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REVIEW

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Ketogenic diets and β-hydroxybutyrate in the prevention and treatment of diabetic kidney disease: current progress and future perspectives

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Abstract

Diabetic kidney disease (DKD) is the main cause of end-stage renal disease. Ketogenic diets (KD) is a high-fat, low-carbohydrate diet. KD produces ketone bodies to supplement energy in the case of insufficient glucose in the body. β-Hydroxybutyrate (BHB) is the main component of ketone bodies. BHB serves as "ancillary fuel" substituting (but also inducing) anti-oxidative, anti-inflammatory, and cardio-protective features by binding to several target proteins, including histone acylation modification, or G protein-coupled receptors (GPCRs). KD have been used to treat epilepsy, obesity, type-2 diabetes mellitus, polycystic ovary syndrome, cancers, and other diseases. According to recent research, KD and the induced BHB delay DKD progression by improving the metabolism of glucose and lipids, regulating autophagy, as well as alleviating inflammation, oxidative stress and fibrosis. However, due to some side-effects, the role and mechanism of action of KD and BHB in the prevention and treatment of DKD are controversial. This review focuses on recent progress in the research of KD and BHB in clinical and preclinical studies of DKD, and provides new perspectives for DKD treatment.

Keywords Ketogenic diets (KD), β-hydroxybutyrate (BHB), Diabetic kidney disease (DKD)

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Introduction

A comprehensive global epidemiological report for 2021 revealed that approximately 529 million individuals were diagnosed with diabetes [1]. Uncontrolled diabetes could lead to oxidative stress, inflammation signaling activation, and the release of pro-inflammatory cytokines. These events cause several complications including macro- and microvascular complications [2]. As a main microvascular complication, diabetic kidney disease (DKD) is a serious life-threatening condition that is characterized by persistent albuminuria and progressive decline in renal function or lead to end stage renal disease [3]. The clinical management of DKD includes the use of renin angiotensin aldosterone system inhibitors, glucagon-like peptide-1 receptor agonists, sodium glucose co-transporter protein 2 inhibitors (SGLT2i), and mineralocorticoid receptor antagonists. However, these interventions do not effectively prevent the progression of DKD and are associated with side effects, such as hyperkalemia, hypoglycemia, and urinary tract infections. Consequently, the exploration of novel mechanisms and strategies to prevent and treat DKD is of paramount importance.

Ketogenic diets (KD) are a topic of considerable interest, which characterized by their high fat and low carbohydrate content. These diets are designed to limit carbohydrate intake, thereby forcing the body to utilize fat for energy production, which simultaneously leads to the generation of ketone bodies. The primary ketone bodies include acetoacetate, β-hydroxybutyrate (BHB), and acetone, with BHB being produced predominantly [4]. Extensive research has demonstrated that, despite certain side effects, KD or KD induced BHB can alleviate inflammation, fibrosis, and oxidative stress associated with diabetes mellitus (DM), obesity, and kidney disease [5–7]. Recent studies have highlighted the potential of KD, as well as some ketogenic methods, in both the prevention and treatment of DKD [8–10]. Therefore, KD may represent a novel dietary therapeutic approach for managing DKD.

This review aims to summarize the latest research advancements in the application of KD to DKD and to explore the underlying preventive and therapeutic mechanisms of KD in the context of DKD. Additionally, we will examine the controversies surrounding the treatment of DKD based on KD.This is a literature review. We searched for publications in the PubMed, Web of Science, and Embase databases.The search was performed using the Medical Subject Headings (MeSH) terms for "ketogenic diets (KD)", "β-hydroxybutyrate (BHB)", and "ketone body" in conjunction with the MeSH terms for "diabetic kidney disease(DKD)", "diabetes" and "kidney". In the initial screening, references unrelated to the topic content were excluded. In the second screening, duplicate references were removed. This review is limited to studies published in English from the establishment of the database up to September 2024. Studies were included in this literature review if they met the following criteria: (a) This is an English-language publication. (b) The use of KD or BHB in the treatment of DKD. (c) The use of KD or BHB in the treatment of kidney diseases.

History of KD

In 1911, Guelp and Marie first reported that fasting reduced the severity of seizures in 20 patients with epilepsy. However, the descriptions of the participants and the methodology in this study were not sufficiently detailed [11]. This seminal finding was soon followed by the recognition that an increase in BHB levels, a byproduct of fasting, was pivotal in alleviating epilepsy symptoms. In 1921, Woodyatt discovered that a diet low in carbohydrates and high in fat could lead to an increase in BHB levels, thereby laying the groundwork for subsequent research [12]. Wilder built upon these findings and proposed the implementation of a low-carbohydrate, high-fat diet for patients with epilepsy, which has been shown to alleviate their symptoms. Wilder was the first to designate this unique dietary approach as KD [13].

KD have gradually evolved into four primary variants: ①long-chain triglyceride (LCT) diet; ②medium-chain triglyceride (MCT) diet; ③modified Atkins diet (MAD); and ④low glycemic-index therapy (LGID). The LCT diet, being the most traditional form, remains the most widely utilized, with lipid-to-non-lipid ratios typically set at 4:1 or 3:1 [14, 15]. The MCT diet generates a higher level of ketone bodies during hepatic fat metabolism compared to the LCT diet [16]. Generally, the MCT diet is administered with a caloric intake that accounts for 30–60% of MCT calories; however, it may lead to increased gastrointestinal side effects [17]. The MAD, which has a lipid-to-non-lipid ratio ranging from 1:1 to 1.5:1 (and occasionally up to 4:1), offers a more flexible dietary approach. LGID requires that the carbohydrate-to-fat ratio be adjusted to maintain a blood glucose index of less than 50 [18]. Recent investigations have suggested that the therapeutic scope of KD extends beyond its established efficacy in epilepsy, with emerging evidence indicating its potential utility in the management of DKD and DM [19], Alzheimer's disease [20], intestinal flora [21], polycystic ovary syndrome [22], cancer [23], Parkinson's disease [24], brain injury [25], and various other diseases.

