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Research Progress on the Application and Mechanisms of β-Hydroxybutyrate Supplementation in Cardiovascular Diseases

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Abstract:

The prevention and treatment of cardiovascular diseases have always been a focal point in related fields. This paper explores the application and underlying mechanisms of exogenous and endogenous β-hydroxybutyrate supplementation in addressing cardiovascular diseases, including myocardial ischemia, myocardial infarction, diabetic cardiomyopathy, hypertension, myocardial inflammation, hypertrophic cardiomyopathy, and heart failure. Exogenous β-hydroxybutyrate supplementation offers a rapid and direct energy source for the heart, thereby aiding in the prevention and management of cardiac injury. Notably, the overall efficacy of exogenous β-hydroxybutyrate is markedly superior to that of endogenous β-hydroxybutyrate. Endogenous fatty acids, derived from a ketogenic diet, undergo oxidation to form β-hydroxybutyrate in the body for energy production. However, this process is significantly influenced by glucose and lipid metabolism, particularly in the context of underlying health conditions. Currently, the use of a ketogenic diet is not advocated for the prevention or treatment of myocardial ischemia, myocardial infarction, diabetic cardiomyopathy, or hypertension.

Keywords:

β-Hydroxybutyrate
Ketogenic diet
Cardiovascular diseases
Nutritional ketosis

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1. Introduction

The global fatality rate of cardiovascular diseases (CVD) has been increasing year by year [1], and it has become one of the severe public health problems in China. In 2019, the number of deaths from CVD in rural and urban areas accounted for 46.74% and 44.26% of the total deaths, respectively [2]. It is predicted that the domestic CVD mortality rate will reach 1,973.8 per 100,000 people from 2020 to 2030 [3]. Therefore, exploring effective strategies to control the progression of CVD is of great significance for reducing the risk of death and improving the current status of the disease.

β-hydroxybutyrate (β-OHB), which accounts for 70% of ketone bodies, is the main substance that provides energy and exerts protective effects on the heart. It controls the occurrence or development of CVD by reducing vascular fibrosis and promoting endothelial cell proliferation. Studies have suggested that the compensatory increase of β-OHB is a risk factor for the occurrence of CVD. When heart injury occurs, metabolic patterns change, leading to a decrease in glycolytic capacity and a shift to ketone body oxidation as the main energy source. Therefore, supplementing β-OHB can prevent the production of more compensatory products that may aggravate heart injury [4]. However, in the prevention or treatment of different types of CVD, exogenous and endogenous β-OHB supplementation has shown varying results, such as protection or damage, and its role in various CVD remains controversial. This article summarizes the supplements and functions of β-OHB, reviews its application in the prevention and treatment of CVD, summarizes its mechanism of action, and provides references for related applications such as early clinical prevention and treatment of CVD and drug development.

2. Supplementation of β-OHB

2.1. Exogenous β-OHB supplementation

Exogenous β-OHB supplementation elevates blood ketone levels, with a blood β-OHB concentration >0.5 mmol/L, resulting in nutritional ketosis and a shift in overall metabolism. This enhancement increases the heart's ability to oxidize β-OHB, elevates mitochondrial redox potential, and ultimately increases the free energy of ATP hydrolysis. In CVD, exogenous β-OHB is often supplemented through ketone salts or ketone esters. Ketone salts, primarily in the form of sodium, calcium, magnesium, etc., are commonly used exogenous β-OHB supplements. Ester-based β-OHB supplements are classified into monoesters and diesters based on whether they contain β-OHB and/or its precursors. Ketone esters have a faster absorption rate and ability to elevate blood ketones than ketone salts. Only 50% of serum β-OHB can be detected after oral administration of ketone salts, and levels return to normal after 24 hours [1,5].

Exogenous β-OHB supplementation plays a crucial role in controlling obesity, improving metabolic status, enhancing athletic performance, and serving as an anti-aging metabolite. In maintaining and protecting cardiovascular health, exogenous β-OHB infusion increases the heart rate of healthy elderly individuals by 25% and resting myocardial blood flow by 75% [6]. Aerobic perfusion of high-concentration β-OHB in healthy mice can increase the β-OHB oxidation rate, generating a large number of reducing equivalents through the citric acid cycle without causing a burden on the heart, indicating the safety of exogenous β-OHB application for the heart [7].

2.2. Endogenous β-OHB supplementation

The ketogenic diet (KD) is a dietary plan that combines high fat, low carbohydrates, and moderate protein, primarily satisfying the high-energy demands of cardiac metabolism by promoting fatty acid oxidation in hepatocytes to produce ketones. The KD lowers the metabolic efficiency of the citric acid cycle in hepatocytes, causing an accumulation of acetyl-CoA that cannot enter the cycle. This leads to the production of ketones, mainly β-OHB, which are transported through the blood to high-energy tissues like the heart, brain, and skeletal muscles for oxidation and utilization. The KD is classified into classic KD, medium-chain triglyceride KD, modified Atkins diet, and low glycemic index treatment based on lipid content. Diets with a lower lipid content have shorter fatty acid chain lengths, resulting in faster metabolism to β-OHB and an earlier onset of effects [8].

Initially used to control refractory epilepsy, the KD has proven effective in treating neurological diseases such as Parkinson's disease, Alzheimer's disease, and autism spectrum disorders. Its therapeutic role in cardiovascular health has gained increasing attention in recent years.

