

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

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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.

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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).



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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 (β OHb), 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).

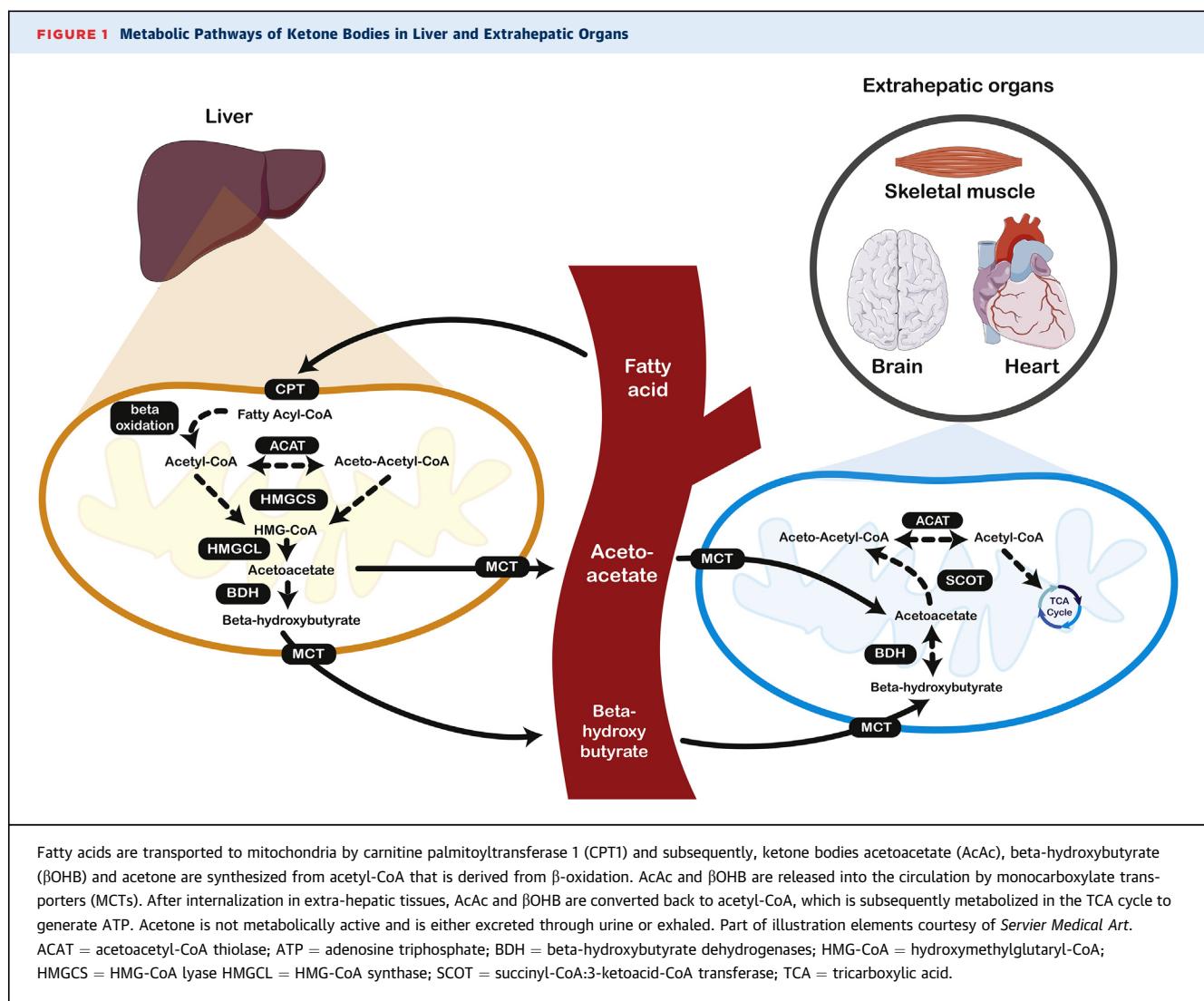
Cardiac diseases are associated with loss of metabolic flexibility. Even in early stages of structural heart diseases, substrate utilization switches from fatty acids to glucose utilization, and oxidative metabolism is reduced (14). This metabolic reprogramming results in a fuel preference pattern that 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).

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 β OHb and cardiac utilization thereof are also increased in patients with diabetes and arrhythmic 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).

