not exceed the supraphysiologic threshold.

In summary, under mild, persistent hyperketonemia conditions such as those during SGLT2i treatment, the heart readily utilizes BHOB instead of FFAs, oxidizing it preferentially[43]. The use of ketones as fuels results in the conversion of oxygen consumption into work efficiency at the mitochondrial level. Furthermore, SGLT2i-influenced hemoconcentration facilitates the release of oxygen into the tissues, establishing a synergy with the shift of metabolic substrate[43]. Enhanced oxidation of ketones in the heart may account for the aforementioned benefits; in patients with T2DM, ketosis may confer cardioprotection as a compensatory mechanism rather than an adverse mechanism during hyperglycemic episodes[44]. Because SGLT2is exert cardioprotective effects in patients with T2DM or HF[2-13], future studies should investigate whether ketosis is the central mechanism underlying the effects of these drugs; such information will provide insights into the target population for SGLT2i prescription, adverse effects of these drugs, use of dietary adjuvants, and assessment of drug safety. Furthermore, future studies should determine the levels of ketones that affect energy metabolism and cardiac contractility. Insights from these studies may clarify the mechanisms underlying the positive and negative effects of ketones and guide strategies for harnessing these ancillary fuels for selective benefits.

5. Renal Benefits of SGLT2is May be Mediated Through Altered Ketone Metabolism and Improved Renal Fuel Energetics

Similar to the heart, the kidney is highly metabolically active, with approximately 80% of its energy consumption driven by sodium and glucose reabsorption through the Na^+/K^+ ATPase pump and SGLT2 transporter. In patients with T2DM, enhanced activities of Na^+/K^+ ATPase and SGLT2

transporter increase renal oxygen consumption[45]. A discrepancy between impaired oxygen delivery due to hyperglycemia-associated vascular damage and increased oxygen demand due to enhanced sodium and glucose reabsorption through SGLT2 upregulation predisposes the diabetic kidney to hypoxia[22]. Chronic hypoxia accelerates the development of diabetic kidney disease (DKD), even in the absence of hyperglycemia or oxidative stress[22]. By inhibiting sodium and glucose reabsorption in the proximal renal tubule, SGLT2is reduce energy consumption in this segment with high oxygen demands. Notably, the blocked sodium is reabsorbed in later tubule segments, where ketones can serve as fuels. In patients with CKD or kidney failure, ketones may serve as high-efficiency oxygen sources that can prevent hypoxia in the kidney[31,37].

SGLT2i-induced low-grade ketonemia has been hypothesized to confer renoprotection through mechanisms similar to those employed in the myocardium[15,46]. In a rat model of T2DM, renal oxygen consumption substantially increased (approximately doubled) in renal cortical tissue, particularly proximal tubular cells; treatment with phlorizin (a nonselective SGLT2i) mitigated the increase in Na^+/K^+ ATPase activity and reduced renal oxygen consumption[47]. SGLT2i-induced increases in ketone levels confer renoprotection through the suppression of mTOR complex 1 (mTORC1) signaling in the proximal tubule[48,49]. The hyperactivation of mTORC1 in the affected kidneys resulted in a shift from lipolysis to ketolysis in the context of ATP production. In mice, empagliflozin increased the levels of endogenous ketones and 1,3-butanediol (a ketone precursor) prevented reductions in renal ATP yield as well as organ damage[48].

The renoprotective effects of empagliflozin could be blocked through the deletion of Hmgcs2, which encodes the rate-limiting enzyme of endogenous ketogenesis. In a rat model of T2DM, ketones mitigated podocyte damage and proteinuria by inhibiting the hyperactivation of mTORC1[48]. These findings indicate that the renoprotective effects of SGLT2is are mediated through increased ketone levels, which, in turn, mitigate the hyperactivation of mTORC1, thereby ameliorating impaired renal lipolysis and renal damage in patients with proteinuric or nonproteinuric DKD[48].

SGLT2is trigger the sirtuin-1 (SIRT-1) gene regulator, which has been implicated in gluconeogenesis and ketogenesis. Certain genetic variations in SIRT1 are associated with increased susceptibility to DKD. The renoprotective effects of SGLT2is may stem from their SIRT1-activating ability[50]. The activation of the SIRT1/AMPK pathway creates an energy-deprived state by inhibiting the protein kinase B/mTOR pathway. Such metabolic changes are accompanied by reduced oxidative stress, restored mitochondrial function, increased contractility, and enhanced autophagy[51,52]. These coordinated cellular responses result from the SGLT2i-induced activation of SIRT-1, leading to systemic starvation and altered energy metabolism, thereby strengthening the renoprotective benefits of SGLT2is[51,52].

Although the mechanisms underlying the effects of SGLT2is remain to be fully elucidated, a widely recognized hypothesis suggests that these inhibitors exert their beneficial effects on the diabetic kidney by promoting ketogenic nutrient deprivation–related signaling through SIRT1, peroxisome proliferator-activated receptor γ coactivator (PGC)-1α, and fibroblast growth factor (FGF) 21[53]. These enzymes and associated transcription factors serve as the master regulators of nutrient and cellular homeostasis, enhancing gluconeogenesis, fatty acid oxidation, and ketogenesis—the hallmark features of SGLT2i treatment. The SIRT1/PGC-1α/FGF21 pathway promotes autophagy—a lysosome-dependent degradative pathway that cleanses the cytosol of dysfunctional organelles, thereby alleviating cellular stress, reduc-

ing inflammation, and conferring nephroprotection[53]. An inverse correlation has been observed between SGLT2 activity and the SIRT1/PGC-1α/FGF21 pathway. The SGLT2i-induced enhancement of the SIRT1/PGC-1α/FGF21 signaling not only explains the induction of ketogenesis and erythrocytosis by these drugs but also helps preserve renal function in patients with T2DM[53].

The aforementioned potential mechanisms mediate the renoprotective effects of SGLT2is through increased levels of circulating ketones. However, none of the large clinical trials we reviewed involved the measurement of ketone levels. Therefore, the renal benefits of SGLT2is cannot be conclusively attributed to increased ketone levels and improved fuel energetics. Further studies are needed to clarify the relevance of these mechanisms to the observed renal benefits.