Side effects of KD

Side effects to KD are significant factors influencing treatment adherence. More than 40 adverse effects have been associated with KD, with the most notable

being gastrointestinal discomfort, hyperlipidemia, kidney stones, and osteoporosis (as illustrated in Fig. 1) [26]. Gastrointestinal discomfort is the most frequently reported side effect, primarily presenting as constipation, nausea, and vomiting [27]. This may be related to the high fat content inherent in the KD. Effective measures for alleviating these symptoms include the administration of enemas, increased dietary fiber intake, and the use of medications to manage nausea and vomiting [28, 29]. KD may induce transient hyperlipidemia; in a single-center prospective study, 389 children with epilepsy treated with KD experienced hyperlipidemia at a rate of 50.8%. Following adjustments to the high-fat content of KD and administering atorvastatin (10 mg/kg) for three months, the lipid profiles of all children returned to normal [29]. However, it remains uncertain whether KD can lead to long-term hyperlipidemia [30].

The side effects in the urinary system is the formation of kidney stones. One study reported that 3 out of 150 children treated with KD developed uric acid stones [31]. Follow-up assessments of children undergoing KD treatment for up to six years revealed that 7 children developed kidney stones [30]. Potassium citrate has been shown to reduce the incidence of kidney stones in patients following KD by up to sevenfold through the alkalinization of urine and the dissolution of free calcium, thereby countering acidosis and bone demineralization [32]. A controversial side effect of KD or BHB is osteoporosis. Simm et al. reported that bone mineral content and density in patients with refractory epilepsy treated with KD decreased by an average of 0.16 standard deviations per year [33]. Conversely, some studies have suggested that the KD does not adversely affect bone composition or mineral content [34, 35]. The acidic environment induced by the KD is implicated in the development of osteoporosis, and the use of alkalinizing agents may provide better prevention against this condition [36]. Meanwhile, patients receiving KD treatment can supplement with vitamin D and calcium to prevent osteoporosis. Additionally, there are reports indicating that BHB may improve osteoporosis in ovariectomized rats [37]. BHB inhibits the abnormal activation of osteoclasts caused by microgravity, thereby improving osteoporosis [38]. However, there is currently a lack of clinical research on the potential of BHB to improve osteoporosis. Further research is needed to determine whether BHB can improve osteoporosis in humans.

Overall, the therapeutic benefits of the KD and BHB outweigh the associated risks. The KD has been utilized as a therapeutic approach for a considerably longer period than BHB, whether BHB presents additional side effects requires further investigation. The most significant risk associated with the direct supplementation of KD and BHB is ketoacidosis [39]. Thus, it is essential to

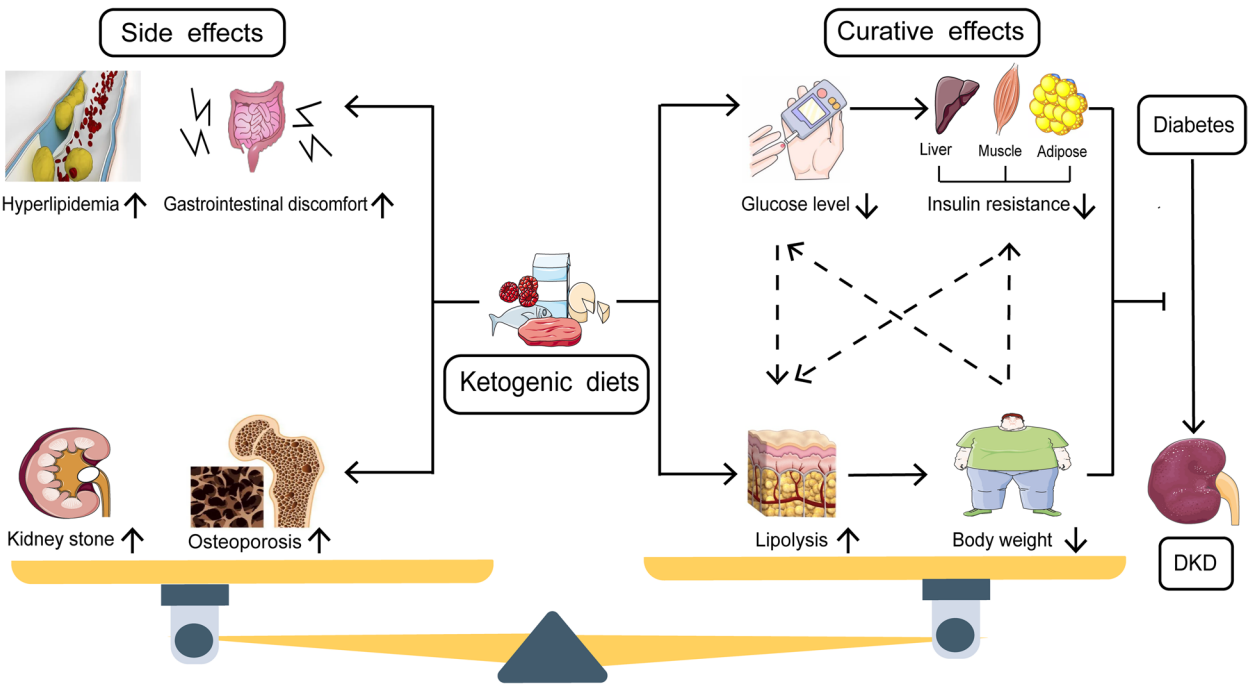

Fig. 1 Ketogenic diets (KD) in the treatment of diabetic kidney disease (DKD): a double-edged sword. KD improve glycolipid metabolism, bodyweight loss, and alleviate insulin resistance. However, they may lead to side-effects such as hyperlipidemia, gastrointestinal discomfort, osteoporosis, or kidney stones. Dotted lines mean that the process needs to be verified. Solid lines denote that the process has been proven