Dietary intervention presents the greatest opportunity to alter cardiovascular outcomes, including improving or eliminating heart risk factors, preventing myocardial infarction, stroke, and cardiovascular death, and reducing the burden on heart plaques [9]. The KD can improve heart function and delay aging in elderly mice by reducing oxidative stress, enhancing mitochondrial function, promoting autophagy flux, decreasing left ventricular end-systolic diameter, and reducing cardiomyocyte cross-sectional area [10].

3. Application and mechanism of exogenous β-OHB in CVD

3.1. Exogenous β-OHB supplementation prevents myocardial ischemia-reperfusion injury by reducing reactive oxygen species

Myocardial ischemia leads to cellular hypoxia, where the myocardium does not have sufficient oxygen for glucose glycolysis to produce energy. Therefore, β-OHB generated by the liver becomes the primary energy source for cardiomyocytes. The heart drives ketogenesis through 3-hydroxy-3-methylglutaryl-CoA synthase and succinyl-CoA transferase (SCOT), where β-OHB can accumulate to 23.9 nmol per milligram of myocardial tissue. This nourishes the heart through the coronary arteries, accelerating functional recovery from ischemia/reperfusion (I/R) injury [11]. In mice with myocardial ischemia under continuous β-OHB exposure, a concentration of 10 mmol/L was found to be optimal for preventing I/R injury. β-OHB enhances the expression of forkhead box O3 (FoxO3) by promoting histone acetylation in cardiomyocytes, thereby inhibiting caspase-1-mediated pyroptosis and preventing acute myocardial I/R injury [12]. Reactive oxygen species (ROS) regulate mitochondrial membrane permeability during myocardial I/R, causing irreversible heart damage. β-OHB reduces ROS generation by decreasing the microtubule-associated protein 1 light chain 3B-II (LC3B-II)/LC3-I protein ratio and enhancing lysosome-associated membrane protein-2 content in the myocardium. This promotes autophagic flux, reduces mitochondrial ROS production, and mitigates oxidative and endoplasmic reticulum stress, ultimately lowering serum troponin I, creatine kinase (CK), and lactate dehydrogenase (LDH) levels. It also reduces infarct size, minimizing heart damage caused by I/R in mice [13].

3.2. Exogenous β-OHB supplementation reduces myocardial infarction size by decreasing the number of apoptotic cells

Severe myocardial ischemia leads to myocardial infarction (MI), and elevated β-OHB is an independent risk factor for cardiac death three years after MI patient discharge [14]. Exogenous β-OHB supplementation effectively prevents MI. In rats administered intravenous ketone esters and subjected to MI modeling, β-OHB increased 40-fold to maintain energy supply after MI. Compared to the MI group, there was a reduction in infarct size and the number of apoptotic cells in the infarct zone [15]. Injecting β-OHB into MI rats also treats heart function impairment caused by MI. After three weeks of injection, MI rats showed activation of the Notch homolog 1/hairy and enhancer of split 1 (Notch1/Hes1) pathway, inhibiting cardiomyocyte apoptosis and endoplasmic reticulum stress. This reduced myocardial infarction size, significantly lowered serum LDH and CK isoenzyme levels, and improved cardiac function and pathological changes in acute MI rats [16].

3.3. Exogenous β-OHB supplementation enhances antioxidant capacity to prevent and treat diabetic cardiomyopathy

Elevated levels of ROS and nitrogen in patients with diabetic hyperglycemia are major factors in the development of diabetic cardiomyopathy (DCM). ROS causes oxidative stress damage, leading to cardiomyocyte apoptosis and cardiac dysfunction [17]. Four weeks of ketone ester feeding enhances mitochondrial biogenesis and increases antioxidant stress capacity in diabetic db/db mice, improving cardiac systolic and diastolic function and preventing the progression of the disease to DCM [18]. Oxidative stress induces the accumulation of collagen 4 (COL4) and thickening of the basement membrane, leading to cardiac microvascular fibrosis in diabetic rats. Ten weeks of ketone ester intake can inhibit the production of COL4, promote the generation of copper-zinc superoxide dismutase, reduce nitrotyrosine levels, and alleviate cardiac microvascular fibrosis [19]. Thioredoxin 1 (Trx1) plays an antioxidant protective

role in DCM. Treating cardiomyocytes with β-OHB for 16 hours upregulates Trx1 through protein acetylation, protecting the heart [20]. In diabetic patients, the heart's intake of glucose, lactic acid, and pyruvate decreases, while the intake of β-OHB increases. β-OHB can downregulate the NOD-like receptor protein 3 (NLRP3) inflammasome in the human body, inhibit inflammatory responses, and thereby reduce left ventricular hypertrophy in diabetic patients [21].

3.4. Exogenous β-OHB supplementation improves vascular function in hypertensive populations

Supplementing with exogenous β-OHB can effectively prevent hypertension. Healthy individuals who consume ketone esters experience an increase in systolic blood pressure, heart rate, and biventricular function, along with a decrease in systemic vascular resistance. Obesity is a risk factor for hypertension. Obese individuals who drink ketone ester beverages can lower blood sugar and inflammation, thereby reducing blood pressure, increasing heart rate, and improving vascular function [22]. When rats drink diluted water with a low dose of ketone esters for four weeks, it can expand blood vessels by activating potassium channels and nitric oxide synthase, improving endothelium-dependent and -independent vasodilation in aged spontaneously hypertensive rats (SHRs). However, it may cause vascular damage in young and healthy rats, indicating that exogenous β-OHB can treat and reverse the decline in vascular function that comes with age [23].