6. Multidirectional Effects of Ketones Beyond Fuel Energetics

In addition to serving as vital alternative metabolic fuels, ketones modulate inflammation and sympathetic activity, reduce oxidative stress, ameliorate hypoxia, attenuate fibrosis, and mitigate mitochondrial dysfunction, thereby conferring cardiorenal protection[22].

6.1 Anti-Inflammatory Effects

BHOB modulates inflammation through several pathways, such as those involving hydroxycarboxylic acid receptor 2 (HCAR2), FFA receptor-3, and NLRP3 inflammasome[16]. Activation of these pathways increases the release of proinflammatory cytokines, such as interleukin (IL)-1β and tumor necrosis factor-α, which mediate the pathogenesis of HF and CKD[31].

BHOB activates HCAR2, which inhibits lipolysis in adipocytes, possibly as a feedback mechanism to regulate the availability of fatty acid precursors essential for ketone metabolism. Moreover, HCAR2 has been demonstrated to mediate the anti-atherosclerotic effects of nicotinic acid in animal models[54]. By inhibiting FFA receptor-3, BOHB likely reduces heart rate and sympathetic activity, which mediate the cardiovascular benefits of SGLT2is[54]. Animal experiments have revealed the involvement of many inflammasome-related genes and proteins in kidney diseases[55]. Notably, the NLRP3 inflammasome mediates the development of various chronic and acute kidney diseases by regulating inflammation, pyroptosis, apoptosis, and fibrosis[55]. SGLT2is block the activation of the NLRP3 inflammasome and reduces the secretion of the proinflammatory cytokines IL-1β and IL-18 both in vitro (isolated human immune cells) and in vivo (mouse model of NLRP3-mediated disease)[56]. Similarly, in a study involving 71 patients with T2DM and a high cardiovascular risk, SGLT2is reduced the levels of IL-1β, tumor necrosis factor-α, and insulin but increased that of circulating BHOB. Ex vivo experiments with macrophages replicated the in vivo inhibitory effects of high BOHB and low insulin levels on the activation of the NLRP3 inflammasome, indicating that SGLT2is suppressed its activation, thereby alleviating inflammation and exerting cardiovascular effects[37].

6.2 Antioxidative Stress

Excessive reactive oxygen species production may induce inflammation and pathologic signaling. In various cells, ketones suppress oxidative stress by inhibiting histone deacetylases (HDACs)[57], which indirectly leads to the hyperacetylation of proteins, thereby alleviating inflammation and regulating autophagy.[57] Furthermore, HDAC inhibition ameliorates cardiac hypertrophy through anti-inflammatory effects on nuclear factor (NF)-κB target genes[58]. In a study comprising 37 patients with T2DM and high cardiovascular risk, 3-month canagliflozin treatment significantly mitigated LV diastolic dysfunction[59]. Similarly, in the EMPA-REG OUTCOME

trial involving 97 patients with T2DM and CVD (LVEF, approximately 58%), 6-month empagliflozin treatment significantly reduced LV mass compared with the effects of a placebo without considerably altering end systolic or diastolic volume or LVEF60. The researchers suggested that their results partially explain the cardiovascular benefits of empagliflozin[60]. Therefore, the SGLT2i-induced increase in ketone availability may confer myocardial benefits through HDAC inhibition–mediated antioxidative effects.

HDACs have been implicated in the development and progression of various renal diseases; thus, HDAC inhibition may be a promising therapeutic strategy for these diseases[61]. Inhibiting HDACs protects the kidneys through the regulation of multiple pathways, such as through the suppression of the transforming growth factor-β and NF-κB pathways, augmentation of apoptosis, and inhibition of angiogenesis[61]. In a study involving both db/db mice and human patients with diabetes, the expression of SGLT2 was upregulated and that of SIRT1 (an HDAC-inhibitor) was downregulated in the kidneys; nonetheless, canagliflozin-mediated inhibition of SGLT2 transporters restored SIRT1 expression by preventing the entry of intracellular glucose from the apical to the proximal tubular cells[62]. The researchers recommended canagliflozin as a therapeutic strategy for DKD. Ketone-mediated HDAC inhibition has been correlated with global changes in transcription, including the transcription of genes encoding the oxidative stress resistance factors FOXO3A and MT2. Ketone increases histone acetylation at the Foxo3a and Mt2 promoters; both anti–oxidative stress genes are activated through the selective inhibition of HDACs. Increased FOXO3A and MT2 activities confer substantial protection against oxidative stress[63]. Thus, during SGLT2i treatment, ketone utilization in the kidney shifts from the mitochondrial pathway to the nuclear pathway; this shift inhibits HDACs and protects against oxidative stress while providing an alternative fuel source because of the downregulation of succinyl-CoA:3-oxoacid CoA transferase[64].

6.3 Amelioration of Hypoxia

Hypoxia contributes to common pathologic conditions, such as the loss of glomerular and peritubular microvasculature and the recruitment of inflammatory and immune cells, leading to tubulointerstitial fibrosis and extracellular matrix accumulation[65]. Hypoxia-inducible factors (HIFs; specifically, HIF-1α and HIF-2α) mediate the metabolic switch from aerobic ATP production (through oxidative phosphorylation) to anaerobic glycolysis to sustain ATP production under hypoxia[66]. HIF-2α increases oxygen supply by inducing (and regulating) erythropoietin production and upregulating vascular endothelial growth factor expression[67]. However, overexpression of HIF-1α accelerated the development of glomerulosclerosis in an animal model of DKD[68]. SGLT2is likely induce the expression of HIF-2α and suppress that of HIF-1α, thereby alleviating cellular stress and renal hypoxia and enhancing nutrient deprivation–related signaling; these changes may promote erythropoiesis, suppress proinflammatory and profibrotic pathways, and inhibit organelle dysfunction, thereby preventing or decelerating DKD progression[69]. The effects of SGLT2is on erythropoiesis may be mediated through erythropoietin production and be independent of glycemic control[70].

In patients with DKD, SGLT2is ameliorate anemia by increasing the levels of hemoglobin, hematocrits, and erythrocytes[70]. In an experimental study, hyperketonemia induced through a single session of 7.5% 3-BHOB infusion resulted in approximately 30% increases in the level of erythropoietin and the bone marrow uptake of glucose; the findings may explain the thus-far unknown association between SGLT2i treatment and increased erythropoiesis[71]. In the EMPA-REG OUTCOME trial, an

exploratory analysis revealed that the cardiorenal benefits of empagliflozin are mediated through an increase in hematocrit levels[72]. Although this increase might have resulted from the modest diuretic effects of SGLT2is, which lead to hemoconcentration, the trial associated acute hyperketonemia with increased erythropoietin and hematocrit levels[72]. Together, the findings suggest that SGLT2i-induced ketones ameliorate renal hypoxia, thereby restoring inefficient erythropoiesis in patients with DKD and conferring not only renal but also cardiovascular protection.