monitor the duration and stage of treatment, as well as to assess biochemical indicators, such as ketone concentrations in blood or urine. Currently, there is not enough data to determine which method, KD or BHB, is superior in terms of safety and effectiveness.

Metabolism processing of ketone body

Fatty acids undergo β-oxidation in the mitochondria to form acetyl-CoA (Ac-CoA), which is further metabolized by other enzymes to produce BHB in liver [40, 41]. BHB is exported from the liver via the transporter SLC16A6. In the kidneys, urinary BHB is reabsorbed in the proximal tubules through sodium-coupled monocarboxylate transporters 1 (SMCT1) and 2 (SMCT2). Ketonuria, characterized by the presence of ketone bodies in urine, occurs when the BHB concentration in the glomerular filtrate exceeds the reabsorptive capacity of the proximal tubules [42]. Upon entering the bloodstream, BHB is taken up by renal cells through monocarboxylic acid transporters 1 (MCT1) and 2 (MCT2), where it is subsequently converted into acetoacetate (AcAc) by β-hydroxybutyrate dehydrogenase 1 (BDH1). AcAc is then transformed into acetoacetyl-CoA by succinyl-CoA transferase (SCOT). This acetoacetyl-CoA undergoes cleavage to yield Ac-CoA, which is integrated into the tricarboxylic acid (TCA) cycle to facilitate energy production [43–45]. SCOT is a key enzyme in the metabolism of ketone bodies; however, hepatocytes lack SCOT expression, which prevents the liver from utilizing BHB as an energy source [46, 47].

During prolonged fasting, blood concentrations of BHB reaches levels of 6–8 mmol/L [48]. Concentrations of BHB ranging from 0.5 to 3 mmol/L may confer beneficial effects on tissue metabolism, a state commonly referred to as nutritional ketosis. However, when the concentration of ketone bodies in the blood exceeds 5 to 10 times that observed during nutritional ketosis, ketoacidosis may occur [49]. Therefore, when employing KD for the treatment of kidney disease, it is essential to monitor the concentration of ketones in blood or urine to prevent the onset of ketoacidosis.

Function and mechanism of BHB

BHB is the primary component of ketone bodies, accounting for approximately 70% of the ketone bodies present in circulation. Within the cytoplasm, BHB is converted into BHB-CoA, which can then enter the nucleus to facilitate histone β-hydroxybutyrylation. This process modulates histone acylation and, consequently, influences gene expression [50]. BHB also functions as a ligand for G protein-coupled receptors (GPCRs), specifically activating GPR109A and GPR41, which contribute to its anti-inflammatory, anti-tumor, and energy-expenditure regulatory effects [51–55]. Additionally, BHB inhibits the NOD-like receptor protein inflammasome (NLRP3) by preventing K(+) efflux, which reduces ASC oligomerization and inhibits speck formation [56, 57]. Furthermore, BHB suppresses endoplasmic reticulum stress and attenuates insulin/insulin-like growth factor (IGF-1) signaling, thereby enhancing stress resistance [58, 59].

Recent research has illustrated that BHB activates nuclear factor erythroid 2-related factor 2 (Nrf2), thereby mitigating oxidative stress and apoptosis [60]. Furthermore, BHB has been implicated in various signaling pathways, including Janus kinase/signal transducer and activator of transcription [61], insulin/phosphoinositide 3-kinase [62, 63], and unfolded protein response (UPR), suggesting its potential role in disease amelioration [64]. Collectively, these findings highlight the multifaceted role of BHB in metabolic regulation and signal transduction, underscoring its importance in maintaining homeostasis and potentially in the treatment of various diseases.

Potential role and mechanism of KD or KD-induced BHB in protecting the kidney

KD prevents and treats DKD by enhancing glucose and lipid metabolism, alleviating insulin resistance, and promoting weight loss (as illustrated in Fig. 1) [65–67]. Mechanistically, KD or KD-induced BHB exerts anti-inflammatory, anti-fibrotic, anti-oxidative stress, and autophagy effects on renal tissues and cells (as illustrated in Fig. 2) [9, 10]. In this review, we elaborate on the potential mechanisms by which KD protects the kidneys from various pathological processes.

Control glucose

Effective management of blood glucose levels and enhancement of glucose metabolism are crucial for delaying the progression and improving the prognosis of DKD [68]. The low carbohydrate content of KD reduces insulin secretion while enhancing insulin sensitivity [18]. Additionally, the high fat content of KD promotes fat oxidation, leading to a reduction in body fat and an improvement in insulin resistance [69].

