JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 13, 2021

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Therapeutic Potential of Ketone Bodies for Patients With Cardiovascular Disease

JACC State-of-the-Art Review

Salva R. Yurista, MD, PhD,[a] Cher-Rin Chong, PhD,[b,c] Juan J. Badimon, PhD,[d] Daniel P. Kelly, MD,[e] Rudolf A. de Boer, MD, PhD,[a] B. Daan Westenbrink, MD, PhD[a]

ABSTRACT

Metabolic perturbations underlie a variety of cardiovascular disease states; yet, metabolic interventions to prevent or treat these disorders are sparse. Ketones carry a negative clinical stigma as they are involved in diabetic ketoacidosis. However, evidence from both experimental and clinical research has uncovered a protective role for ketones in cardiovascular disease. Although ketones may provide supplemental fuel for the energy-starved heart, their cardiovascular effects appear to extend far beyond cardiac energetics. Indeed, ketone bodies have been shown to influence a variety of cellular processes including gene transcription, inflammation and oxidative stress, endothelial function, cardiac remodeling, and cardiovascular risk factors. This paper reviews the bioenergetic and pleiotropic effects of ketone bodies that could potentially contribute to its cardiovascular benefits based on evidence from animal and human studies.

Ketone bodies are endogenous metabolites produced by the liver, in particular under conditions of prolonged fasting, insulin deprivation, and extreme exercise (1). Growing evidence suggests that ketones may be beneficial for patients with cardiovascular disease (CVD) (2–4). Interventions that enhance circulating ketone levels result in increased myocardial ketone oxidation and improved cardiac function (2–5). In addition to the expected role of ketones as an efficient substrate for (cardiac) metabolism, as they require less oxygen per molecule of ATP generated, ancillary cardioprotective effects of ketone bodies beyond energetics have also recently been identified. More importantly, regardless of the method used to increase ketone delivery to the heart, a general favorable effect has been observed in CVD (6,7). The scope of this paper is to review the evidence and discuss the pleiotropic effects of ketone bodies beyond bioenergetics.

KETONE METABOLISM: KETOGENESIS AND KETOLYSIS

Systemic ketone metabolism has been reviewed in detail previously (1,8). In this section, we provide a brief overview of ketone body metabolism (**Figure 1**).

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]University Medical Center Groningen, University of Groningen, Department of Cardiology, Groningen, the Netherlands; [b]Basil Hetzel Institute for Translational Research, The Queen Elizabeth Hospital, Australia; [c]Adelaide Medical School, University of Adelaide, Adelaide, Australia; [d]AtheroThrombosis Research Unit, Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA; and the [e]Cardiovascular Institute, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA. Subodh Verma, MD, PhD, served as Guest Associate Editor for this paper. Javed Butler, MD, MPH, MBA, served as Guest Editor-in-Chief for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 1, 2020; accepted December 14, 2020.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2020.12.065

HIGHLIGHTS

- Data from experimental and human studies suggest that ketone bodies exert protective effects in patients with CVD.
- Administration of exogenous ketones may become an alternative to a ketogenic diet as a means of elevating ketone bodies.
- Future studies should assess the clinical impact of increasing ketone utilization in patients with or at risk of developing CVD.

Under the influence of a reduced insulin to glucagon ratio, such as occurs with fasting, fatty acids are mobilized and converted into ketone bodies by the liver. Ketones are then transferred from the liver, which cannot oxidize ketones by itself, to peripheral tissues where they undergo terminal oxidation donating reducing equivalents to the electron transport chain. Ketones provide ancillary fuels for multiple organs during prolonged fasting, during severe carbohydrate restriction, or after periods of very intense exercise. Under these extreme conditions, up to 300 g of ketone bodies are produced in the liver per day, which constitutes approximately 5% to 20% of the total energy expenditure (9). Ketogenesis includes a series of reactions that leads to the formation of the ketone bodies acetoacetate (AcAc), beta-hydroxybutyrate (βOHB), and acetone. Ketogenesis primarily occurs in hepatocytes, and to a lesser extent in kidney epithelia, astrocytes, and enterocytes. The process of ketone body oxidation, or ketolysis, can occur in almost every cell (1,9).

CARDIAC METABOLISM IN NORMAL HEART AND HEART DISEASE

Cardiac metabolism has been discussed in detail elsewhere (10,11). Here, we provide a brief review of cardiac fuel utilization in the healthy and diseased heart.

Under normal conditions, fatty acyl-CoA, primary metabolites of fatty acid, is the preferred substrate in the adult heart to produce ATP (~40% to 60%), and interestingly, the heart consumed only little glucose (12). Lactate, ketone bodies, and amino acids can also contribute to oxidative cardiac metabolism, but their relative contribution is limited by low availability. Of note, myocardial ketone oxidation is known to be proportional to its arterial concentrations, indicating that circulating ketone levels are a major determinant of myocardial ketone body oxidation rates (13).

Cardiac diseases are associated with loss of metabolic flexibility. Even in early stages of structural heart diseases, substrate utilization switches from fatty acids to glucose utilization, and oxidative metabolism is reduced (14). This metabolic reprogramming results in a fuel preference pattern that is similar to the fetal state. The majority of evidence indicates that the reduced capacity to utilize fatty acids sets the stage for myocardial energy starvation, contributing to the pathogenesis of heart failure (HF) (15). Intriguingly, in the context of reduced fatty acid oxidation, the failing heart appears to reprogram metabolism to increased reliance on ketone bodies as a fuel source (2,16,17).