3.5. Exogenous β-OHB supplementation activates antioxidant pathways to reduce myocardial damage caused by myocardial inflammation

When the heart is damaged by lipopolysaccharide (LPS) and doxorubicin (DOX), mitochondrial oxidative stress and inflammatory responses occur. Glycolysis of glucose is insufficient for energy supply, subsequently enhancing the synthesis and utilization of the auxiliary fuel β-OHB, improving the heart's resistance to myocardial inflammatory responses. In human vascular endothelial cells, β-OHB activates antioxidant pathways by inhibiting histone deacetylase (HDAC) activity, reducing mitochondrial superoxide production, and enhancing the expression of antioxidant genes *Foxo3a* and metallothionein 2A (*Mt2*). This increases mitochondrial basal oxygen consumption rate and respiratory reserve capacity [24]. Twenty days of ketone ester gavage significantly increases β-OHB in mouse myocardium, activates the Foxo3A/Mt2 pathway through HDAC, reduces myocardial oxidative stress, improves mitochondrial respiratory function, and can prevent myocardial sepsis caused by LPS [25]. Gavaging mice with β-OHB shows that β-OHB can increase the expression of matrix metalloproteinase 9 by activating the extracellular signal-regulated kinase 1/2 pathway, inhibit apoptosis, reduce oxidative stress, and maintain mitochondrial membrane integrity. This treats the decline in heart function caused by DOX and reduces cardiotoxicity [26].

3.6. Exogenous β-OHB supplementation treats cardiomyocyte hypertrophy in mice with hypertrophic cardiomyopathy

Transverse aortic contraction (TAC) is a common method for inducing hypertrophic cardiomyopathy (HCM) in animal models. Two weeks of treatment with drinking water containing 20% ketone ester reduced cardiomyocyte hypertrophy and cardiac fibrosis in TAC mice, delaying the deterioration of cardiac function. However, acute intravenous infusion of β-OHB for one hour only increased cardiac output and improved cardiac metabolism in TAC mice [27]. Current evidence suggests that a single acute exogenous β-OHB supplementation has limited effects on the treatment of HCM, only affecting cardiac metabolism. The role of exogenous β-OHB supplementation in human patients has not yet been explored, and the mechanism of action has not been elucidated or discussed, which needs to be supplemented in subsequent research.

3.7. Exogenous β-OHB supplementation exerts antioxidant effects to slow down the occurrence and development of heart failure

Heart failure (HF) is the end-stage manifestation of CVD, and the elevation of β-OHB in late-stage myocardium is a compensatory response to cardiomyocyte injury [28]. In HF patients, the ratio of β-OHB production to consumption increases by three times compared to healthy adults. The

compensatory increase in serum β-OHB concentration is positively correlated with the decrease in ejection fraction, and excessive accumulation impairs cardiac function [29]. Ketosis induced by β-OHB supplementation leads to cardiac metabolic reprogramming, which helps reduce cardiac dysfunction and disease progression during HF development. After oral administration of a ketone ester drink for six minutes, β-OHB increased by 12.9 times, which was positively correlated with left ventricular mass and diameter, negatively correlated with left ventricular ejection fraction, and characterized by reduced mitochondrial oxidative metabolism [30]. Intravenous injection of β-OHB increased cardiac output by 40% and left ventricular ejection fraction by 8% in HF patients, without impairing myocardial energy utilization efficiency [31,32]. Treatment of HF rabbit cardiomyocytes with β-OHB showed higher reduced glutathione (GSH) levels than HF cells, indicating that β-OHB exerts antioxidant effects to treat HF-induced cardiac function damage [33]. Oral administration of ketone esters for one week in mice and two days in rats, followed by TAC combined with apical MI surgery (TAC/MI) for HF modeling, showed that oral ketone esters prevented the decrease in left ventricular ejection fraction caused by HF and improved left ventricular dysfunction. However, the improvement in the myocardial infarction area was better with two weeks of oral ketone ester treatment compared to two days of preoperative ketone ester prevention [34]. In the treatment of HF, β-OHB downregulates the oxidase 2/glycogen synthase kinase 3β (NADPH oxidase 2/glycogen synthase kinase-3β, NOX2/GSK-3β) pathway, increases the number of cardiac T regulatory cells to inhibit inflammation, improves diastolic function and fibrosis in HF mice, and promotes the recovery of cardiac function [35].

4. Application and mechanism of endogenous ketogenic diet in cardiovascular diseases

4.1. Endogenous ketogenic diet cannot prevent myocardial ischemia-reperfusion injury

When KD is consumed for a certain period as a preventative measure, the heart's β-OHB remains at supernormal levels. However, in sudden cardiac ischemia and hypoxia, it is difficult for the myocardium to oxidize β-OHB for energy. In obese rats, two weeks of KD intervention led to inhibited mitochondrial biogenesis and adiponectin systems, significantly reducing the levels of cardiac antioxidants superoxide dismutase 2 (SOD2) and catalase (CAT), thereby impairing the recovery of left ventricular function after isolated ischemia/reperfusion (I/R) [36]. KD also struggles to rapidly provide sufficient energy to treat I/R injury due to the slow increase in endogenous β-OHB levels. The anaerobic oxidation of glucose alone cannot meet the high energy demand of the heart, making the therapeutic effect of KD on I/R potentially unoptimistic [15], although direct evidence is still lacking.