6.4 Attenuation of Fibrosis

According to several animal studies and clinical trials, SGLT2 inhibition is an effective approach for treating fibrosis; SGLT2is exert protective effects across organs and influence key fibrosis-related processes[73]. Notably, mTORC1 regulates numerous cellular functions by modulating nutrient, energy, and growth factor signals[74]. The hyperactivation of mTORC1 has been associated with hypertrophy, inflammation, and impaired mitochondrial bioenergetics[74,75]. SGLT2i-induced increases in ketone levels mitigates mTORC1 hyperactivation in patients with nonproteinuric or proteinuric DKD, thereby ameliorating impaired renal lipolysis and renal damage[48]. Knocking out a gene that encodes for the rate-limiting enzyme of endogenous ketogenesis eliminated the renoprotective effects of SGLT2is, indicating direct correlations of hyperketonemia with reduced fibrosis and inflammation[22]. In a nondiabetic mouse model of transverse aortic constriction–induced HF, empagliflozin treatment improved the function of isolated cardiomyocytes by enhancing oxidative phosphorylation, calcium transients, and contractility. Additionally, empagliflozin treatment improved cardiac function[76]. Further experiments revealed that empagliflozin increased AMPK activity and inhibited mTORC1 to attenuate cardiac hypertrophy and protect the heart against HF progression. Thus, empagliflozin suppresses adverse cardiac remodeling, fibrosis, and HF progression without reducing blood glucose levels or causing diuresis[76].

Although multiple recent studies have explored profibrotic growth factors or cytokines and the associated signaling pathways, data on the SGLT2i-induced antifibrotic effects of ketones remain limited. Future studies should investigate the cellular and molecular mechanisms underlying the SGLT2i-induced antifibrotic effects of ketones.

6.5 Mitigation of Mitochondrial Dysfunction

Mitochondrial dysfunction is associated with diverse pathologies, including diabetes, CVD, CKD, and metabolic diseases. Abnormal mitochondrial functions reduce the activity of various mitochondrial health regulators, such as SIRT1-7 and PGC-1α[77]. Under nutrient-deprived and energy-deprived conditions, PGC-1α is activated through 2 key metabolic factors, AMPK and SIRT1[53,77]. In various experimental models, SGLT2is increased the activation of these mediators of mitochondrial metabolism[78,79]. In a mouse model of T2DM, the intake of a ketogenic diet significantly increased mitochondrial size, mitochondrial function, and PGC-1α and SIRT1 levels[80]. A recent review suggested that a ketogenic diet can mitigate mitochondrial dysfunction by promoting mitochondriogenesis, mitochondrial dynamics, and bioenergetic pathways, thereby alleviating inflammation and oxidative damage[81]. A recent study revealed increased levels of mitochondrial reactive oxygen species production and fibrosis-related and apoptosis-related proteins in human renal proximal tubular cells cultured in high-glucose media[82]. In this study, empagliflozin treatment reduced mitochondrial reactive oxygen species levels by mitigating excess mitochondrial fission and autophagy. However, few clinical studies have clarified the mitochondria-related benefits of SGLT2is, particularly their ketone-mediated effects on mitochondrial function. Therefore, further

studies are needed to elucidate the mechanisms underlying the SGLT2i-mediated mitigation of mitochondrial dysfunction and to gather evidence for the use of these drugs for cardiorenal benefits.

6.6 Modulation of Sympathetic Activity

Chronic sympathetic overactivity leads to numerous metabolic disorders, including diabetes, HF, CKD, and CVD. Mechanistic studies have revealed that ketones suppress sympathetic activity through G protein-coupled receptor 41, which is most abundantly expressed in the sympathetic ganglia[83]. SGLT2 mediates sympathetic activity; its inhibition may confer cardiovascular benefits by reducing renal afferent nervous activity and suppressing central reflex mechanisms that contribute to generalized sympathetic activation[84]. A review of large clinical trials indicated no reflex increase in heart rate (a surrogate marker for sympathetic blockade) following an SGLT2i-induced reduction in blood pressure; these effects may reduce the risk of arrhythmia (and sudden cardiac death) in SGLT2i users[85].

7. SGLT2is and Ketoacidosis

7.1 The potential risk of diabetic ketoacidosis in Type 1 Diabetes Mellitus

Individuals with diabetes may face challenges in effectively using and dosing insulin therapy due to concerns about hypoglycemia and weight gain. SGLT2is may present as an appealing treatment option for patients diagnosed with type 1 diabetes mellitus (T1DM) due to their significant reduction in glycemic variability, insulin needs, HbA1c levels, body weight, and blood pressure without increasing the risk of hypoglycemia[86]. Moreover, it is reasonable that the long-term cardiovascular and renal benefits observed in patients with T2DM (as well as in non-diabetic individuals with HF or CKD) could also be applicable to individuals with T1DM, particularly those with concurrent LV and/or renal impairments. Despite the increasing utilization of these agents, primarily off-label, in the management of T1DM, concerns persist regarding the increased risk of diabetic ketoacidosis (DKA) associated with their use[54]. In addition, euglycemic diabetic ketoacidosis (euDKA) is a severe complication of SGLT2i treatment.