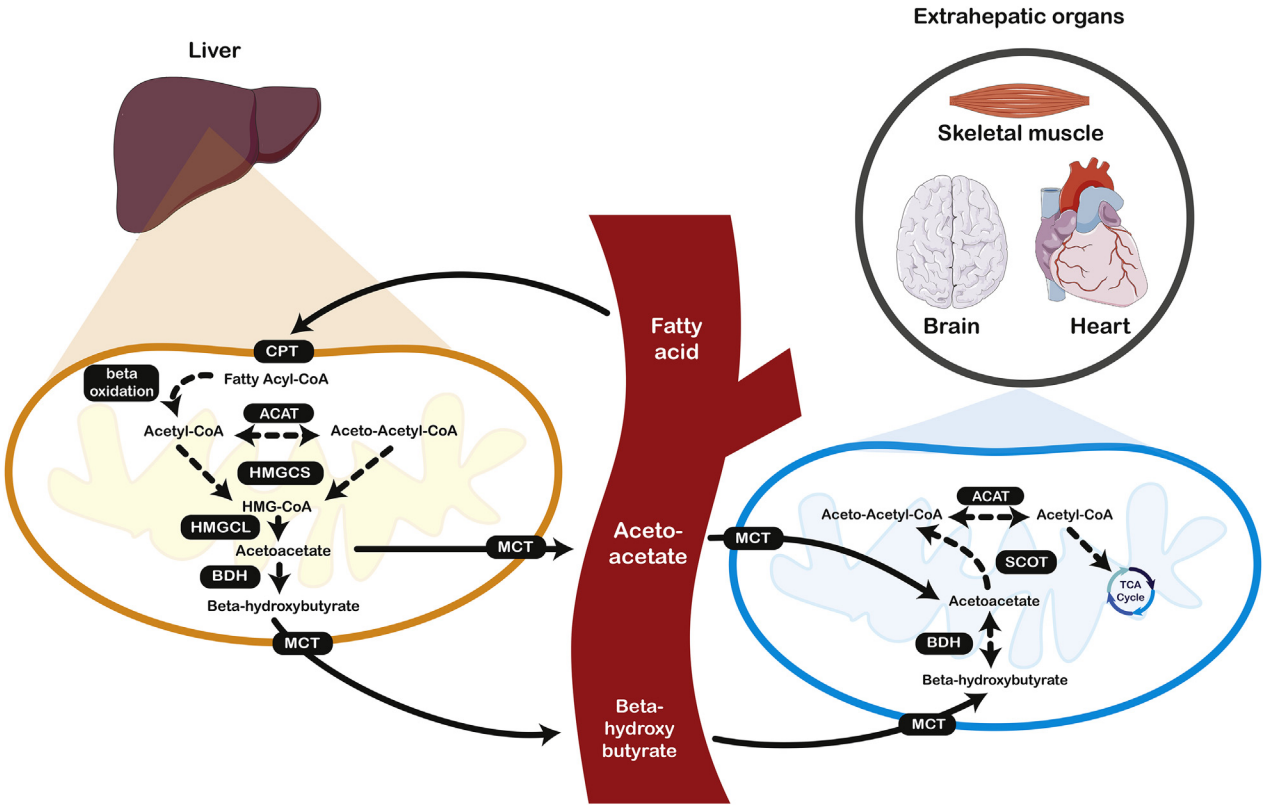
ABBREVIATIONS AND ACRONYMS

BDH = beta-hydroxybutyrate dehydrogenases
CVD = cardiovascular disease
HF = heart failure
KD = ketogenic diet
KE = ketone ester
KS = ketone salts
MCT = medium-chain triglycerides
βOHB = beta-hydroxybutyrate

EVIDENCE FOR INCREASED KETONE OXIDATION IN HEART FAILURE. Although metabolic perturbations in HF have been studied since the 1930s, it took more than 80 years before the metabolic switch toward increased ketone metabolism was discovered by 2 independent research groups in 2016 (16,17). In a critical follow-up study, Horton et al. (2) provided compelling evidence that the shift toward increased ketone utilization is adaptive. Separate studies demonstrated that circulating ketone concentrations and cardiac ketone utilization are increased in a variety of clinical conditions, including heart failure with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (16–19). Increased acetone levels have been detected in the breath of HFrEF patients, and were inversely related to cardiac function and prognosis (20). Moreover, plasma βOHB and cardiac utilization thereof are also increased in patients with diabetes and arrhythmogenic cardiomyopathy, suggesting that the ketogenic shift is a universal cardiac response to stress (21,22).

In a murine model of HFrEF, ketone body oxidation accounts for approximately 20% of cardiac energy production (23). This is roughly similar to what has been observed in clinical studies using coronary sinus sampling, where the contribution of ketone oxidation to myocardial ATP production increases from 6.4% in control subjects to 16.4% in patients with HFrEF (12). Importantly, there is a strong correlation between circulating KB concentrations and cardiac ketone oxidation in patients with or without HF, indicating that circulating ketone concentrations determine the contribution of ketones to the cardiac diet (12).

FIGURE 1 Metabolic Pathways of Ketone Bodies in Liver and Extrahepatic Organs



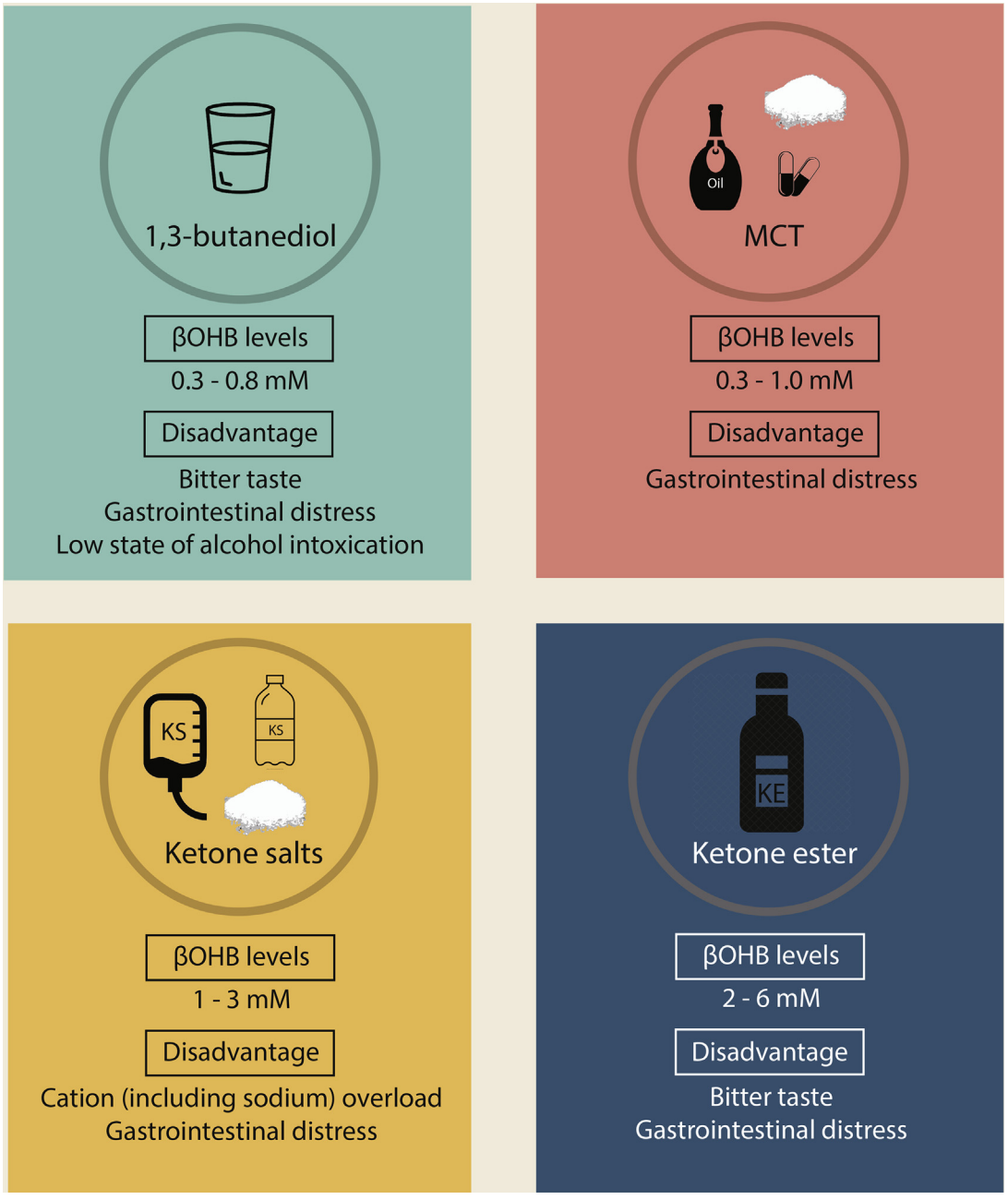
Fatty acids are transported to mitochondria by carnitine palmitoyltransferase 1 (CPT1) and subsequently, ketone bodies acetoacetate (AcAc), beta-hydroxybutyrate (βOHB) and acetone are synthesized from acetyl-CoA that is derived from β-oxidation. AcAc and βOHB are released into the circulation by monocarboxylate transporters (MCTs). After internalization in extra-hepatic tissues, AcAc and βOHB are converted back to acetyl-CoA, which is subsequently metabolized in the TCA cycle to generate ATP. Acetone is not metabolically active and is either excreted through urine or exhaled. Part of illustration elements courtesy of *Servier Medical Art*.
ACAT = acetoacetyl-CoA thiolase; ATP = adenosine triphosphate; BDH = beta-hydroxybutyrate dehydrogenases; HMG-CoA = hydroxymethylglutaryl-CoA; HMGCS = HMG-CoA lyase HMGCL = HMG-CoA synthase; SCOT = succinyl-CoA:3-ketoacid-CoA transferase; TCA = tricarboxylic acid.