4.2. Endogenous ketogenic diet has a negative effect on the prevention and treatment of myocardial infarction

The effectiveness of KD in preventing MI is not significant. After four weeks of KD feeding, MI modeling was performed on mice, revealing a decrease in both glycolysis-related enzymes and β-OHB metabolism under hypoxic conditions, insufficient to provide adequate energy to the myocardium [15]. The therapeutic effect of KD after MI also shows negative outcomes, with long-term KD intervention increasing overall mortality [9]. A male with no history of heart disease developed Type II MI after four weeks of KD intervention, although the specific mechanism remains unclear [37]. In humans with MI, there is a sharp compensatory increase in β-OHB in the heart, causing damage. KD cannot timely replenish β-OHB and is difficult to reverse cardiomyocyte death, leading to the continuous deterioration of heart function.

4.3. Endogenous ketogenic diet can prevent but not treat diabetic cardiomyopathy

Eight weeks of KD can exert anti-apoptotic protective effects through the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway, enhancing mitochondrial function, reducing oxidative stress, controlling blood glucose in db/db mice, and preventing disease progression to DCM [38]. However, long-term KD treatment shows negative effects. Increased glucose availability in the myocardium of diabetic mice leads to reduced ketone body utilization and suppressed expression of key ketogenic enzymes such as D-β-OHB dehydrogenase 1 (BDH1)

and 3-oxoacid CoA transferase [39]. Twelve weeks of KD weakens interleukin-33/suppression of tumorigenicity 2 ligand (IL-33/ST2L) signaling in T regulatory cells, reduces mitochondrial function in DCM mice, inhibits fatty acid oxidation, and elevates glycolysis levels. This results in cardiac fibroblast activation and interstitial fibrosis, which are not conducive to improving heart function in DCM [40]. While KD plays a role in preventing diabetes progression to DCM, its effect on treating myocardial damage in established DCM is minimal due to sufficient energy provision by hyperglycemia-induced glycolysis in the absence of significant changes in related enzymes.

4.4. Endogenous ketogenic diet should be prohibited in the treatment of hypertension

KD induces oxidative stress, inflammatory responses, and fibrosis, leading to glucose and lipid metabolism disorders in spontaneously hypertensive rats (SHRs). Endogenously generated β-OHB cannot exert its beneficial effects and instead aggravates hypertension by activating the renin-angiotensin-aldosterone system. Therefore, KD should be prohibited in the treatment of hypertensive patients. Four weeks of KD increases the activity of the mammalian target of the rapamycin (mTOR) pathway in SHRs, promoting β-OHB-induced cardiac fibroblast fibrosis progression through the mTOR pathway. This reduces antioxidant glutathione (GSH) content, increases the production of oxidative product malondialdehyde (MDA), elevates systolic blood pressure, and adversely affects the heart [41]. KD also upregulates the nuclear factor-κB pathway, inhibiting the expression of endothelial nitric oxide synthase and platelet-endothelial cell adhesion molecules in SHRs' mesenteric arteries, while promoting the expression of interleukin-1β and tumor necrosis factor-α. This impairs endothelial function and exacerbates mesenteric artery hypertension [42]. The effects of KD in secondary hypertension have not been explored, and studies on its preventative role in both primary and secondary hypertension are lacking.

4.5. Endogenous ketogenic diet reduces myocardial inflammation

Using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) myocardial uptake to detect myocardial inflammation in rats showed that a 7-day KD reduced ^{18}F-FDG uptake, indicating a significant therapeutic effect on the myocardium compared to 2 and 4 days. This suggests that entering a ketotic state requires continuous KD intervention for a period of time [43]. Current evidence indicates the beneficial role of KD in myocardial inflammation, but further research is needed. It can be actively applied to patients and animal models with myocardial inflammation for validation and mechanistic exploration.

4.6. Endogenous ketogenic diet exerts antioxidant effects to prevent and treat hypertrophic cardiomyopathy

A 4-week KD increased BDH1 by 2.8 times in mice after transverse aortic constriction (TAC), and the contribution of β-OHB to energy supply through the tricarboxylic acid cycle increased by 25%, providing sufficient energy to prevent the occurrence of pressure-overload cardiac hypertrophy [44]. KD treats pathological cardiomyocyte hypertrophy and left ventricular systolic dysfunction in TAC mice by inhibiting the mTOR pathway, enhancing BDH1 and SCOT, and suppressing phenylephrine [45]. To confirm the role of BDH1 in HCM, BDH1-overexpressing mice were used, showing that increased BDH1 effectively reduces TAC-induced cardiac oxidative stress injury [46]. Specific knockout of the *BDH1* gene in cardiomyocytes resulted in decreased left ventricular ejection fraction and increased left and right ventricular end-diastolic volumes after TAC, leading to pathological heart deterioration. However, feeding a KD to BDH1 knockout mice one week before and four weeks after TAC significantly improved heart function and reduced mortality [47]. The preventive and therapeutic effects of KD in HCM mice mainly rely on upregulating the expression of ketone metabolism-related enzymes, increasing myocardial β-OHB concentration, and enhancing the contribution of β-OHB to energy supply. However, research discussing the effects of KD in HCM patients is still lacking.