Numerous studies have corroborated the conclusions stated above [70]. Following the administration of KD to Akita mice with type 1 diabetes (T1D), Fujita and collaborators observed improvements in chronic hyperglycemia [65]. Similarly, in db/db mice with type 2 diabetes (T2D), fasting blood glucose levels decreased significantly after the KD intervention [66]. In a non-randomized interventional study, healthy participants exhibited a reduction in fasting serum insulin levels following a 3-day KD regimen. Utilizing the homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative indices of insulin sensitivity, the participants demonstrated an

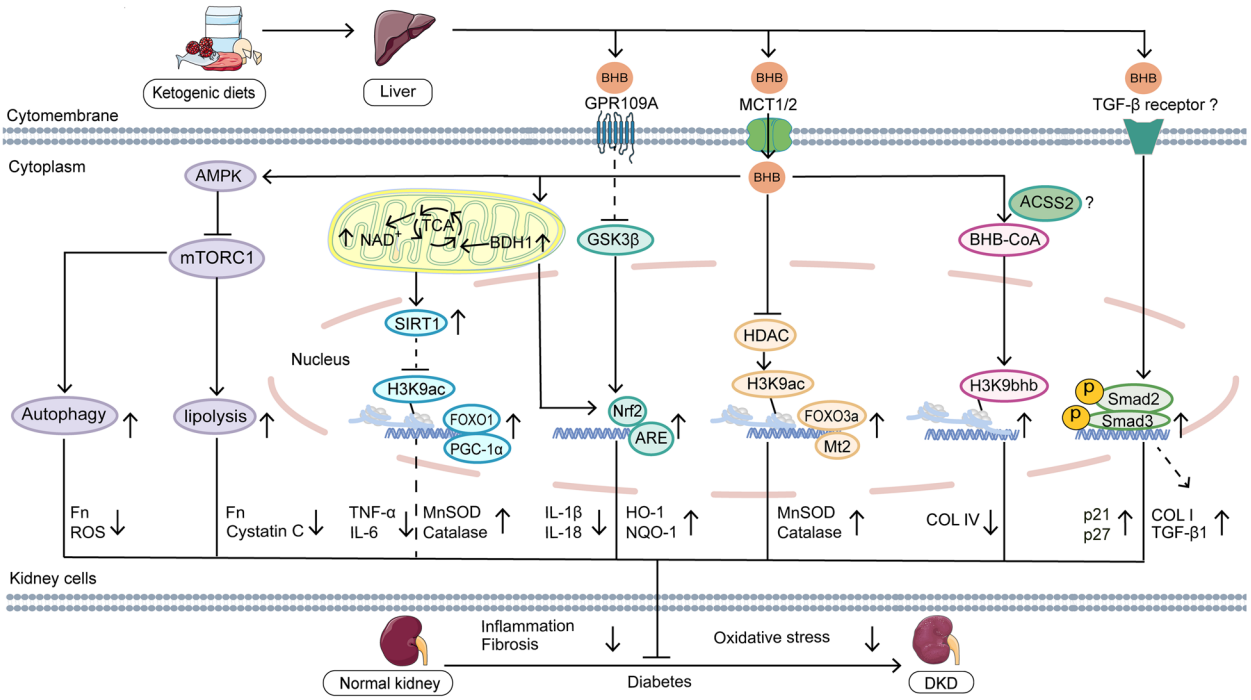

Fig. 2 Overview of the potential mechanism of ketogenic diets or BHB in protecting the kidneys and alleviating DKD. Ketogenic diets induce the synthesis of ketone bodies (mainly BHB) as an alternative energy source in the liver. BHB activates AMPK and inhibits mTORC1, which promotes autophagy and lipolysis, and alleviates ROS and fibrosis in DKD. BHB also enhances BDH1 expression in mitochondria, or inhibits GSK3β in the cytoplasm, which promotes nuclear translocation of Nrf2 and transcription/activation of antioxidant genes such as HO-1 and NQO-1. BHB enters cells through MCT1 and MCT2, and then inhibits HDAC directly. It increases expression of H3K9ac and the transcription of FOXO3a and Mt2, and antioxidant-stress enzymes such as MnSOD and catalase. BHB can be catalyzed to produce the BHB coenzyme A (BHB-CoA) by acyl-CoA synthetase 2 (ACSS2), which promotes H3K9bhb and transcriptional activation of MMP-2, and reduces the expression of COL IV. BHB may bind to the TGF-β receptor, promoting the phosphorylation of Smad2 and Smad3, which enhance the expression of p21 and p27. However, BHB may also promote the generation of collagen fibers and TGF-β1 through the same pathway.BHB enhances the production of NAD^+ in mitochondria, activates SIRT1, which may lead to increased H3K9ac, thereby promoting the transcription of FOXO1 and PGC-1α. It also decreases the expression of TNF-α and IL-6, while increasing the levels of antioxidant enzymes such as MnSOD and catalase

enhancement in insulin sensitivity [71]. Further investigation confirmed that in patients with T2D, the adoption of a KD resulted in a notable reduction in glycosylated hemoglobin (HbA1c) levels and fasting blood glucose compared to their pre-intervention values. Additionally, HOMA-IR decreased substantially from an initial value of 6.9 to 3.5, indicating a marked improvement in insulin sensitivity [72]. Several studies have shown that, compared to low-fat diets, low-energy diets, medium carbohydrate diets, and Mediterranean diets, a KD offers significant advantages in reducing HbA1c levels and can more effectively decrease the need for hypoglycemic medications among patients [67, 73–76].