A meta-analysis of 13 randomized controlled trials (RCTs) with 5397 participants found that SGLT2is significantly increased the risk of DKA in participants with T1DM (risk ratio [RR] 4.49; 95% confidence interval [CI] 2.88 to 6.99) in a dose-dependent manner, with a 4.9-fold higher rate at high doses of SGLT2is (defined as canagliflozin 300mg, dapagliflozin 10mg, empagliflozin 25mg, and sotagliflozin 400mg) (34 events per 1000 person-years) than with low doses (defined as dapagliflozin 2.5mg or 1.0mg, empagliflozin 5mg, and sotagliflozin 75mg) (7 events per 1000 person-years)[87]. Sotagliflozin has also been associated with an increased risk of DKA in patients with T1DM (RR 3.93; 95% CI 1.94 to 7.96) compared with placebo in a meta-analysis of 6 RCTs with 3238 participants. A larger magnitude of basal insulin dose reduction was associated with increased risk of DKA, whereas higher baseline HbA1c was associated with a lower risk[88]. In 351 patients with T1DM treated with canagliflozin as an add-on to insulin, the incidence of DKA was 5.1% with canagliflozin 100 mg and 9.4% with canagliflozin 300 mg dose. All serious adverse effects of DKA were associated with precipitating factors (e.g., flu, pneumonia, insulin pump failure or malfunction, or inappropriate insulin use)[89]. In a study investigating the efficacy of empagliflozin as an adjunctive to insulin therapy, the incidence of DKA in patients with T1DM was higher among empagliflozin users (10 mg, 4.3%; 25 mg, 3.3%) than among placebo users (1.2%)[90].

SGLT2is have the potential to serve as a supplementary treatment to insulin therapy for individuals with T1DM. However, given the higher risk of DKA associated with their use, it is imperative that these medications are prescribed exclusively to carefully selected patients who possess a comprehensive

understanding of the associated risks, as well as the preventive and treatment measures. The principal considerations for the safe use of SGLT2is in individuals with T1DM include the patients' willingness and ability to adhere to protocols for monitoring ketone levels and effectively responding to elevated ketone levels, in addition to having access to healthcare professionals in case of increased blood or urine ketone levels. Strict adherence to the specific guidelines outlined by local regulatory authorities for each formulation of SGLT2i is essential[54].

7.2 The potential risk of DKA in T2DM

SGLT2is are considered to have a moderate efficacy in reducing blood glucose levels. However, their utilization is extensive in the management of T2DM due to their supplementary benefits such as weight reduction, lowering of blood pressure, and notable positive impacts on cardiac and renal functions. These medications are now recommended in various clinical guidelines for the treatment of T2DM in patients with existing CVD or those at a higher risk for it, as well as in individuals with HF and/or CKD, regardless of their diabetes status. It is important to consider the potential risks of DKA in this particular patient population.

In a large cohort study conducted using insurance claims data from the United States, the incidence of DKA in SGLT2i users was 0.5 per 1000 T2DM patient-years, which accounted for approximately one-third of all DKA cases[91]. In a comprehensive review of 39 RCTs involving 60 580 patients with T2DM (including 85 patients with DKA), the risk of DKA was significantly higher in SGLT2i users than in nonusers (0.18% vs 0.09%, respectively)[92].

Despite the availability of sufficient data on DKA incidence, very few studies have specifically addressed SGLT2i-associated euDKA events. A review of 105 cases of DKA in SGLT2i users revealed that 35% of all patients with DKA had euDKA with glucose levels of <200 mg/dL[93]. Similarly, a study analyzing adverse event data from the US Food and Drug Administration reported that SGLT2i use was associated with an approximately 7-fold increase in DKA cases, of which 71% involved euDKD[94].

8. The Potential Mechanisms of SGLT2i-induced Ketoacidosis

The precise mechanisms underlying SGLT2i-associated ketoacidosis remain unknown. SGLT2i-induced DKA may result from an increase in glucagon level compared with insulin level, which contributes to lipolysis, excessive FFA production, and increased hepatic ketogenesis. Under prediabetic or diabetic conditions, this process occurs due to relative or absolute insulin deficiency[95]. SGLT2is may reduce the renal clearance of ketones by enhancing the tubular reabsorption of ketones filtered from the plasma[96]. Furthermore, SGLT2is exacerbate negative fluid balance and negative sodium balance through osmotic diuresis, aggravating the hypovolemic state in patients with DKA, which increases the levels of glucose, cortisol, and epinephrine; these changes activate insulin resistance, lipolysis, and ketogenesis, thereby worsening ketoacidosis[54]. Factors associated with the incidence of DKA in SGLT2i users include severe insulinopenia, pregnancy, autoimmune diabetes, low-carbohydrate diet intake, and previous DKA[54]. Moreover, DKA may be precipitated by acute events (e.g., infection, myocardial infarction, surgery, trauma, or pancreatitis), alcohol consumption, ketogenic diet intake, vigorous exercise, inappropriate insulin dose reduction, noncompliance with insulin administration, or insulin pump malfunction[54].

Taken together, although the precise pathophysiology of DKA is not completely understood, evidence suggests its multifactorial nature, with SGLT2 inhibition facilitating the development of ketogenesis and acidosis[97]. Several factors influence the risk of DKA in SGLT2i users; many acute or preexisting conditions can make patients susceptible to DKA. These findings may guide clinical strategies for preventing

DKA in SGLT2i users.

9. Clinical management for SGLT2i-associated DKA

Ketoacidosis is a rare but severe adverse event associated with the use of SGLT2is. Patients who develop DKA while using SGLT2is typically exhibit symptoms such as nausea, vomiting, abdominal pain, and malaise. Laboratory tests commonly show an anion gap metabolic acidosis along with the presence of serum and urinary ketones. Notably, unlike classic DKA cases, these patients may have blood glucose levels below 250 mg/dl, a condition known as "euglycemic DKA". The relatively normal glucose levels can lead to a delay in recognizing the condition, especially in emergency room settings, both by patients and healthcare providers[54].

International consensus guidelines for T1DM have endorsed two published patient management protocols in this setting. One is the STICH protocol, which involves ceasing SGLT2is use, administering bolus insulin, limiting carbohydrate intake to 30 grams or less, and ensuring adequate hydration[98]. The other is the STOP DKA protocol, which entails discontinuing the SGLT2is, testing ketones, oral consumption of fluids and carbohydrates, and following specific instructions for supplemental insulin and carbohydrate intake[99].

Patients with T2DM who are using SGLT2is and are considered to be at risk for DKA should be advised by their healthcare provider to monitor their urine or blood ketone levels whenever they feel unwell. If ketones are detected, patients should be directed to discontinue SGLT2i use, increase fluid intake, and consume additional carbohydrates along with full-dose insulin therapy until ketone levels normalize and symptoms improve. In cases of high ketone levels, inability to tolerate oral fluids and carbohydrates, development of rapid breathing or vomiting, or any indications of hemodynamic instability or neurological dysfunction, patients should be instructed to seek medical assistance immediately[98].