STRATEGIES TO INDUCE KETOSIS RELEVANT TO HEART FAILURE. In general, a BHB level ≥0.5 mmol/l has been considered as a cut-off point for entry into ketosis (24). Circulating ketone body concentrations range between 0.1 to 0.25 mmol/l in healthy subjects. Prolonged exercise or >24 h of fasting can increase ketone levels above 1 mmol/l. Ketosis can also be achieved by a ketogenic diet (KD) or by ingesting ketone precursors, such as 1,3-butanediol or medium-chain triglyceride (MCT). Alternatively, exogenous sources of ketones, such as ketone salts (KS) or ketone esters (KE), can be ingested. The KD has become extremely popular, both within and outside of the medical arena. KD consists of a very low-carbohydrate and high-fat diet that forces the body into endogenous ketosis (25). Although sustained KD can raise blood βOHB to 2 to 4 mmol/l (10), long-term compliance is low, often due to gastrointestinal (GI) distress.

Ketosis can also be achieved through ketone supplementation; in this review we will focus on the 4 principal methods (**Figure 2**).

The βOHB precursor 1,3-butanediol is widely available nontoxic alcohol and has been shown to increase blood βOHB concentrations by 0.3 to 0.8 mmol/l in healthy individuals (26,27). Side effects include an unpleasant taste, nausea, and GI distress. In addition, 1,3-butanediol has been reported to induce euphoria and dizziness, which could be related to alcohol intoxication (26). MCT are also considered to be precursors of ketones, as MCT supplementation increases blood ketone levels to 0.3 to 1.0 mmol/l and the side effects are generally limited to mild GI distress at high doses (28,29). Of the exogenous ketones, both KS and KE have been tested in clinical trials and cause sustained increases in circulating βOHB concentrations,

FIGURE 2 **Different Methods to Induce Nutritional Ketosis**



Several ketone supplementation approaches including 1,3-butanediol, medium-chain triglyceride (MCT), ketone salts (KS), and ketone ester (KE) have been explored for their ability to raise circulating ketone levels in various preclinical and clinical scenarios. βOHB = beta-hydroxybutyrate.

although the ketogenic effects of KE are more pronounced than for KS (1 to 3 mmol/l vs. 2 to 6 mmol/l, respectively) (10,30,31). Although KS are more palatable than KE, the doses required to achieve ketosis are associated with a substantial sodium load, which may limit their chronic use in patients with CVD. However, KE are more expensive and bitter-tasting than KS. GI distress after ingestion of KE or KS is generally mild, infrequent, and dose-related (30).

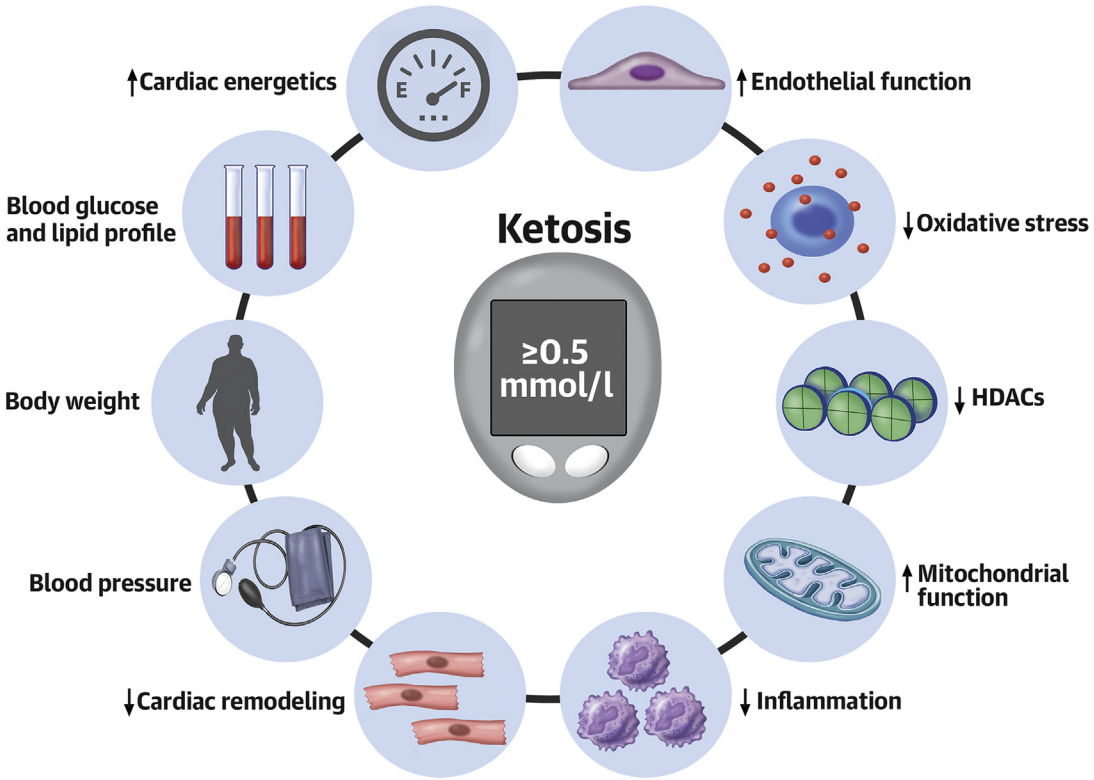
TABLE 1 Clinical Trials Utilizing Nutritional Ketones for CVD or CVD-Related Conditions