However, Ellenbroek and colleagues have indicated that long-term KD interventions do not lead to a reduction in blood glucose levels. Their analysis of the pancreatic islet tissue from each mouse revealed a 50% reduction in alpha-cell mass [77]. The reasons why the study conducted by Ellenbroek and colleagues yielded results that contradict those of other researchers may be attributed to two factors: ①the prolonged duration of KD use; and ② the use of mice that did not exhibit DM. The impact of KD treatment duration warrants further investigation in future research. According to the majority of studies, the ketogenic diet lowers blood sugar levels, increases insulin sensitivity, and reduces insulin resistance.

Loss in body weight

Obesity is recognized as an independent risk factor for DKD [78]. Weight reduction has been shown to decrease the incidence of DKD and to mitigate its progression. KD, characterized by its low carbohydrate content, has been demonstrated to suppress appetite, induce satiety, and increase energy expenditure, thereby facilitating weight loss [79].

A study by Moriconi and colleagues examining KD in obese patients with T2D revealed significant reductions in both HbA1c levels and body weight [67]. A randomized trial conducted by Tay and colleagues compared the effects of a KD with those of a high-carbohydrate,

low-fat diet in obese adults with T2D over a 52-week period. While both diets facilitated weight loss, the KD demonstrated a more pronounced hypoglycemic effect [80]. Furthermore, the KD was shown to outperform both a low-calorie diet and a medium-carbohydrate diet in terms of weight loss [72, 81, 82]. In a 16-week study, individuals with obesity and T2D who adhered to a KD regimen experienced an average weight loss of 6.6% and a 16% reduction in HbA1c levels [83].When utilized for the management of T2D, the KD has been associated with weight loss among study participants with minimal side effects [74, 75]. However, animal studies have produced mixed results concerning the impact of KD on body weight. Some reports indicate that KD can effectively reduce the body weight of db/db mice, a model for T2D [9], while similar outcomes were not observed in other obese mouse models [84].

The variations in body weight observed among different rodent models (rats and mice) of DM are not uniform [77, 85]. These discrepancies may be attributed to species-specific factors, the duration of the intervention, and the differential responses of various tissues. Consequently, further animal studies are warranted to elucidate these findings.

Ameliorate the disorder of lipid metabolism

KD stimulates hepatic lipid oxidation, suppresses lipogenesis and lipoprotein assembly, and enhances the clearance of circulating triglycerides (TG) and HDL. This process contributes to maintaining a balance in lipid homeostasis and energy regulation [86, 87]. KD inhibit the activation of synthesize 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) while activating HMG-CoA lyase (HMGCL), thereby promoting the production of ketone bodies and concurrently reducing the synthesis of endogenous total cholesterol (TC) [88, 89]. The observed reduction in LDL levels may be associated with weight loss and decreased insulin levels linked to KD. However, the increased levels of TC and saturated fatty acids in KD components could potentially elevate LDL levels. Some studies have reported unchanged LDL levels, highlighting the uncertainty surrounding the impact of KD on LDL levels [79]. A study utilizing the Akita rat model of KD intervention demonstrated that reductions in TC and TG levels were associated with decreased expression of genes involved in fatty acid synthesis (FASN) and oxidation (acd11) [65]. A meta-analysis examining the effects of KD in patients with DM and obesity indicated that KD consumption significantly improves lipid profiles and enhances glucose metabolism [74]. According to two multicenter controlled trials involving obese patients, the increases in HDL levels and decreases in TG levels were more pronounced in the KD group compared to those adhering to conventional and low-fat diets [90, 91].The impact of KD on lipid metabolism was found to be superior to that of a low-fat diet. However, some reports have suggested that KD may not improve lipid metabolism and could potentially exacerbate dyslipidemia, leading to a pro-inflammatory state [77]. In a short-term study, KD was observed to cause an increase in fasting levels of free fatty acids and total TC in serum [71]. Consequently, some researchers have proposed that increasing the plant-based content of KD may mitigate dyslipidemia and provide enhanced kidney protection [92]. In summary, KD intervention can lower TC and TG concentrations in the blood of patients with DKD, thereby improving lipid metabolism and ultimately enhancing prognosis.

Relieve oxidative stress

Oxidative stress is a primary contributor to DKD development. The underlying mechanism involves reactive oxygen species (ROS) generated by polyol pathways, advanced glycation end products, and reduced nicotinamide adenine dinucleotide phosphate oxidase, which damaged glomeruli and renal tubules directly, leading to proteinuria and fibrosis [93, 94].

Research indicates that administering KD to db/db and Akita mice can reverse the histological changes associated with DKD. This effect may be due to the upregulation of antioxidant stress genes, including superoxide dismutase 1 (SOD1) and dual oxidase 1 [8]. Dual oxidase 1, also known as DUOX1 or ThOX1, is a member of the NOX family of enzymes and plays a role in regulating immune suppression, otoconia formation, and thyroid function [95]. In a study utilizing a high glucose-induced DKD cell model, KD intervention resulted in an increased expression of Nrf2 in proximal renal tubular cells, which in turn diminished ROS production and provided renal protection [9]. Furthermore, in the context of acute kidney injury induced by paraquat, BHB was shown to protect against kidney damage by reducing lipid peroxidation (malonaldehyde) and enhancing intracellular antioxidant defenses, including SOD, catalase, and glutathione [96]. Recent investigations have demonstrated that KD enhances the expression of BDH1 in the kidneys of both humans and mice, which in turn increases the metabolic flux of BHB, AcAc, succinate, and fumarate, while inhibiting the nuclear translocation of Nrf2. This process contributes to the alleviation of renal oxidative stress [97]. In human embryonic kidney 293 (HEK293) cells, BHB has been shown to induce the acetylation of histone H3 at lysine 9 (H3K9ac) and lysine 14 (H3K14ac)

in a dose-dependent manner, resulting in an upregulation of mRNA expression for forkhead transcription factor 3a (FOXO3a) and metallothionein 2 (Mt2) to 1.8 and 1.5 times their baseline levels, respectively. Chromatin immunoprecipitation analysis targeting the promoters of FOXO3a and Mt2, utilizing two distinct primer pairs for each promoter, revealed an increase in the acetylation of histone H3K9 [98]. KD can alleviate oxidative stress in the kidneys by modulating metabolic pathways and epigenetic mechanisms, thereby potentially providing therapeutic benefits for DKD.