4.7. Endogenous ketogenic diet prevents and treats heart failure by reducing oxidative stress

During the progression of HF, the body's reliance on ketone bodies for energy increases due to decreased glycolysis and fatty acid oxidation. Lipid supplementation is beneficial for mitochondrial repair in HF hearts [48]. Mice with specific knockout of the skeletal muscle ketone

body breakdown rate-limiting enzyme gene underwent TAC and developed HF after five weeks. Elevated fasting circulating β-OHB concentrations were detected, which inhibited cardiac NLRP3 inflammasome activation, reduced cardiac inflammation, and slowed the progression of HF. This suggests that chronic accumulation of β-OHB is an effective way to control HF progression [49]. KD regulates the expression of glucose and fatty acid metabolism-related enzymes in HF, increases myocardial β-OHB concentration, and prevents HF progression. A 4-week KD increased BDH1 protein expression by 1.9 times in TAC/MI-induced HF mice, demonstrating improved myocardial ketone utilization in HF mice through increased ketone delivery and uptake, and upregulation of antioxidant gene control [44]. KD is also used in the treatment of HF mice. An 8-week intermittent KD preserves ketogenesis in the liver, increases the levels of cardiac antioxidant enzymes SOD2, CAT, and glutathione peroxidase 1, reduces oxidative stress, and improves cardiac systolic and diastolic function [50].

5. Safety and potential risks of β-OHB

Currently, the application of β-OHB supplementation in CVD remains controversial. Its effects depend not only on the glucose and lipid metabolism status of the underlying disease itself but also on the formula, dosage, intake method, intervention timing, and duration of the supplementation.

The updating of β-OHB intake concentration and the ratio of KD nutrients is a hot topic in the field of β-OHB supplementation research. High concentrations of β-OHB treatment on human vascular endothelial cells led to reduced cell viability and induced oxidative stress at 48 hours, while low concentrations of β-OHB treatment significantly reduced cell viability at 72 hours [51]. In protecting heart function in CVD patients, preferential oxidation of short-chain fatty acids for energy promotes the preservation of ejection fraction in HF patients [52]. Excessive intake of β-OHB can cause fat intolerance, hyperketonemia, and metabolic acidosis in humans. It can also lead to side effects in the digestive, urinary, and respiratory systems due to fatty acid oxidation-induced hepatitis. Certain patients with chronic underlying diseases are contraindicated for KD intervention [53].

The intake method also affects the available amount of β-OHB to the heart. Using a ketone ester tracer for intravenous injection in humans, it was observed that the heart has the strongest uptake, while oral administration shows more ketone ester retention in the gastrointestinal tract and reduced availability to the heart [54]. There is no significant difference in the effect between oral ketone ester drinks and nasal feeding, both can increase blood β-OHB levels [1].

Early intervention is essential when using KD for treatment. The NLRP3 inflammasome is activated within the first hour to one day of cardiac pressure overload, and starting KD after two days of heart injury cannot inhibit inflammation [55]. With prolonged intervention time, the effect of β-OHB on the heart shifts from protective to detrimental. Both 16 weeks of intraperitoneal injection of β-OHB and KD maintain high levels of β-OHB in rats, promoting histone acetylation and transcriptional activation of the silent information regulator 7 promoter, which in turn inhibits the transcription of mitochondrial and ribosomal-encoded genes, exacerbating cardiac apoptosis and fibrosis, leading to impaired heart function [56].

In terms of improving effectiveness, combining exogenous and endogenous supplementation, as well as combining KD with exercise, yields better results. A 6-week intervention of KD combined with ketone salts in overweight and obese adults induced higher nutritional ketosis in the first two weeks compared to KD intervention alone, with lower urinary nitrogen excretion and reduced nitrogen loss [57]. KD combined with exercise therapy can lower blood glucose in diabetic mice, improve insulin sensitivity, and effectively alleviate lipid metabolism disorders caused by KD [58].

6. Conclusion

In summary, exogenous β-OHB supplementation has a better effect, providing the heart with sufficient alternative energy substances quickly and directly, preventing and treating heart injury. It activates the FoxO3a/MT2A and Notch1/Hes1 pathways, inhibits the NOX2/GSK-3β pathway to reduce apoptosis, oxidative stress, and inflammatory response, increases ketone metabolism-related enzymes, maintains heart energy supply, and alleviates discomfort caused by CVD. Endogenous

KD supplementation requires further oxidation in the body to generate β-OHB for energy supply, which is greatly influenced by the glucose and lipid metabolism status of the underlying disease itself and plays a role in preventing CVD. In diabetic patients, it can exert an anti-apoptotic effect by activating the PI3K/AKT pathway, protecting the heart and preventing progression to DCM. However, in the treatment of DCM, it activates the IL-33/ST2l pathway, exacerbating cardiac fibrosis. The action pathways of exogenous and endogenous β-OHB supplementation are shown in **Figure 1**.