Clinical Trial Identifier	First Author (Ref. #), Year	Intervention, Condition/Disease	Participants	Major Outcomes
–	Cox et al. (31), 2016	Ketone ester with carbohydrate (KE (±CHO) vs. control.	N = 35 high-performance athletes	KE decreased glycolysis and plasma lactate, increased intramuscular triacylglycerol oxidation during exercise.
–	Stubbs et al. (81), 2017	KE vs. KS in health.	N = 15 healthy adults	KE and KS lowered blood glucose, free fatty acids, and triglyceride concentrations.
–	Holdsworth et al. (86), 2017	KE vs. placebo in health.	N = 12 well-trained male athletes	KE increased insulin levels and glucose uptake during 2-h glucose clamps, as well as muscle glycogen.
–	Gormsen et al. (4), 2017	KS infusion vs. placebo; to investigate effects of ketones on MGU and myocardial blood flow.	N = 8, age 50 to 68 yrs healthy adults	KS infusion reduced MGU and increased myocardial blood flow.
–	Stubbs et al. (67), 2018	KE vs. isocaloric dextrose drink in health.	N = 15 healthy adults	KE reduced plasma insulin, ghrelin, glucagon-like peptide-1, and peptide tyrosine levels.
–	Myett-Cote et al. (76), 2018	KE vs. placebo in health.	N = 10, age 18–35 yrs healthy volunteers	KE reduced the glycemic response and markers of insulin sensitivity without affecting insulin secretion.
NCT03461068	Myett-Cote et al. (75), 2019	KE vs. taste-matched placebo; cross-over trial; to investigate effects if ingestion before oral glucose tolerance test could reduce blood glucose.	N = 15, age 30–65 yrs individuals with obesity	KE lowered glucose and NEFA AUC with no increase in circulating insulin.
–	Soto-Mota et al. (87), 2019	KE for 28 days to investigate safety profile.	N = 24; age 19–70 yrs healthy adults	No effect on body weight or composition, fasting blood glucose, cholesterol, triglyceride or electrolyte concentrations, nor blood gases or renal function.
NCT03073356	Nielsen et al. (3), 2019	KS infusion vs. placebo; to investigate effects of ketones on cardiac efficiency.	N = 24 HFrEF patients and 10 age-matched healthy volunteers	KS infusion in patients with HFrEF improved CO and reduced SVR in a dose-dependent manner without impairing MEE.
NCT03603782	Cuenoud et al. (88), 2020	DL-BHB; to evaluate metabolism of ketones in whole body using ketone tracer ^{11}C-acetoacetate.	N = 15 healthy adults	Tracer study showed that ketones are rapidly absorbed by heart and kidney.
NCT03531554	Bleeker et al. (89), 2020	KE+CHO vs. CHO alone; to investigate if KE ingestion prior to exercise could boost muscular ATP homeostasis.	N = 5; age 17–45 yrs confirmed VLCADD by genetic profiling	VLCADD-specific plasma acylcarnitine levels, quadriceps glycolytic intermediate levels and in vivo Pi/PCr ratio were all improved by KE + CHO compared with CHO.
NCT03889210	–	KE vs. placebo, in the pre-diabetic patients.	N = 18; age >18 yrs pre-diabetic patients with at least 1 episode of acute pancreatitis	Awaiting study outcome.
NCT03817749	–	KE vs. placebo; in the pre-diabetic patients.	N = 15; age 30–69 yrs pre-diabetic patients	Awaiting study outcome.
NCT03226197	–	KE drink, open-label; to assess the feasibility and safety of delivering a ketone drink via nasogastric tube.	N = 10, age >18 yrs, comatose survivor out-of-hospital cardiac arrest patients	Awaiting study outcome.

BMI = body mass index; CHO = carbohydrate; CVD = cardiovascular disease; DL-BHB = DL-beta-hydroxybutyrate; EPO = erythropoietin; HFrEF = heart failure with reduced ejection fraction; KE = ketone esters; KS = ketone salts; MGU = myocardial glucose uptake; NEFA = nonesterified fatty acids; VLCADD = very long-chain acyl-CoA dehydrogenase deficiency.

Sodium-glucose cotransporter inhibitors (SGLT2i) are drugs that stimulate urinary glucose excretion and have recently received considerable interest because of their cardiovascular benefits in HF patients with and without diabetes (32). SGLT2i reduce insulin levels and stimulate lipolysis, which in turn drives ketone production in the liver (33). Accordingly, SGLT2i induce mild ketosis in both diabetic and nondiabetic subjects (34). Some authors have suggested that CV benefits during SGLT2i are mediated by the increases in circulating ketone bodies (34,35), but a causal link remains controversial. We and others have shown that SGLT2i increased ketone levels in nondiabetic small and large animal models of HF, accompanied by increased myocardial markers of ketone oxidation and normalization of cardiac ATP (5,36). A recent study showed that SGLT2i attenuated the Nod-like receptor protein 3 (NLRP3) inflammasome activity in patients with diabetes and that this was

CENTRAL ILLUSTRATION **Bioenergetic and Pleiotropic Effects of Ketone Bodies**



Yurista, S.R. et al. J Am Coll Cardiol. 2021;77(13):1660–9.

Beyond their contribution to energy generation, ketone bodies may exert salutary effects on endothelial function, oxidative stress, mitochondrial function, inflammation, cardiac remodeling, and other systemic extracardiac effects on body weight, blood pressure, glycemia, and lipid profile. HDACs = histone deacetylases.

explained by enhanced βOHB concentrations and decreased serum levels of insulin (37). In addition, previous studies demonstrated that ketone bodies possess antioxidative activity and other pleiotropic effects beyond cardiac energetics (38,39). Thus, mild ketosis induced by SGLT2i might benefit patients with HF through multiple mechanism. Further mechanistic studies are required to define the mechanisms underlying the cardiovascular benefits of SGLT2i that may be related to substrate metabolism or a signaling role of ketone bodies.