Inhibit inflammation and fibrosis

The persistent inflammatory and fibrotic state within renal tissue serves as a crucial pathological and physiological foundation for the development of DKD. Reducing the inflammatory profile associated with DKD and slowing the progression of renal fibrosis are essential for enhancing patient prognosis.

Short-term KD interventions have demonstrated an increase in fibroblast growth factor 21 (FGF21) levels and a reduction in interleukin (IL)−1β secretion by macrophages [99]. Wan and colleagues identified that the overexpression of BDH1, a rate-limiting enzyme in the metabolism of ketone bodies, mitigated inflammation and fibrosis in DKD. The KD enhances the production of BHB, which upregulates BDH1 expression, propelling TCA and decreasing the nuclear translocation of Nrf2. This process increases Nrf2 activity and reduces the release of IL-18 and IL-1β [97]. Treatment with BHB has been shown to alleviate glomerulosclerosis in Sprague–Dawley rats with DM. Further studies demonstrated that BHB induced β-hydroxybutyrylation of histone H3 at lysine 9 (H3K9bhb) and upregulated matrix metalloproteinase-2 (MMP-2) expression [10]. The authors hypothesized that the significant increase in H3K9bhb expression at the MMP-2 promoter region could enhance both the protein and mRNA expression of MMP-2, leading to a reduction in the synthesis of collagen fibrin IV (COL IV). However, they found that the levels of transforming growth factor-beta (TGF-β)/Smad3 remained unaffected [10]. Additionally, the precursor metabolite of BHB, 1,3-butanediol (1,3-BD), was found to inhibit the mammalian target of rapamycin (mTOR), enhance lipolysis in tubular epithelial cells, and increase adenosine triphosphate levels, thereby alleviating podocyte damage [100].

However, some researchers have observed an increase enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS) activity in the kidneys of patients with DM and in a rat proximal tubule cell line (RPTC). They also found that BHB stimulates the production of transforming growth factor-beta 1 (TGF-β1) and collagen fibrin I (COL I), while promoting epithelial-to-mesenchymal transition, which in turn exacerbates renal fibrosis [101]. In HK-2 cells, an increase in BHB levels activated the TGF-β signaling pathway, leading to enhanced protein expression of P21 and P27. Additionally, this increase in BHB levels also stimulated collagen production mediated by TGF-β and Smad3, potentially linked to the dosage of BHB. Consequently, the concentration range of BHB may be a crucial factor influencing the alterations in renal fibrosis [102].

Regulate autophagy

Autophagy is a cellular mechanism that enables the degradation and recycling of aged and damaged proteins and organelles, thereby maintaining cellular homeostasis. An enhanced autophagic function, characterized by the timely clearance of damaged cellular components and the retardation of cellular senescence, is advantageous for the prognosis of DKD [103].

In db/db mice, the administration of BHB was shown to increase the levels of autophagy markers, including LC3 (Map1lc3a), p62 (Sqstm1), and beclin (Atg6), as well as enhance autophagic flux in the kidneys [9]. Molecular modeling and docking studies conducted by Fang and colleagues indicated that BHB regulates, at least in part, the Nrf2 antioxidant response through glycogen synthase kinase 3β (GSK3β). This regulatory action leads to a reduction in the activity of aging-related β-galactosidase and the expression of p16INK4A and p21, which are key mediators of the aging signal in podocytes following DM injury [104]. Clinical research supports the notion that ketogenic diet (KD) intervention can elevate FGF21 levels and enhance autophagic function [71]. Collectively, these findings suggest that KD may prevent the progression of renal injury in DM and improve prognosis by promoting autophagy. However, studies specifically addressing the relationship between KD and DKD are limited. Therefore, further investigations are necessary to elucidate the precise mechanisms by which KD enhances autophagy in DKD.

Activate Sirtuin 1

Sirtuin 1 (SIRT1) is an nicotinamide adenine dinucleotide (NAD+) dependent class III histone deacetylase (HDAC) that belongs to the sirtuin family of proteins. Acting as a critical epigenetic regulator, SIRT1 plays an indispensable role in cellular survival, regulation of gene expression, DNA damage repair, stress responses, metabolic homeostasis, and the aging process [105, 106]. Activation of SIRT1 improves insulin sensitivity and regulates blood glucose level: SIRT1 can directly deacetylate and activate peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), thereby promoting mitochondrial biogenesis and enhancing cellular energy efficiency, which in turn strengthens tissue responsiveness to insulin [107]. SIRT1 also indirectly modulates key molecules

in the insulin signaling pathway, such as insulin receptor substrate 2 (IRS2) by influencing members of the forkhead transcription factors (FOXO) family, ultimately alleviating insulin resistance [108–110].