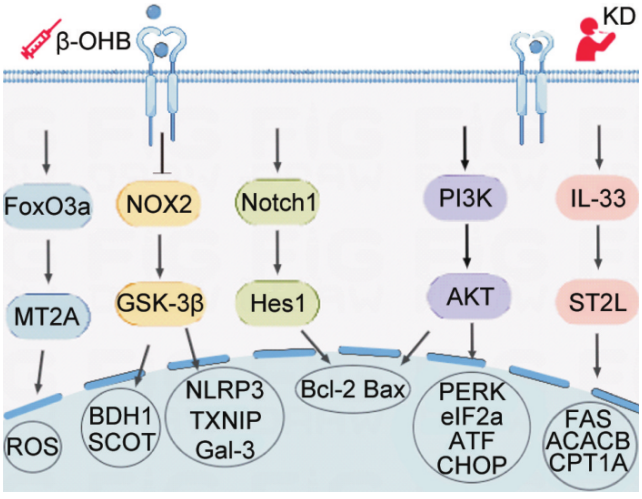

Figure 1. The mechanisms of exogenous and endogenous β-hydroxybutyrate (β-OHB) in the prevention and treatment of cardiovascular diseases. KD: ketogenic diet; FoxO3a: forkhead box O3a; MT2A: metallothionein 2A; ROS: reactive oxygen species; NOX2: NADPH oxidase 2; GSK-3β: glycogen synthase kinase-3β; BDH1: D-β-OHB dehydrogenase 1; SCOT: succinyl-CoA transferase; NLRP3: NOD-like receptor protein 3; TXNIP: thioredoxin-interacting protein; Gal-3: galectin-3; Hes1: hairy and enhancer of split 1; Bcl-2: B-cell lymphoma-2; Bax: Bcl-2-associated X protein; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; PERK: protein kinase R-like endoplasmic reticulum kinase; eIF2α: eukaryotic initiation factor 2α; ATF4: activating transcription factor 4; CHOP: enhancer-binding protein homologous protein; IL-33: interleukin-33; ST2L: suppression of tumorigenicity 2 ligand; FAS: fatty acid synthetase; ACACB: acetyl-CoA carboxylase beta; CPT1A: carnitine palmitoyltransferase 1A.

Currently, there is insufficient direct evidence for the use of exogenous β-OHB supplementation in the treatment of myocardial ischemia and prevention of HCM, and endogenous KD supplementation has not been explored for the treatment of myocardial ischemia, prevention of hypertension, and myocardial inflammation. An overview of the therapeutic effects of CVD is provided in **Table 1**.

Table 1. Comparison of the preventive (P) and therapeutic (T) effects of exogenous and endogenous β-hydroxybutyrate supplementation on cardiovascular diseases

Types of cardiovascular diseases	Exogenous		Endogenous	
	P	T	P	T
Myocardial ischemia reperfusion	○	−	×	−
Myocardial infarction	○	○	×	×
Diabetic cardiomyopathy	○	○	○	×
Hypertension	○	○	−	×
Myocardial inflammation	○	○	−	○
Hypertrophic cardiomyopathy	−	○	○	○
Heart failure	○	○	○	○

○: protective effect, ×: harmful effect, −: no direct evidence to support its use.

Although this review highlights a number of studies mentioning oxidative stress markers involved in the development and progression of CVD, there are no definitive biochemical markers that can indicate whether, which, and how to supplement β-OHB. More research is needed to fill this current gap.

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Disclosure statement

The authors declare no conflict of interest.

References

[1] Stubbs BJ, Cox PJ, Evans RD, et al., 2017, On the Metabolism of Exogenous Ketones in Humans. Front Physiol, 8: 848.

[2] Ma LY, Wang ZW, Fan J, et al., 2022, Interpretation of China Cardiovascular Health and Disease Report 2021. Chin Gen Pract, 25(27): 3331–3346.

[3] Wang XF, Lu YL, Sun XC, et al., 2023, Cardiovascular Death Trend and Prediction Analysis of the Elderly in China from 2009 to 2019. Mod Prev Med, 50(1): 39–45.

[4] Abdul KA, Clarke K, Evans RD, 2020, Cardiac Ketone Body Metabolism. Biochim Biophys Acta Mol Basis Dis, 1866(6): 165739.

[5] Falkenhain K, Daraei A, Forbes SC, et al., 2022, Effects of Exogenous Ketone Supplementation on Blood Glucose: A Systematic Review and Meta-Analysis. Adv Nutr, 13(5): 1697–1714.

[6] Gormsen LC, Svart M, Thomsen HH, et al., 2017, 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, 6(3): e005066.

[7] Ho KL, Karwi QG, Wagg C, et al., 2021, Ketones Can Become the Major Fuel Source for the Heart But Do Not Increase Cardiac Efficiency. Cardiovasc Res, 117(4): 1178–1187.

[8] Leone A, De AR, Lessa C, et al., 2019, Food and Food Products on the Italian Market for Ketogenic Dietary Treatment of Neurological Diseases. Nutrients, 11(5): 1104.

[9] Williams KA, 2019, Nutrition, Risk Factors, Prevention, and Imaging: The 2018 Mario Verani Lecture. J Nucl Cardiol, 26(1): 86–91.

[10] Yu Y, Wang F, Wang J, et al., 2020, Ketogenic Diet Attenuates Aging-Associated Myocardial Remodeling and Dysfunction in Mice. Exp Gerontol, 140: 111058.

[11] Lindsay RT, Dieckmann S, Krzyzanska D, et al., 2021, β-Hydroxybutyrate Accumulates in the Rat Heart During Low-Flow Ischaemia with Implications for Functional Recovery. Elife, 10: e71270.

[12] Dong AQ, Zhang XL, Lin SP, et al., 2022, β-Hydroxybutyric Acid Inhibits Cell Death and Reduces Myocardial Ischemia-Reperfusion Injury. Chin Heart J, 34(01): 12–17.

[13] Yu Y, Yu Y, Zhang Y, et al., 2018, Treatment with D-β-Hydroxybutyrate Protects Heart from Ischemia/Reperfusion Injury in Mice. Eur J Pharmacol, 829: 121–128.

[14] Liu W, Jiang Z, Yao YT, et al., 2022, Effect of Plasma β-Hydroxybutyric Acid on Cardiac Death in Patients with ST-Segment Elevation Myocardial Infarction. J Guizhou Med Univ, 47(12): 1448–1452.