Patients should be provided with information regarding the potential risk of euDKA and should be well-informed about the factors that increase the risk of ketosis, such as acute illness, decreased carbohydrate consumption, and insufficient insulin administration. In order to reduce the risk of DKA, it is recommended to discontinue the use of SGLT2is during episodes of severe acute medical illness and stop SGLT2is at least three days prior to any planned surgical procedures[100]. The reintroduction of SGLT2is following an episode of DKA should be approached cautiously, with a thorough reevaluation of the risk-to-benefit ratio. This decision should be made based on compelling indications, such as the presence of established CVD, HF, or CKD, and with adequate patient education[54].

10. Conclusion

SGLT2is were originally introduced as glucose-lowing agents for the treatment of diabetes. These drugs also confer cardiorenal benefits, such as by protecting individuals—regardless of their diabetes status—against HF and CKD. Pathophysiologic mechanisms underlying the cardiorenal effects of SGLT2is are under investigation. SGLT2i-induced low-grade hyperketonemia supplies ancillary fuels in most cells and exerts anti-inflammatory, anti-oxidative, antihypoxic, antifibrotic, and anti-mitochondrial-dysfunction effects, thus mediating the cardiorenal effects of SGLT2is (Figure 2). However, the use of SGLT2is may result in ketoacidosis because of their ketogenic effects secondary to enhanced lipolysis and increased glucagon levels; these effects may lead to ketoacidosis in the presence of other contributory factors. Therefore, ketones can be both beneficial and harmful, depending on the level of ketone elevation[54]. Additional studies are required to elucidate the mechanisms underlying the positive and negative effects of SGLT2i-induced ketogenesis and to devise optimal strategies for harnessing these ancillary fuels

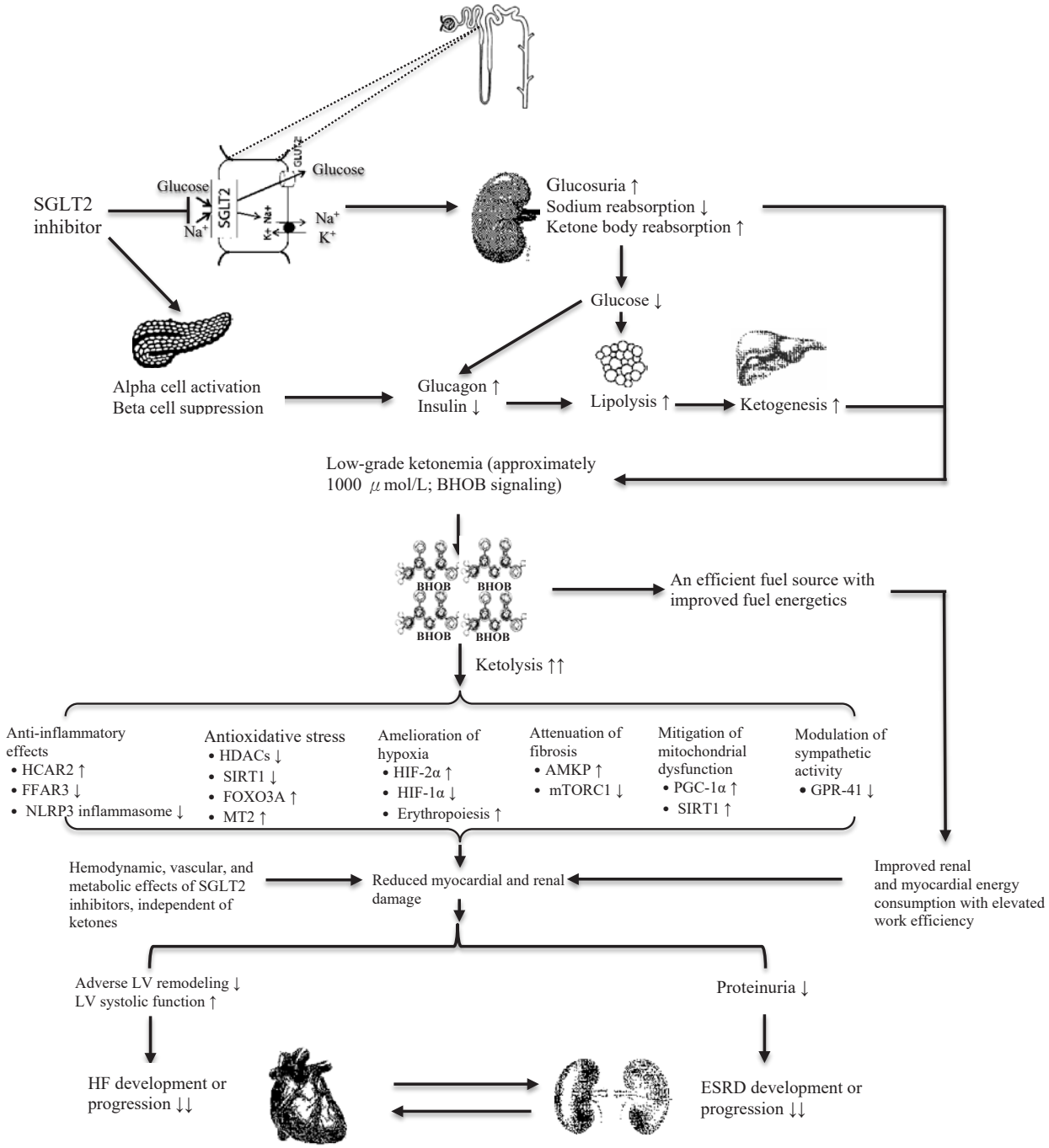

Figure 2. Potential Mechanisms Underlying SGLT2 Inhibitor–Induced Effects of Ketones on Cardiorenal System.
SGLT2 inhibitors induce low-grade ketonemia, thereby conferring myocardial and renal benefits through BHOB signaling.
Abbreviations: AMPK, adenosine monophosphate–activated protein kinase; BHOB, β-hydroxybutyrate; ESRD, end-stage renal disease; FFAR3, free fatty acid receptor-3; GPR-41, G protein-coupled receptor 41; HCAR2, hydroxycarboxylic acid receptor-2; HDAC, histone deacetylase; HF, heart failure; HIF, hypoxia-inducible factor; LV, left ventricular; mTORC1, mammalian target of rapamycin complex 1; NLRP3, nod-like receptor family protein-3; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; SGLT2, sodium-glucose cotransporter-2; SIRT-1, sirtuin-1.

for cardiorenal benefits.