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 |

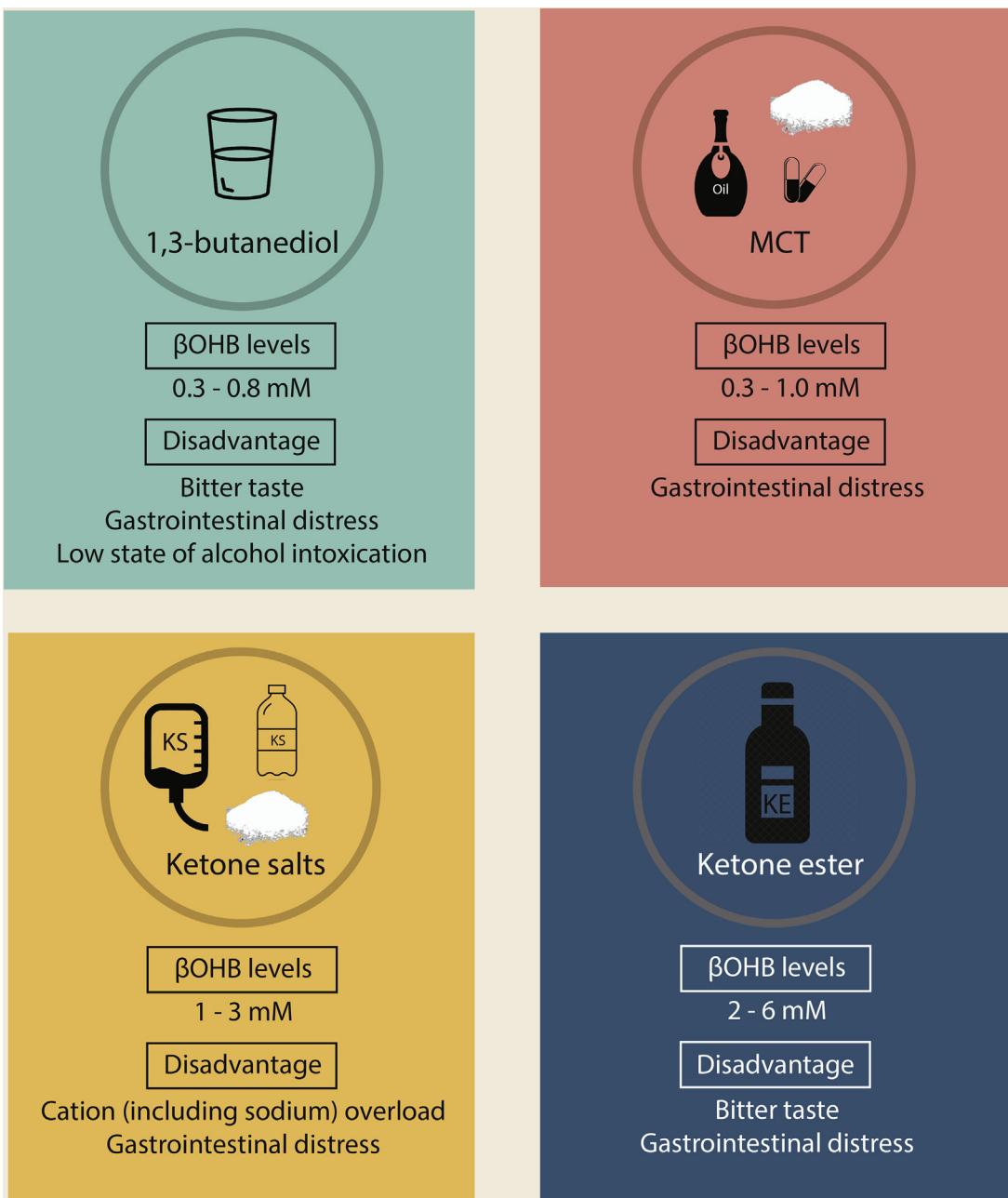


STRATEGIES TO INDUCE KETOSIS RELEVANT TO HEART FAILURE. In general, a BHB level ≥ 0.5 mmol/l has been considered as a cut-off point for entry into ketosis (24). Circulating ketone body concentrations range between 0.1 to 0.25 mmol/l in healthy subjects. Prolonged exercise or >24 h of fasting can increase 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 β OHb 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 β OHb precursor 1,3-butanediol is widely available nontoxic alcohol and has been shown to increase blood β OHb 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 β OHb 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).