[15] Zou Z, Sasaguri S, Rajesh KG, et al., 2002, Dl-3-Hydroxybutyrate Administration Prevents Myocardial Damage After Coronary Occlusion in Rat Hearts. Am J Physiol Heart Circ Physiol, 283(5): H1968–H1974.

[16] Liu TT, Dong HY, Ma YL, et al., 2022, D-β-Hydroxybutyric Acid Improves Acute Myocardial Infarction in Rats by Activating Notch1/Hes1 Pathway and Inhibiting Endoplasmic Reticulum Stress. Med J West Chin, 34(12): 1736–1742.

[17] Dai B, Li H, Fan J, et al., 2018, MiR-21 Protected Against Diabetic Cardiomyopathy Induced Diastolic Dysfunction by Targeting Gelsolin. Cardiovasc Diabetol, 17(1): 123.

[18] Thai PN, Miller CV, King MT, et al., 2021, Ketone Ester D-β-Hydroxybutyrate-(R)-1,3 Butanediol Prevents Decline in Cardiac Function in Type 2 Diabetic Mice. J Am Heart Assoc, 10(19): e020729.

[19] Qi H, Gu L, Xu D, et al., 2021, β-Hydroxybutyrate Inhibits Cardiac Microvascular Collagen 4 Accumulation by Attenuating

Oxidative Stress in Streptozotocin-Induced Diabetic Rats and High Glucose Treated Cells. Eur J Pharmacol, 899: 174012.

[20] Oka SI, Tang F, Chin A, et al., 2021, β-Hydroxybutyrate, a Ketone Body, Potentiates the Antioxidant Defense via Thioredoxin 1 Upregulation in Cardiomyocytes. Antioxidants (Basel), 10(7): 1153.

[21] Zhao J, Peng HL, Han JL, et al., 2023, Relationship between Serum β-Hydroxybutyric Acid Concentration and Left Ventricular Hypertrophy in Patients with Diabetic Kidney Disease. J Clin Nephrol, 23(01): 24–30.

[22] Walsh JJ, Neudorf H, Little JP, et al., 2021, 14-Day Ketone Supplementation Lowers Glucose and Improves Vascular Function in Obesity: A Randomized Crossover Trial. J Clin Endocrinol Metab, 106(4): e1738–e1754.

[23] McCarthy CG, Waigi EW, Yeoh BS, et al., 2022, Low-Dose 1,3-Butanediol Reverses Age-Associated Vascular Dysfunction Independent of Ketone Body β-Hydroxybutyrate. Am J Physiol Heart Circ Physiol, 322(3): H466–H473.

[24] Qian LW, Deng Y, Li T, et al., 2021, Study on the Mechanism of Keto-β-Hydroxybutyric Acid in Alleviating Oxidative Stress in Mitochondria of Vascular Endothelial Cells in Inflammatory State. J Sichuan Univ (Med Sci), 52(6): 954–959.

[25] Ji L, He Q, Liu Y, et al., 2022, Ketone Body B-Hydroxybutyrate Prevents Myocardial Oxidative Stress in Septic Cardiomyopathy. Oxid Med Cell Longev, 2022: 2513837.

[26] Liu Y, Wei X, Wu M, et al., 2020, Cardioprotective Roles of β-Hydroxybutyrate Against Doxorubicin Induced Cardiotoxicity. Front Pharmacol, 11: 603596.

[27] Takahara S, Soni S, Phaterpekar K, et al., 2021, Chronic Exogenous Ketone Supplementation Blunts the Decline of Cardiac Function in the Failing Heart. ESC Heart Fail, 8(6): 5606–5612.

[28] Nagao M, Toh R, Irino Y, et al., 2016, β-Hydroxybutyrate Elevation as a Compensatory Response Against Oxidative Stress in Cardiomyocytes. Biochem Biophys Res Commun, 475(4): 322–328.

[29] Murashige D, Jang C, Neinast M, et al., 2020, Comprehensive Quantification of Fuel Use by the Failing and Nonfailing Human Heart. Science, 370(6514): 364–368.

[30] Monzo L, Sedlacek K, Hromanikova K, et al., 2021, Myocardial Ketone Body Utilization in Patients with Heart Failure: The Impact of Oral Ketone Ester. Metabolism, 115: 154452.

[31] White H, Heffernan AJ, Worrall S, et al., 2021, A Systematic Review of Intravenous β-Hydroxybutyrate Use in Humans - A Promising Future Therapy? Front Med (Lausanne), 8: 740374.

[32] Nielsen R, Møller N, Gormsen LC, et al., 2019, Cardiovascular Effects of Treatment with the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. Circulation, 139(18): 2129–2141.

[33] Thai PN, Seidlmayer LK, Miller C, et al., 2019, Mitochondrial Quality Control in Aging and Heart Failure: Influence of Ketone Bodies and Mitofusin-Stabilizing Peptides. Front Physiol, 10: 382.

[34] Yurista SR, Matsuura TR, Silljé HHW, et al., 2021, Ketone Ester Treatment Improves Cardiac Function and Reduces Pathologic Remodeling in Preclinical Models of Heart Failure. Circ Heart Fail, 14(1): e007684.

[35] Liao S, Tang Y, Yue X, et al., 2021, β-Hydroxybutyrate Mitigated Heart Failure with Preserved Ejection Fraction by Increasing Treg Cells via Nox2/GSK-3β. J Inflamm Res, 14: 4697–4706.

[36] Liu J, Lloyd SG, 2013, High-Fat, Low-Carbohydrate Diet Alters Myocardial Oxidative Stress and Impairs Recovery of Cardiac Function After Ischemia and Reperfusion in Obese Rats. Nutr Res, 33(4): 311–321.