Table 1 lists clinical trials utilizing nutritional ketones for CVD or CVD-related conditions.

KETONE BODIES: PLEIOTROPIC EFFECTS BEYOND CARDIAC ENERGETICS

Besides the effects of ketones on (cardiac) energetics, several pleiotropic effects of ketones have been identified that may provide additional CV benefit (Central Illustration).

ENDOTHELIAL FUNCTION. Treatment with 1,3-butanediol increased nitric oxide synthase activity in resistance arteries from Dahl salt-sensitive rats (40). In the clinical setting, βHOB infusion increased myocardial blood flow by about 75% and induced vasodilatation (3,4). βHOB infusion also increased local cerebral and renal blood flow in humans (41,42). In addition, KD-fed animals had increased endothelial nitric oxide synthase protein expressions (43). These findings suggest that βOHB is a potent endothelium-dependent vasodilator that may be beneficial for patients with CVD.

OXIDATIVE STRESS AND MITOCHONDRIAL FUNCTION. Cardiac overexpression of beta-hydroxybutyrate dehydrogenases 1 (BDH1) in mice resulted in 1.7-fold increase in cardiac ketone body oxidation, increased expression of antioxidant superoxide dismutase,

and suppressed oxidative stress after transaortic constriction (TAC) (44). Histone deacetylases (HDACs) serve critical roles in transcriptional regulation, and βOHB can inhibit class I HDACs. This resulted in the suppression of mitochondrial oxidative stress via activation of Foxo3a and Mt2 promoter genes (38). In animals, βOHB infusion reduced mitochondrial stress in the myocardium after ischemia/reperfusion injury (45). In isolated mitochondria, βOHB provided an alternate fuel in the context of limited substrate availability, thereby improving redox state and mitochondrial membrane potential (2). KD was reported to mitigate lethal mitochondrial cardiomyopathy and increase the number of cardiac mitochondria (46,47). Together, these data suggest that ketone bodies have the potential to mitigate salutary effects on oxidative stress and mitochondrial function in CVD.

INFLAMMATION. NLRP3 inflammasome plays an important role in the heart, as its activation has a detrimental effect on loss of functional myocardium (48). βOHB also has a direct anti-inflammatory action as it specifically inhibits NLRP3 inflammasome in LPS-stimulated human monocytes. βOHB reduced the expression of the NLRP3 inflammasome pathway components, such as NLRP3 and caspase-1, and also limits the release of proinflammatory cytokines IL-1β and IL-18 (38,49). In the clinical setting, KD resulted in reduced circulating inflammation markers compared with a low-fat diet (50). Although limited, these findings provide the evidence that ketone bodies can directly target inflammation in a way that may be beneficial for CVD.

CARDIAC REMODELING. Cardiac remodeling refers to alterations in molecular, cellular and interstitial myocardium, which lead to changes in heart size, shape, structure, and function as the result of myocardial injury, and it has been recognized as an important determinant of the clinical course of HF (51). Increasing circulating ketone concentrations via KD or infusion of βOHB ameliorated pathological cardiac remodeling and improved cardiac function in small and large animal models of HF (2,45,52,53). In addition, mice with cardiac-specific overexpression of BDH1 are more resistant to maladaptive cardiac remodeling after TAC (44). Conversely, a combination of pressure overload/ischemic insult resulted in more severe cardiac dysfunction and exaggerated pathological cardiac remodeling in mice with cardiac-specific knockout of BDH1 (2). Pathological cardiac remodeling in response to pressure-overload was also more pronounced in mice with cardiomyocyte-specific knockout of succinyl-CoA:3-ketoacid-CoA transferase (54). Our group has demonstrated that KE improves cardiac function with reduction in pathological cardiac remodeling in animal models of HF, associated with increased markers myocardial uptake and oxidation of ketones (55).

KD reduced cardiac remodeling after TAC and was associated with lower circulating leptin and insulin concentrations, consistent with the concept that these hormones directly stimulate cardiac growth (52). In isolated cardiomyocytes, ketone bodies exerted antiapoptotic effects via activating the PI3K-Akt pathway, thus increasing Bcl2/Bax ratio and decreasing caspase-3 activity (56). In addition, substantial evidence demonstrated class I and II HDAC involvement in the pathogenesis of HF and its antecedent conditions, such as cardiac hypertrophy and adverse remodeling (57). Interestingly, HDAC inhibitors reduced stress-induced cardiomyocyte death, hypertrophy, and ventricular fibrosis, and thus blunted pathological cardiac remodeling in small and large animal models of HF (57–59). A previous observation that βOHB specifically inhibits class I HDACs (38) raises the possibility that cardiac remodeling might also be reduced upon elevating βOHB.

EFFECT OF KETONES ON CARDIOVASCULAR RISK FACTORS. Blood pressure. In a study in high salt-sensitive hypertensive rats, mild ketosis induced by 1,3-butanediol reduced blood pressure, possibly mediated by reduced NLRP3 inflammasome activity (60). Although the effects of exogenous ketones on blood pressure are not well described, it has been reported that a KD results in a slight but temporary reduction in systolic blood pressure (61,62). Further studies are warranted to elucidate the effects of ketosis on blood pressure.

Body weight. In animals, administration of KE R,S-1,3-butanediol acetoacetate diester (BD-AcAc2) reduced body weight (63,64), whereas another type of KE D-β-hydroxybutyrate-(R)-1,3-butanediol monoester (BD-BHB) did not. BD-BHB and BD-AcAc2 did, however, lower plasma leptin levels and decrease food intake in rodents (65,66). In healthy volunteers, BD-BHB lowered plasma ghrelin levels and reduced hunger. It thus appears that KE reduces appetite, while the effects on body weight are not consistent (67). KS reduced visceral adipocyte volume in rats, but the effects on body weight are limited (68).

The effect of a KD on body weight in animals is inconsistent and appears to be short lived (69–71). In humans, however, there is strong evidence that a KD is a very effective method to induce weight loss (61,72,73). The mechanisms responsible for reduction in body weight include reduced caloric intake, increased satiety, increased energy expenditure, decreased appetite, and reduced ghrelin and leptin levels (65–67).