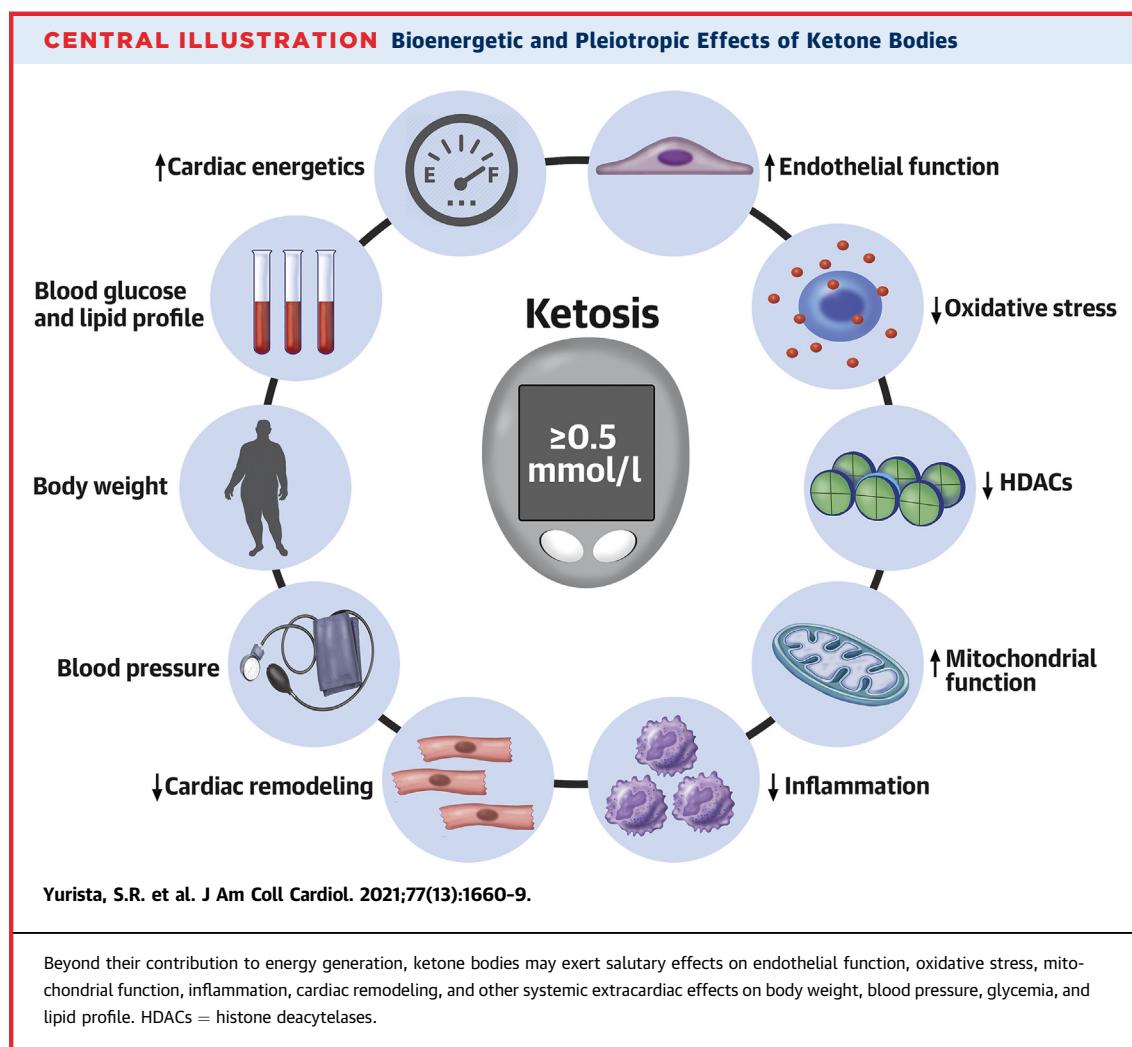
TABLE 1 Clinical Trials Utilizing Nutritional Ketones for CVD or CVD-Related Conditions

| Clinical Trial Identifier | First Author (Ref. #), Year | Intervention, Condition/Disease | Participants | Major Outcomes |
|---------------------------|------------------------------|--|---|---|
| — | Cox et al. (31), 2016 | Ketone ester with carbohydrate (KE (\pm 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 <i>in vivo</i> 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



explained by enhanced β -OHB concentrations and decreased serum levels of insulin (37). In addition, previous studies demonstrated that ketone bodies possess antioxidant 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, β -HOB infusion increased myocardial blood flow by about 75% and induced vasodilatation (3,4). β -HOB 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 β -OHB 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 β OHB 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, β OHB infusion reduced mitochondrial stress in the myocardium after ischemia/reperfusion injury (45). In isolated mitochondria, β OHB 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). β OHB also has a direct anti-inflammatory action as it specifically inhibits NLRP3 inflammasome in LPS-stimulated human monocytes. β OHB reduced the expression of the NLRP3 inflammasome pathway components, such as NLRP3 and caspase-1, and also limits the release of proinflammatory cytokines IL-1 β 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 β OHB 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 β OHB specifically inhibits class I HDACs (38) raises the possibility that cardiac remodeling might also be reduced upon elevating β OHB.

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.

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