[37] Taha A, Ahmed S, Ahmed MR, et al., 2022, Type 2 Myocardial Infarction Related to Very Low Carbohydrate Ketogenic Diet. J Investig Med High Impact Case Rep, 10: 23247096221074879.

[38] Guo Y, Zhang C, Shang FF, et al., 2020, Ketogenic Diet Ameliorates Cardiac Dysfunction via Balancing Mitochondrial Dynamics and Inhibiting Apoptosis in Type 2 Diabetic Mice. Aging Dis, 11(2): 229–240.

[39] Brahma MK, Ha CM, Pepin ME, et al., 2020, Increased Glucose Availability Attenuates Myocardial Ketone Body Utilization. J Am Heart Assoc, 9(15): e013039.

[40] Tao J, Chen H, Wang YJ, et al., 2021, Ketogenic Diet Suppressed T-Regulatory Cells and Promoted Cardiac Fibrosis via

Reducing Mitochondria-Associated Membranes and Inhibiting Mitochondrial Function. Oxid Med Cell Longev, 2021: 5512322.

[41] You Y, Guo Y, Jia P, et al., 2020, Ketogenic Diet Aggravates Cardiac Remodeling in Adult Spontaneously Hypertensive Rats. Nutr Metab (Lond), 17: 91.

[42] Guo Y, Wang X, Jia P, et al., 2020, Ketogenic Diet Aggravates Hypertension via NF-κB-Mediated Endothelial Dysfunction in Spontaneously Hypertensive Rats. Life Sci, 258: 118124.

[43] Clément A, Boutley H, Poussier S, et al., 2020, A 1-Week Extension of a Ketogenic Diet Provides a Further Decrease in Myocardial (18)F-FDG Uptake and a High Detectability of Myocarditis with FDG-PET. J Nucl Cardiol, 27(2): 612-618.

[44] Aubert G, Martin OJ, Horton JL, et al., 2016, The Failing Heart Relies on Ketone Bodies as a Fuel. Circulation, 133(8): 698–705.

[45] Nakamura M, Odanovic N, Nakada Y, et al., 2021, Dietary Carbohydrates Restriction Inhibits the Development of Cardiac Hypertrophy and Heart Failure. Cardiovasc Res, 117(11): 2365–2376.

[46] Uchihashi M, Hoshino A, Okawa Y, et al., 2017, Cardiac-Specific Bdh1 Overexpression Ameliorates Oxidative Stress and Cardiac Remodeling in Pressure Overload-Induced Heart Failure. Circ Heart Fail, 10(12): e004417.

[47] Horton JL, Davidson MT, Kurishima C, et al., 2019, The Failing Heart Utilizes 3-Hydroxybutyrate as a Metabolic Stress Defense. JCI Insight, 4(4): 124079.

[48] Murano C, Binda A, Palestini P, et al., 2021, Effect of the Ketogenic Diet in Excitable Tissues. Am J Physiol Cell Physiol, 320(4): C547–C553.

[49] Byrne NJ, Soni S, Takahara S, et al., 2020, Chronically Elevating Circulating Ketones can Reduce Cardiac Inflammation and Blunt the Development of Heart Failure. Circ Heart Fail, 13(6): e006573.

[50] Guo Y, Liu X, Li T, et al., 2022, Alternate-Day Ketogenic Diet Feeding Protects Against Heart Failure through Preservation of Ketogenesis in the Liver. Oxid Med Cell Longev, 2022: 4253651.

[51] Meroni E, Papini N, Criscuoli F, et al., 2018, Metabolic Responses in Endothelial Cells Following Exposure to Ketone Bodies. Nutrients, 10(2): 250.

[52] Challa AA, Lewandowski ED, 2022, Short-Chain Carbon Sources: Exploiting Pleiotropic Effects for Heart Failure Therapy. JACC Basic Transl Sci, 7(7): 730–742.

[53] Liu SH, Nan WW, Li XL, et al., 2021, Clinical Application and Research Progress of Ketogenic Diet. Progress in Physiological Sciences, 52(6): 445–450.

[54] Luong TV, Nielsen EN, Falborg L, et al., 2023, Intravenous and Oral Whole Body Ketone Dosimetry, Biodistribution, Metabolite Correction, and Kinetics Studied by (R)-[1-11C]β-Hydroxybutyrate ([11C]OHB) PET in Healthy Humans. EJNMMI Radiopharm Chem, 8(1): 12.

[55] Willeford A, Suetomi T, Nickle A, et al., 2018, CaMKIIδ-Mediated Inflammatory Gene Expression and Inflammasome Activation in Cardiomyocytes Initiate Inflammation and Induce Fibrosis. JCI Insight, 3(12): e97054.

[56] Xu S, Tao H, Cao W, et al., 2021, Ketogenic Diets Inhibit Mitochondrial Biogenesis and Induce Cardiac Fibrosis. Signal Transduct Target Ther, 6(1): 54.

[57] Buga A, Kackley ML, Crabtree CD, et al., 2021, The Effects of a 6-Week Controlled, Hypocaloric Ketogenic Diet, with and without Exogenous Ketone Salts, on Body Composition Responses. Front Nutr, 8: 618520.

[58] Zhang Q, Xu L, Xia J, et al., 2018, Treatment of Diabetic Mice with a Combination of Ketogenic Diet and Aerobic Exercise via Modulations of PPARs Gene Programs. PPAR Res, 2018: 4827643.