KD-induced activation of SIRT1 may confer metabolic benefits. The Tozzi group identified that KD enhances SIRT1 expression in the serum and white adipose tissue of mice, thereby regulating blood glucose and triglyceride levels (TG) [111]. Furthermore, BHB influences adipocytes by upregulating uncoupling protein 1 (UCP1) and PR domain containing 16 (PRDM16) via the AMP-activated protein kinase(AMPK)/SIRT1/PGC-1α pathway, resulting in reductions in body weight and lipid levels [112]. Some researchers have suggested that KD may inhibit histone acetylation to delay the aging process through SIRT1 activation [113]. In mice subjected to KD, there is an increase in hepatic autophagy, accompanied by the deacetylation of FOXO3 and elevated SIRT1 levels [114]. Studies involving aged rats indicate that BHB mimics caloric restriction (CR), promoting co-activation and selective interaction between FOXO1 and PGC-1α, which, in turn, suppresses inflammation [115]. SIRT1 has been identified as a therapeutic target for DKD in various studies [116]. The use of SIRT1 inhibitors, such as EX527, exacerbates the progression of DKD [117]. BHB, as an activator of SIRT1, may counteract the effects of SIRT1 inhibitors, potentially leading to improvements in DKD. However, there is a lack of sufficient experimental evidence to demonstrate that either KD or BHB directly regulate SIRT1 for the treatment and prevention of DKD.

Application of KD or BHB in the prevention and treatment of DKD

Few studies have investigated the application of KD in preclinical experiments and clinical trials for the management of DKD (Table 1). This paper offers a comprehensive overview of the research surrounding KD and BHB in the context of DKD.

Clinical trials

KD have been established as effective and safe dietary approaches for reducing blood glucose levels and promoting weight loss [118]. Friedman et al. administered inhibitors of the renal–aldosterone axis to patients with advanced DKD, complemented by KD intervention. Serum levels of creatinine and cystatin C in these patients with advanced DKD decreased by 12%, while proteinuria was reduced by 36% [119]. Notably, 27.7% of patients with chronic kidney disease experienced improved renal function following KD administration, achieving an estimated glomerular filtration rate (eGFR) of $\geq$ 90 mL/min/1.73m^2 [120]. KD treatment in patients with DKD resulted in more significant reductions in waist circumference, lean body mass, eGFR, as well as levels of insulin, HbA1c, fasting blood glucose, LDL-C, and IL-6 compared to those following a low-protein, low-salt diet, with modest increases in HDL-C and LDL-C levels [121]. After infusing BHB, both normal individuals and diabetic patients experienced an increase in renal blood flow and eGFR, but tubular proteinuria was observed [122, 123]. A clinical trial established that the DKD risk was minimized if the BHB level in blood was maintained at 0.09–0.27 mmol/L [124]. A cross-sectional clinical study supports this conclusion, reporting a J-shaped relationship between circulating ketone concentrations and the risk of DKD. In other words, both higher and lower blood ketone concentrations are associated with an increased risk of DKD, whereas moderate ketone levels (e.g., 0.12–0.30 mM) are linked to a reduced risk of DKD in patients with T2D [125]. In conclusion, KD intervention appears to improve renal function in patients with DKD, and may slow disease progression.

Zoccali and colleagues are conducting a multicenter, randomized controlled trial aimed at evaluating the comparative efficacy of KD versus a low-energy standard diet on body weight reduction and metabolic changes in adults with mild-to-moderate non-diabetic chronic kidney disease across varying levels of obesity. This study seeks to elucidate the potential benefits and risks of KD on renal health [126]. Substantial clinical evidence supports the role of KD in reducing the risk of DKD by improving lipid and glucose metabolism. However, further research is necessary to determine whether KD can reverse renal dysfunction in patients with DKD.

Preclinical experiments

KD has been shown to reduce blood glucose levels in mice with T1D and T2D, while simultaneously promoting weight gain. Notably, KD appears to facilitate a more rapid reversal of renal function and molecular alterations compared to morphological changes [8]. Jung and colleagues demonstrated that KD mitigated proteinuria and lowered blood urea nitrogen levels in an animal model of DKD, thereby enhancing renal function [9]. The beneficial effects of KD on renal oxidative stress and inflammation have been linked to its activation of the Nrf2 pathway in db/db mice [97]. Furthermore, 1,3-BD was found to activate AMPK, inhibit mechanistic target of mTORC1, and promote autophagy and lipolysis in kidney cells, thereby improving fibrosis [100].

In terms of histone modification, BHB can increase MMP-2 expression through H3K9bhb, consequently reducing COL IV production in rats with DM [10]. Direct administration of BHB is associated with