List of abbreviations:

AMPK, adenosine monophosphate–activated protein kinase; ATP, adenosine triphosphate; BHOB, β-hydroxybutyrate; CANVAS, canagliflozin cardiovascular assessment study; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EF, fractional extraction; FFAs, free fatty acids; EMPA-REG OUTCOME, empagliflozin cardiovascular outcomes event trial in type 2 diabetes mellitus patients; euDKA, euglycemic diabetic ketoacidosis; FGF, fibroblast growth factor; HbA1c, glycated hemoglobin; HDACs, histone deacetylases; HCAR2, hydroxycarboxylic acid receptor 2; HIFs, hypoxia-inducible factors; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; IL, Interleukin; LV, left ventricular; LVEF, left ventricular ejection fraction; mTORC1, mammalian target of rapamycin complex 1; NF, nuclear factor; NLRP3, nod-like receptor family protein-3; PGC, peroxisome proliferator-activated receptor γ coactivator; RR, risk ratio; RTCs, randomized controlled trials; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; SGLT2is, sodium-glucose cotransporter-2 inhibitors; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SIRT-1, sirtuin-1.

References

1. Bays H. From victim to ally: the kidney as an emerging target for the treatment of diabetes mellitus. Curr Med Res Opin 2009;25(3):671-81.
2. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117-28.
3. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644-57.
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347-57.
5. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383(15):1425-35.
6. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995-2008.
7. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413-24.
8. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16);1451-61.
9. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295-306.
10. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436-46.
11. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388(2):117-27.
12. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2020;384(2):117-28.
13. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2021; 384(2):129-39.
14. 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(7):1115-22.
15. Kashiwagi A, Maegawa H. Metabolic and hemodynamic effects of sodium-dependent glucose cotransporter 2 inhibitors on cardio-renal protection in the treatment of patients with type 2 diabetes mellitus. J Diabetes Investig 2017;8(4):416-27.
16. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. Cell Metab 2017;25(2):262-84.
17. Saucedo-Orozco H, Voorrips SN, Yurista SR, de Boer RA, Westenbrink BD. SGLT2 inhibitors and ketone metabolism in heart failure. J Lipid Atheroscler 2022;11(1):1-19.
18. Qian N, Wang Y. Ketone body metabolism in diabetic and non-diabetic heart failure. Heart Fail Rev 2020; 25(5):817-22.
19. Cahill GF Jr. Starvation in man. N Engl J Med 1970;282(12):668-75.
20. Laffel L. Ketone bodies: A review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev 1999;15(6): 412-26.
21. Herring RA, Shojaee-Moradie F, Stevenage M, et al. The SGLT2 inhibitor dapagliflozin increases the oxidation of ingested fatty acids to ketones in type 2 diabetes. Diabetes Care 2022;45(6):1408-15.
22. Ekanayake P, Mudaliar S. A novel hypothesis linking low-grade ketonemia to cardio-renal benefits with sodium-glucose cotransporter-2 inhibitors. Diabetes Obes Metab

2022;24(1):3-11.
23. Polidori D, Iijima H, Goda M, Maruyama N, Inagaki N, Crawford PA. Intra- and inter-subject variability for increases in serum ketone bodies in patients with type 2 diabetes treated with the sodium glucose co-transporter 2 inhibitor canagliflozin. Diabetes Obes Metab 2018;20(5):1321-6.
24. Yabe D, Iwasaki M, Kuwata H, et al. Sodium-glucose co-transporter-2 inhibitor use and dietary carbohydrate intake in Japanese individuals with type 2 diabetes: A randomized, open-label, 3-arm parallel comparative, exploratory study. Diabetes Obes Metab 2017;19(5):739-43.
25. , Kroon T, Hagstedt T, et. Al. N.D. The SGLT2 inhibitor dapagliflozin promotes systemic FFA mobilization, enhances hepatic β-oxidation, and induces ketosis. J Lipid Res 2022; 63(3):100176.
26. Karwi QG, Lopaschuk GD. Crosstalk proposal: Ketone bodies are an important metabolic fuel for the heart. J Physiol 2021;600(5):1001-4.
27. Funada J, Betts TR, Hodson L, et al. Substrate utilization by the failing human heart by direct quantification using arterio-venous blood sampling. PLoS One 2009;4(10):e7533.
28. Kashiwagi Y, Nagoshi T, Inoue Y, et al. Close linkage between blood total ketone body levels and B-type natriuretic peptide levels in patients with cardiovascular disorders. Sci Rep 2021;11(1):6498.
29. Flores-Guerrero JL, Westenbrink BD, Connelly MA, et al. Association of beta-hydroxybutyrate with development of heart failure: Sex differences in a Dutch population cohort. Eur J Clin Investig 2021; 51(5):e13468.
30. Nielsen R, Moller N, Gormsen LC, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation 2019;139(18):2129-41.
31. Ekanayake P, Hupfeld C, Mudaliar S. Sodium-glucose cotransporter type 2 (SGLT-2) inhibitors and ketogenesis: the good and the bad. Curr Diab Rep 2020;20(12):1-10.
32. Yurista SR, Matsuura TR, Silljé HHW, et al. Ketone ester treatment improves cardiac function and reduces pathologic remodeling in preclinical models of heart failure. Circ Heart Fail 2021;14(1):e007684.
33. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. J Am Coll Cardiol 2019;73(15):1931-44.
34. Verma S, Rawat S, Ho KL, 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(5):575-87.
35. Moellmann J, Mann PA, Kappel BA, et al. The sodium-glucose co-transporter-2 inhibitor ertugliflozin modifies the signature of cardiac substrate metabolism and reduces cardiac mTOR signaling endoplasmic reticulum stress and apoptosis. Diabetes Obes Metab 2022;24(11):2263-72.
36. Monzo L, Sedlacek K, Hromanikova K, et al. Myocardial ketone body utilization in patients with heart failure: The impact of oral ketone ester. Metabolism 2021;115:154452.
37. Kim SR, Lee SG, Kim SH, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. Nat Commun 2020;11(1):2127.
38. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: A state-of-the-art review. JACC Basic Transl Sci 2020;5(6):632-44.
39. Ferrannini E, Baldi S, Scozzaro T, et al. Fasting substrate concentrations predict cardiovascular outcomes in the canagliflozin cardiovascular assessment study (CANVAS). Diabetes Care 2022;45(8):1893-9.
40. Oldgren J, Laurila S, Åkerblom A, et al. Effects of 6 weeks of treatment with dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on myocardial function and metabolism in patients with type 2 diabetes: A randomized, placebo-controlled, exploratory study. Diabetes Obes Metab 2021;23(7):1505-17.
41. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 2021;77(3):243-55.
42. Selvaraj S, Fu Z, Jones P, et al. Metabolomic profiling of the effects of dapagliflozin in heart failure with reduced ejection fraction: DEFINE-HF. Circulation 2022;146(11);808-18.
43. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG outcome trial: A "Thrifty Substrate" hypothesis. Diabetes Care. 2016,39(7):1108-14.
44. Manolis AS, Manolis TA, Manolis AA. Ketone bodies and cardiovascular disease: An alternate fuel source to the rescue. Int J Mol Sci 2023;24(4):3534.
45. Hansell P, Welch WJ, Blantz RC, Palm F. Determinants of kidney oxygen consumption and their relationship to tissue oxygen tension in diabetes and hypertension. Clin Exp Pharmacol Physiol 2013;40(2):123-37.
46. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 2017;60(2):215-25.
47. Körner A, Eklöf AC, Celsi G, Aperia A. Increased renal metabolism in diabetes.Mechanism and functional implications. Diabetes 1994;43(5):629-33.
48. Tomita I, Kume S, Sugahara S, et al. SGLT2 inhibition mediates protection from diabetic kidney disease by promoting ketone body-induced mTORC1 inhibition. Cell Metab 2020;32(3):404-19.e6
49. Inoki K, Mori H,Wang J, et al. mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice. J Clin Invest 2011;121(6):2181-96.
50. Koutentakis M, Kuciński J, Świeczkowski D, Surma S, Filipiak KJ, Gąsecka A. The Ketogenic Effect of SGLT-2 Inhibitors—Beneficial or Harmful? J Cardiovasc Dev Dis 2023;10(11):465.
51. Bragagni A, Piani F, Borghi C. Surprises in cardiology: Efficacy of gliflozines in heart failure even in the absence of diabetes. Eur Heart J Suppl 2021;23(Suppl E):E40-4.
52. Prosperi S, D'Amato A, Severino P, et al. Sizing SGLT2 inhibitors up: From a molecular to a morpho-functional point