Blood glucose. Administration of exogenous ketones in animals reduced blood glucose within a few minutes (74). In obese and nonobese subjects, ingestion of BD-BHB reduced blood glucose without affecting insulin secretion (75,76). The hypoglycemic potential of a KD is, however, a more controversial issue. In animals, some authors have reported that KD caused insulin resistance (77,78), whereas others showed that KD improved glycemic control (56,70). In humans, KD has been reported to lower fasting glucose and improve insulin sensitivity (61,73). Conversely, a large dietary analysis study demonstrated that KD was associated with higher HbA1c and a higher likelihood of having diabetes (79). Further studies are warranted to ascertain any potential role for ketone bodies in monitoring blood glucose, and whether exogenous ketones and KD have different outcomes.

Lipid profile. Dyslipidemia is a well-known risk factor for CVD. In animals, KS has been shown to increase HDL cholesterol and decrease the LDL/HDL ratio (68), whereas KE BD-AcAc2 and BD-BHB did not alter total cholesterol and triglycerides levels (80). Reduced plasma free fatty acid and triglycerides have also been observed in healthy volunteers consuming exogenous ketone drinks containing either KE BD-BHB or KS (81).

Long-term KD increased total cholesterol and triglyceride levels in animals (70,82). In humans, the effect of KD on the lipid profile is more controversial. Some authors reported that KD increased atherogenic apoB-containing lipoproteins and decreased HDL (25), whereas others demonstrated that KD increased HDL and reduced total cholesterol, LDL, and triglyceride levels (61,73,83). KD was reported to reduce insulin levels and further suppress both transcription factors and enzymes fatty acid synthase, stearoyl-CoA desaturase-1, and sterol regulatory element-binding protein-1c, which are involved in lipid synthesis (84). Because ingestion of KE reduces insulin levels, it would be expected that KE would also decrease cholesterol biosynthesis pathways (85). In summary, the impact of exogenous ketones and KD on lipid profile differs, and long-term studies are needed to fully define the effect of ketone bodies in serum lipid concentrations.

SUMMARY AND PERSPECTIVES

Evidence for benefits of ketone bodies in subjects with cardiovascular disease is rapidly emerging. In addition to the role of ketones in provision of an ancillary fuel for the failing heart, ketone bodies may also exert a myriad of pleiotropic effects. Ketone bodies may improve endothelial function, ameliorate oxidative stress, improve mitochondrial function, exert anti-inflammatory actions, and mitigate cardiac remodeling. Other systemic extracardiac effects on body weight, blood pressure, glycemia, and lipid profile may also benefit patients with CVD. Regardless of the pathway to achieve ketosis, ketone bodies have potential clinical applications that require further exploration, including new therapeutic approaches to harness the beneficial effect of ketosis. In the coming years, we will learn whether ketone bodies can be beneficial and optimized to be used in treatment and prevention of CVD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The UMCG, which employs Drs. Yurista, de Boer, and Westenbrink, has received research grants and/or fees from Abbott, AstraZeneca, Bristol Myers Squibb, Novartis, Novo Nordisk, and Roche. Dr. Chong is supported by a fellowship jointly awarded by the National Health & Medical Research Council (GNT1162356) and National Heart Foundation of Australia (102126). Dr. Kelly is supported by NIH R01 HL058493, HL128349, and HL151345; and has served as a scientific consultant for Pfizer, Amgen, and Janssen. Dr. de Boer is supported by the Netherlands Heart Foundation (CVON DOUBLE DOSE, grant 2020-8005, CVON SHE-PREDICTS-HF, grant 2017-21, and CVON RED-CVD, grant 2017-11) and the European Research Council (ERC CoG 818715, SECRETE-HF); and has received personal fees from Abbott, AstraZeneca, Novartis, and Roche. Dr. Westenbrink is supported by the Netherlands Organisation for Scientific Research (NWO VENI, grant 016.176.147) and the Netherlands Heart Foundation Senior Clinical Scientist Grant (2019T064) and CVON DOUBLE DOSE (grant 2020-8005). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. B. Daan Westenbrink, Department of Cardiology, University Medical Center Groningen, P.O. Box 30.001, Groningen 9700RB, the Netherlands. E-mail: b.d.westenbrink@umcg.nl. Twitter: @salvareverentia, @Rudolf_deboer, @WestenbrinkDaan, @CardiologyUMCG.

REFERENCES

1. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. Cell Metab 2017;25:262–84.

2. Horton JL, Davidson MT, Kurishima C, et al. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. JCI Insight 2019;4:e124079.

3. Nielsen R, Møller N, Gormsen LC, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation 2019;139:2129–41.

4. Gormsen LC, Svart M, Thomsen HH, et al. Ketone body infusion with 3-hydroxybutyrate reduces myocardial glucose uptake and increases blood flow in humans: a positron emission tomography study. J Am Heart Assoc 2017;6:e005066.

5. Yurista SR, Silljé HHW, Oberdorf-Maass SU, et al. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail 2019;21:862–73.

6. Bhanpuri NH, Hallberg SJ, Williams PT, et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study. Cardiovasc Diabetol 2018;17:56.

7. Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. Nutr Rev 2019;77:161–80.

8. Robinson AM, Williamson DH. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol Rev 1980;60:143–87.

9. Balasse EO, Féry F. Ketone body production and disposal: effects of fasting, diabetes, and exercise. Diabetes Metab Rev 1989;5:247–70.

10. Abdul Kadir A, Clarke K, Evans RD. Cardiac ketone body metabolism. Biochim Biophys Acta - Mol Basis Dis 2020;1866:165739.

11. Selvaraj S, Kelly DP, Margulies KB. Implications of altered ketone metabolism and therapeutic ketosis in heart failure. Circulation 2020;141:1800–12.

12. Murashige D, Jang C, Neinast M, et al. Comprehensive quantification of fuel use by the failing and nonfailing human heart. Science 2020;370:364–8.

13. Rudolph W, Maas D, Richter J, Hasinger F, Hofmann H, Dohrn P. On the significance of acetoacetate and beta-hydroxybutyrate in human myocardial metabolism. Klin Wochenschr 1965;43:445–51.

14. Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation 1996;94:2837–42.

15. Epstein FH, Kelly DP, Strauss AW. Inherited cardiomyopathies. N Engl J Med 1994;330:913–9.

16. Bedi KC, Snyder NW, Brandimarto J, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation 2016;133:706–16.

17. Aubert G, Martin OJ, Horton JL, et al. The failing heart relies on ketone bodies as a fuel. Circulation 2016;133:698–705.

18. Lommi MDJ. Blood ketone bodies in congestive heart failure. J Am Coll Cardiol 1996;28:665–72.

19. Voros G, Ector J, Garweg C, et al. Increased cardiac uptake of ketone bodies and free fatty acids in human heart failure and hypertrophic left ventricular remodeling. Circ Heart Fail 2018;11:e004953.