of view. Int J Mol Sci 2023;24(18):13848.
53. Packer, M. Role of ketogenic starvation sensors in mediating the renal protective effects of SGLT2 inhibitors in type 2 diabetes. J Diabetes Complications 2020;34(9):107647.
54. Lupsa BC, Kibbey RG, Inzucchi SE. Ketones: The double-edged sword of SGLT2 inhibitors? Diabetologia 2023;66(1):23-32.
55. Komada T, Muruve DA. The role of inflammasomes in kidney disease. Nat Rev Nephrol 2019;15(8):501-20.
56. Youm YH, Nguyen KY, Grant RW, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat Med 2015;21(3):263-9.
57. Seto E, Yoshida M. Erasers of histone acetylation: The histone deacetylase enzymes. Cold Spring Harb Perspect Biol 2014;6(4):a018713.
58. Ooi JY, Tuano NK, Rafehi H, et al. HDAC inhibition attenuates cardiac hypertrophy by acetylation and deacetylation of target genes. Epigenetics 2015;10(5):418-30.
59. Matsutani D, Sakamoto M, Kayama Y, Takeda N, Horiuchi R, Utsunomiya K. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. Cardiovasc Diabetol 2018;17(1):73.
60. Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. Circulation 2019;140(21):1693-702.
61. Hadden MJ, Advani A. Histone deacetylase inhibitors and diabetic kidney disease. Int J Mol Sci 2018;19(9):2630.
62. Umino H, Hasegawa K, Minakuchi H, et al. High basolateral glucose increases sodium-glucose cotransporter 2 and reduces sirtuin-1 in renal tubules through glucose transporter-2 detection. Sci Rep 2018;8(1):6791.
63. Shimazu T, Hirschey MD, Newman J, et al. Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science 2013;339(6116):211-4.
64. Hattori Y. Beneficial effects on kidney during treatment with sodium-glucose cotransporter 2 inhibitors: proposed role of ketone utilization. Heart Fail Rev 2021;26(4):947-52.
65. Hesp AC, Schaub JA, Prasad PV, et al. The role of renal hypoxia in the pathogenesis of diabetic kidney disease: A promising target for newer renoprotective agents including SGLT2 inhibitors? Kidney Int 2020;98(3):579-89.
66. Cai T, Ke Q, Fang Y, et al. Sodium–glucose cotransporter 2 inhibition suppresses HIF-1α-mediated metabolic switch from lipid oxidation to glycolysis in kidney tubule cells of diabetic mice. Cell Death Dis 2020;11(5):390.
67. Liu J, Wei Q, Guo C, et al. Hypoxia, HIF, and associated signaling networks in chronic kidney disease. Int J Mol 2017;18(5):950.
68. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol 2021;17(5):319-34.
69. Packer M. Mechanisms leading to differential hypoxia-inducible factor signaling in the diabetic kidney: Modulation by SGLT2 inhibitors and hypoxia mimetics. Am J Kidney Dis 2021;77(2): 280-6.
70. Maruyama T, Takashima H, Oguma H, et al. Canagliflozin improves erythropoiesis in diabetes patients with anemia of chronic kidney disease. Diabetes Technol Ther 2019; 21(12):713-20.
71. Lauritsen KM, Søndergaard E, Svart M, Møller N, Gormsen LC. Ketone body infusion increases circulating erythropoietin and bone marrow glucose uptake. Diabetes Care 2018;41(2):e152-4.
72. Inzucchi SE, Zinman B, Fitchett D, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. Diabetes Care 2018;41(2):356-63.
73. Shakour N, Karami S, Iranshahi M, Butler AE, Sahebkar A. Antifibrotic effects of sodium-glucose cotransporter-2 inhibitors: A comprehensive review. Diabetes Metab Syndr 2024;18(1):102934.
74. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell 2017;168(6):960-76.
75. Packer M. Longevity genes, cardiac ageing, and the pathogenesis of cardiomyopathy: implications for understanding the effects of current and future treatments for heart failure. Eur Heart J 2020;41(39):3856-61.
76. Li X, Lu Q, Qiu Y, et al. Direct cardiac actions of the sodium glucose co-transporter 2 inhibitor empagliflozin improve myocardial oxidative phosphorylation and attenuate pressure-overload heart failure. J Am Heart Assoc 2021;10(6):e018298.
77. Sorrentino V, Menzies KJ, Auwerx J. Repairing mitochondrial dysfunction in disease. Annu Rev Pharmacol Toxicol 2018;58:353-89.
78. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. Circulation 2022;146(18):1383-405.
79. Packer M. SGLT2 inhibitors: role in protective reprogramming of cardiac nutrient transport and metabolism. Nat Rev Cardiol 2023;20(7):443-62.
80. Roberts MN, Wallace MA, Tomilov AA, et al. A ketogenic diet extends longevity and healthspan in adult mice. Cell Metab 2017;26(3):539-46.
81. Paoli A, Cerullo G. Investigating the link between ketogenic diet, NAFLD, mitochondria, and oxidative stress: A narrative review. Antioxidants (Basel) 2023;12(5):1065.
82. Lee YH, Kim SH, Kang JM, et al. Empagliflozin attenuates diabetic tubulopathy by improving mitochondrial fragmentation and autophagy. Am J Physiol Renal Physiol 2019;317(4):F767-80.
83. Kimura I, Inoue D, Maeda T, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). Proc Natl Acad Sci U S A 2011;108(19):8030-5.
84. Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. J Cardiol 2018;71(5):471-6.
85. Fathi A, Vickneson K, Singh JS. SGLT2-inhibitors: More than just glycosuria and diuresis. Heart Fail Rev

2021;26(3):623-42.
86. Rao L, Ren C, Luo S, Huang C, Li X. Sodium-glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: Meta-analysis of randomized controlled trials. Acta Diabetol 2021;58(7):869-80.
87. Li K, Xu G. Safety and efficacy of sodium glucose cotransporter 2 inhibitors combined with insulin in adults with type 1 diabetes: A meta-analysis of randomized controlled trials. J Diabetes 2019;11(8):645-55.
88. Musso G, Gambino R, Cassader M, Paschetta E. Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: Meta-analysis of randomised controlled trials. BMJ 2019;365:l1328.
89. Henry RR, Thakkar P, Tong C, Polidori D, AlbaM. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. Diabetes Care 2015;38(12):2258-65.
90. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: The EASE trials. Diabetes Care 2018;41(12):2560-9.
91. Wang Y, Desai M, Ryan PB, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. Diabetes Res Clin Pract 2017;128: 83-90.
92. Liu J, Li L, Li S, et al. Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab 2020;22(9):1619-27.
93. Bonora BM, Avogaro A, Fadini GP. Sodium-glucose co-transporter-2 inhibitors and diabetic ketoacidosis: an updated review of the literature. Diabetes Obes Metab 2018;20(1): 25-33.
94. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: Analysis of FAERS data. Diabetes Metab Res Rev 2017;33(8):10.1002/dmrr.2924.
95. Raven LM, Muir CA, Greenfield JR. Sodium glucose cotransporter 2 inhibitor-induced ketoacidosis is unlikely in patients without diabetes. Med J Aust 2023;219(7):293-4.
96. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100(8):2849-52.
97. Sanchez DSM, Larios JFDP, Salas JMG, Salazar JAD, García GL. Euglycemic diabetic ketoacidosis in patients taking sodium-glucose co-transporter 2 (SGLT2) inhibitors: Review of the literature. Int J Med Sci Clin Res 2023;3(4):697-700.
98. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care 2019;42(6):1147-54.
99. Goldenberg RM, Gilbert JD, Hramiak IM, Woo VC, Zinman B. Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: The STOP DKA Protocol. Diabetes Obes Metab 2019;21(10):2192-202.
100. US Food and Drug Administration. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections [Cited 2022 May 2]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious.

鈉葡萄糖共同轉運蛋白-2抑制劑和正常血糖性酮症：朋友還是敵人

曾國賓

義大癌治療醫院 內科部內分泌暨新陳代謝科
義守大學醫學院

摘要

鈉葡萄糖共同轉運蛋白 -2 抑制劑是一種新型的抗糖尿病藥物，最初是為了治療第 2 型糖尿病而研發的。鈉葡萄糖共同轉運蛋白 -2 抑制劑具有促進葡萄糖排泄的作用，進而促進肝糖合成、脂肪酸氧化和脂肪組織的動用，這些效應會適度地增加體內酮體濃度。在正常情況下，健康成年人的心臟較少從葡萄糖來獲得能量，但卻高度依賴脂肪酸氧化來獲得大約 60% 至 90% 三磷酸腺苷的能量。在正常情況下，酮體在三磷酸腺苷能量產生過程中所扮演的角色並不那麼重要。值得注意的是，在心臟衰竭和心臟肥大的情況下，葡萄糖的代謝可能因而減緩運作，轉而促使酮體代謝作為替代燃料來源。這個能量轉換對於心肌細胞的能量改善是至關重要的。此外，有研究指出外源和內源性的酮體給予對於腎臟損傷和腎臟疾病具有某種程度的保護效果。因此，酮體被視為在營養逆境期間能為細胞代謝提供能量演進的一種節約燃料，進而可能改善心臟和腎臟功能。酮體 *β*- 羥基丁酸酯在本質上具有抗炎、抗氧化和抗纖維化作用，可以減輕不良左心室和腎臟重塑或纖維化。鈉葡萄糖共同轉運蛋白 -2 抑制劑之心腎益處部分歸因於慢性低濃度之酮體的產生，以及心肌和腎臟燃料代謝從相對能量效率低的脂肪酸氧化轉變為能量高效的酮體代謝有關。然而，鈉葡萄糖共同轉運蛋白 -2 抑制劑過度誘導酮體的生成對某些患者是有害處的，例如患有第 2 型糖尿病和嚴重急性疾病的患者，以及大量減少胰島素劑量使用的第 1 型糖尿病患者。本篇敘述性綜論概述當前所得到的證據，以提供鈉葡萄糖共同轉運蛋白 -2 抑制劑誘導酮體產生的潛在可能之機轉對於心腎系統之正面和負面影響。