20. Marcondes-Braga FG, Batista GL, Gutz IGR, et al. Impact of exhaled breath acetone in the prognosis of patients with heart failure with reduced ejection fraction (HFrEF). One year of clinical follow-up. PLoS One 2016;11:e0168790.

21. Song J-P, Chen L, Chen X, et al. Elevated plasma β-hydroxybutyrate predicts adverse outcomes and disease progression in patients with arrhythmogenic cardiomyopathy. Sci Transl Med 2020;12:eaay8329.

22. Mizuno Y, Harada E, Nakagawa H, et al. The diabetic heart utilizes ketone bodies as an energy source. Metabolism 2017;77:65–72.

23. Ho KL, Zhang L, Wagg C, et al. Increased ketone body oxidation provides additional energy for the failing heart without improving cardiac efficiency. Cardiovasc Res 2019;115:1606–16.

24. Volek JS, Phinney SD. The Art and Science of Low Carbohydrate Performance: A Revolutionary Program to Extend Your Physical and Mental Performance Envelope. Miami, FL: Beyond Obesity LLC, 2012.

25. Kwiterovich PO Jr. Effect of a High-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA 2003;290:912.

26. Shaw DM, Merien F, Braakhuis A, Plews D, Laursen P, Dulson DK. The effect of 1,3-butanediol on cycling time-trial performance. Int J Sport Nutr Exerc Metab 2019;29:466–73.

27. Scott BE, Laursen PB, James LJ, et al. The effect of 1,3-butanediol and carbohydrate supplementation on running performance. J Sci Med Sport 2019;22:702–6.

28. Cunnane SC, Courchesne-Loyer A, Vandenberghe C, et al. Can ketones help rescue brain fuel supply in later life? implications for cognitive health during aging and the treatment of Alzheimer's disease. Front Mol Neurosci 2016;9:53.

29. Harvey CJ d C, Schofield GM, Williden M, McQuillan JA. The effect of medium chain triglycerides on time to nutritional ketosis and symptoms of keto-induction in healthy adults: a randomised controlled clinical trial. J Nutr Metab 2018;2018:1–9.

30. Stubbs BJ, Cox PJ, Kirk T, Evans RD, Clarke K. Gastrointestinal effects of exogenous ketone drinks are infrequent, mild, and vary according to ketone compound and dose. Int J Sport Nutr Exerc Metab 2019;29:596–603.

31. Cox PJ, Kirk T, Ashmore T, et al. Nutritional ketosis alters fuel preference and thereby endurance performance in athletes. Cell Metab 2016;24:256–68.

32. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413–24.

33. Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21:512–7.

34. Ferrannini E, Baldi S, Frascerra S, et al. Shift to fatty substrate utilization in response to sodium–glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes 2016;65:1190–5.

35. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors. J Am Coll Cardiol Basic Transl Sci 2020;5:632–44.

36. 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;73:1931–44.

37. Kim SR, Lee S-G, Kim SH, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. Nat Commun 2020;11:2127.

38. Shimazu T, Hirschey MD, Newman J, et al. Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science 2013;339:211–4.

39. Youm Y-H, Nguyen KY, Grant RW, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat Med 2015;21:263–9.

40. Mccarthy CG, Chakraborty S, Schreckenberger Z, Wenceslau CF, Joe B. Abstract 829.1: β-hydroxybutyrate (βHOB) increases nitric oxide synthase activity in resistance arteries from dahl salt-sensitive rats [abstr]. FASEB J 2019;33.

41. Hasselbalch SG, Knudsen GM, Holm S, Hageman LP, Capaldo B, Paulson OB. Transport of D-glucose and 2-fluorodeoxyglucose across the blood-brain barrier in humans. J Cereb Blood Flow Metab 1996;16:659–66.

42. Fioretto P, Trevisan R, Velussi M, et al. Glomerular filtration rate is increased in man by the infusion of both D,L-3-hydroxybutyric acid and sodium D,L-3-hydroxybutyrate. J Clin Endocrinol Metab 1987;65:331–8.

43. Ma D, Wang AC, Parikh I, et al. Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. Sci Rep 2018;8:6670.

44. Uchihashi M, Hoshino A, Okawa Y, et al. Cardiac-specific Bdh1 overexpression ameliorates oxidative stress and cardiac remodeling in pressure overload-induced heart failure. Circ Hear Fail 2017;10.

45. Yu Y, Yu Y, Zhang Y, Zhang Z, An W, Zhao X. Treatment with D-β-hydroxybutyrate protects heart from ischemia/reperfusion injury in mice. Eur J Pharmacol 2018;829:121–8.

46. Krebs P, Fan W, Chen Y-H, et al. Lethal mitochondrial cardiomyopathy in a hypomorphic Med30 mouse mutant is ameliorated by ketogenic diet. Proc Natl Acad Sci U S A 2011;108:19678–82.

47. Al-Zaid NS, Dashti HM, Mathew TC, Juggi JS. Low carbohydrate ketogenic diet enhances cardiac tolerance to global ischaemia. Acta Cardiol 2007; 62:381–9.

48. Mezzaroma E, Toldo S, Farkas D, et al. The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. Proc Natl Acad Sci U S A 2011;108:19725–30.

49. Bae HR, Kim DH, Park MH, et al. β-Hydroxybutyrate suppresses inflammasome formation by ameliorating endoplasmic reticulum stress via AMPK activation. Oncotarget 2016;7:66444–54.

50. Forsythe CE, Phinney SD, Fernandez ML, et al. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. Lipids 2008;43:65–77.

51. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000;35: 569–82.

52. Duda MK, O'Shea KM, Lei B, et al. Low-carbohydrate/high-fat diet attenuates pressure overload-induced ventricular remodeling and dysfunction. J Card Fail 2008;14:327–35.

53. Snorek M, Hodyc D, Sedivý V, et al. Short-term fasting reduces the extent of myocardial infarction and incidence of reperfusion arrhythmias in rats. Physiol Res 2012;61:567–74.

54. Schugar RC, Moll AR, André d'Avignon D, Weinheimer CJ, Kovacs A, Crawford PA. Cardiomyocyte-specific deficiency of ketone body metabolism promotes accelerated pathological remodeling. Mol Metab 2014;3:754–69.

55. 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 Hear Fail 2021;14: e007684.

56. Guo Y, Zhang C, Shang F-F, et al. Ketogenic diet ameliorates cardiac dysfunction via balancing mitochondrial dynamics and inhibiting apoptosis in type 2 diabetic mice. Aging Dis 2020;11:229.

57. Xie M, Hill JA. HDAC-dependent ventricular remodeling. Trends Cardiovasc Med 2013;23: 229–35.

58. Kong Y, Tannous P, Lu G, et al. Suppression of class I and II histone deacetylases blunts pressure-overload cardiac hypertrophy. Circulation 2006; 113:2579–88.

59. Wallner M, Eaton DM, Berretta RM, et al. HDAC inhibition improves cardiopulmonary function in a feline model of diastolic dysfunction. Sci Transl Med 2020;12:eaay7205.

60. Chakraborty S, Galla S, Cheng X, et al. Salt-responsive metabolite, β-hydroxybutyrate, attenuates hypertension. Cell Rep 2018;25:677–89.e4.

61. Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074–81.

62. Cicero AFG, Benelli M, Brancaleoni M, Dainelli G, Merlini D, Negri R. Middle and long-term impact of a very low-carbohydrate ketogenic diet on cardiometabolic factors: a multicenter, cross-sectional, clinical study. High Blood Press Cardiovasc Prev 2015;22:389–94.

63. Davis RAH, Deemer SE, Bergeron JM, et al. Dietary R, S -1,3-butanediol diacetoacetate reduces body weight and adiposity in obese mice fed a high-fat diet. FASEB J 2019;33:2409–21.

64. Deemer SE, Davis RAH, Gower BA, et al. Concentration-dependent effects of a dietary ketone ester on components of energy balance in mice. Front Nutr 2019;6:56.

65. Srivastava S, Kashiwaya Y, King MT, et al. Mitochondrial biogenesis and increased uncoupling protein 1 in brown adipose tissue of mice fed a ketone ester diet. FASEB J 2012;26:2351–62.

66. Kashiwaya Y, Pawlosky R, Markis W, et al. A ketone ester diet increases brain malonyl-coa and uncoupling proteins 4 and 5 while decreasing food intake in the normal wistar rat. J Biol Chem 2010;285:25950–6.

67. Stubbs BJ, Cox PJ, Evans RD, Cyranka M, Clarke K, de Wet H. A ketone ester drink lowers human ghrelin and appetite. Obesity (Silver Spring) 2018;26:269–73.

68. Caminhotto R de O, Komino ACM, de Fatima Silva F, et al. Oral β-hydroxybutyrate increases ketonemia, decreases visceral adipocyte volume and improves serum lipid profile in Wistar rats. Nutr Metab (Lond) 2017;14:31.

69. Kennedy AR, Pissios P, Otu H, et al. A high-fat, ketogenic diet induces a unique metabolic state in mice. Am J Physiol Endocrinol Metab 2007;292: E1724–39.

70. Douris N, Melman T, Pecherer JM, et al. Adaptive changes in amino acid metabolism permit normal longevity in mice consuming a low-carbohydrate ketogenic diet. Biochim Biophys Acta - Mol Basis Dis 2015;1852:2056–65.

71. Shimizu K, Saito H, Sumi K, Sakamoto Y, Tachi Y, Iida K. Short-term and long-term ketogenic diet therapy and the addition of exercise have differential impacts on metabolic gene expression in the mouse energy-consuming organs heart and skeletal muscle. Nutr Res 2018;60: 77–86.

72. Partsalaki I, Karvela A, Spiliotis BE. Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents. J Pediatr Endocrinol Metab 2012;25:697–704.

73. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–90.

74. Ari, Murdun, Koutnik, et al. Exogenous ketones lower blood glucose level in rested and exercised rodent models. Nutrients 2019;11:2330.

75. É Myette-Côté, Caldwell HG, Ainslie PN, Clarke K, Little JP. A ketone monoester drink reduces the glycemic response to an oral glucose challenge in individuals with obesity: a randomized trial. Am J Clin Nutr 2019;110:1491–501.

76. É Myette-Côté, Neudorf H, Rafiei H, Clarke K, Little JP. Prior ingestion of exogenous ketone monoester attenuates the glycaemic response to an oral glucose tolerance test in healthy young individuals. J Physiol 2018;596:1385–95.

77. Jornayvaz FR, Jurczak MJ, Lee H-Y, et al. A high-fat, ketogenic diet causes hepatic insulin resistance in mice, despite increasing energy expenditure and preventing weight gain. Am J Physiol Metab 2010;299:E808–15.

78. Bielohuby M, Sisley S, Sandoval D, et al. Impaired glucose tolerance in rats fed low-carbohydrate, high-fat diets. Am J Physiol Metab 2013;305:E1059–70.

79. Churuangsuk C, Lean MEJ, Combet E. Lower carbohydrate and higher fat intakes are associated with higher hemoglobin A1c: findings from the UK National Diet and Nutrition Survey 2008-2016. Eur J Nutr 2020;59:2771–82.

80. Desrochers S, Dubreuil P, Brunet J, et al. Metabolism of (R,S)-1,3-butanediol acetoacetate esters, potential parenteral and enteral nutrients in conscious pigs. Am J Physiol Metab 1995;268: E660–7.

81. Stubbs BJ, Cox PJ, Evans RD, et al. On the metabolism of exogenous ketones in humans. Front Physiol 2017;8:848.

82. Ellenbroek JH, van Dijck L, Töns HA, et al. Long-term ketogenic diet causes glucose intolerance and reduced β- and α-cell mass but no weight loss in mice. Am J Physiol Metab 2014;306:E552–8.

83. Tay J, Luscombe-Marsh ND, Thompson CH, et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. Diabetes Care 2014;37:2909–18.

84. Kennedy AR, Pissios P, Otu H, et al. A high-fat, ketogenic diet induces a unique metabolic state in mice. Am J Physiol Metab 2007;292:E1724–39.

85. Veech RL. Ketone ester effects on metabolism and transcription. J. Lipid Res 2014;55:2004–6.

86. Holdsworth DA, Cox PJ, Kirk T, Stradling H, Impey SG, Clarke K. A ketone ester drink increases postexercise muscle glycogen synthesis in humans. Med Sci Sport Exerc 2017;49:1789–95.

87. Soto-Mota A, Vansant H, Evans RD, Clarke K. Safety and tolerability of sustained exogenous ketosis using ketone monoester drinks for 28 days in healthy adults. Regul Toxicol Pharmacol 2019; 109:104506.

88. Cuenoud B, Hartweg M, Godin J-P, et al. Metabolism of exogenous D-beta-hydroxybutyrate, an energy substrate avidly consumed by the heart and kidney. Front Nutr 2020;7:13.

89. Bleeker JC, Visser G, Clarke K, et al. Nutritional ketosis improves exercise metabolism in patients with very long-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis 2020;43:787–99.

KEY WORDS cardiovascular disease, heart failure, ketones, pleiotropic effects