Table 1 Application of KD or BHB in the prevention and treatment of DKD

Study type	Patient characteristic/Model species	Intervention and dose	Results	Ref
Clinical Trials	Patients with obesity and DKD	KD (less than 50 g of carbohydrate daily) p.o	↓body weight, ↓FBG, ↓insulin resistance, ↓fasting insulin, ↓albuminuria, ↓serum creatinine, ↓cystatinC	[119]
	Patients with obesity and CKD	KD (between 20 and 50 g of carbohydrate daily) p.o	↓body weight, ↓fat mass ↑eGFR	[120]
	Patients with T2D and DKD	KD (less than 20 g of carbohydrate daily) p.o	↓FBG,↓HbA1c, ↑LDL,↑HDL, ↓IL-6 ↓total daily insulin	[121]
	Normal man and patients with T1D	Acetoacetic acids(25 or 15 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) i.v	↑eGFR,↑RPF, ↑tubular proteinuria	[122]
	Normal man and patients with T1D	D,L-3-hydroxybutyric acids(30 and 40 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) i.v	↑eGFR,↑RPF, ↑tubular proteinuria	[123]
In vivo	Akita mice and db/db mice	KD(5%carbohydrate, 8%protein, 87% fat) p.o	↓blood glucose, ↓ACR	[8]
	db/db mice	KD(10%carbohydrate,10% protein, and 80% fat) p.o	↓body weight, ↓BUN to creatinine ratio, ↓urine albumin to creatinine ratio, ↑LC3I/II, ↓ROS	[9]
	db/db mice	KD (74.2% fat,8.9% protein, and 3.2%carbohydrates) p.o	↓kidney to body weight ratio, ↓blood glucose, ↓ACR, ↓ROS, ↓IL-1β,↓IL-18, ↑BDH1, ↑Nrf2	[97]
	STZ-induced Male Sprague Dawley rats	BHB (160, 200, and 240 mg/kg/day) i.h	↓serum creatinine, ↓24 h urine protein, ↑MMP-2, ↓COL IV, ↑H3K9bhb	[10]
	STZ-induced mices	BHB(100 mg/kg/day) i.h	↓albuminuria, ↓GSK3β, ↑Nrf2	[104]
	db/db mice	1,3-BD (normal diets contain a 20% 1,3-BD solution) p.o	↓Fibronection, ↓urinary albumin, ↓mTORC1	[100]
In vitro	HK-2 cells	BHB (10 mM)	↓ROS, ↑LC3I/II, ↑Atg6, ↑Nrf2, ↑phosphorylation of AMPK, ↑p62 degradation	[9]
	HK-2 cells	BHB (5 mM)	↓IL-1β, ↓IL-18, ↓ROS, ↑BDH1, ↑Nrf2	[97]
	HK-2 cells	BHB (0.1 to 10 mM)	↑TGF-β1, ↑Smad2/3, ↑p21WAF1/p27kip1	[102]
	HEK293 cells	BHB (not described)	↑H3K9ac, ↑H3K14ac, ↑FOXO3a, ↑Mt2	[98]

Table 1 (continued)

Study type	Patient characteristic/Model species	Intervention and dose	Results	Ref
	podocytes	BHB (not described)	↓GSK3β, ↑Nrf2, ↑HO-1,↑NQO-1 ↓$p16^{INK4A}$,↓p21, ↓γH2AX	[104]
	RPTC cells	BHB(1 mM)	↑COLI, ↑TGF-β1, ↓E-cadherin	[101]

Abbreviations: ↑ upregulation, ↓ downregulation, ⟷ no effect, *KD* ketogenic diets, *FBG* fasting blood glucose, *DKD* diabetic kidney disease, *TC* total cholesterol, *TG* triglycerides, *HbA1c* Hemoglobin A1c, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *T2D* type2 diabetes, *T1D* type1 diabetes, *LDL* low-density lipoproteins, *HDL* high-density lipoprotein, *IL-6* interleukin-6, *IL-1β* interleukin-1β, *IL-18* interleukin-18, *ROS* reactive oxygen specie, *RPF* renal plasma flow, *ACR* ablumin to creatinine ration, *BUN* blood urea nitrogen, *Atg6* beclin, *P62* Sqstm1, *LC3I/II* Map1lc3al to Map1lc3all ration, *BDH1* β-hydroxybutyrate dehydrogenase 1, *Nrf2* nuclear factor erythroid 2-related factor 2, *MMP-2* matrix metalloproteinase-2, *COL IV* collagen fibrin IV, *H3K9bhb* β-hydroxybutyrated histone H3 lysine 9, *$p16^{INK4A}$* $p16^{INK4A}$ is one of the four members that make up the p16 gene, *γH2AX* H2AX histone protein is rapidly phosphorylated at the serine-139 position, *mTORC1* mechanistic target of rapamycin complex 1, *1,3-BD* 1,3-butanediol, *HK-2 cells* human renal tubular epithelial cells, *HEK293 cells* human embryonic kidney cell 293, *H3K9ac* acetylated histone H3 lysine9, *H3K14ac* acetylated histone H3 lysine14, *FOXO3a* forkhead transcription factor 3a, *Mt2* metallothionein 2, *GSK3β* glycogen synthase kinase 3β, *HO-1* heme oxygenase-1, *NQO-1* dependent reductase, *RPTC cells* COL I, collagen fibrin I, *TGF-β1* transforming growth factor-1, *AMPK* AMP-activated protein kinase

decreased proteinuria, reduced renal hypertrophy, and improved histological features in mice with streptozotocin-induced DM [104]. BHB was found to modulate levels of ROS, IL-1β, and IL-18 in HK-2 cells by regulating BDH1 expression. An increase in BDH1 expression in mitochondria promotes the TCA cycle and facilitates the nuclear translocation of Nrf2 [97]. In HEK293 cells, BHB has been shown to directly inhibit histone deacetylase (HDAC), promote H3K9ac, enhance the transcription of FOXO3a and Mt2, and increase the production of antioxidant stress enzymes such as manganese superoxide dismutase (MnSOD) and catalase [98]. Researchers have reported that BHB plays a role in inducing GSK3β inhibition and promoting the nuclear translocation of Nrf2, which protects podocytes from senescence [104].

The protective effect of KD and BHB it produces on DKD remains a subject of controversy. An in vitro study indicated that elevated renal levels of BHB could be detrimental, as it activates the TGF-β/Smad3 pathway, resulting in increased collagen fiber production and reduced cell proliferation [102]. Zhang and colleagues found that in db/db mice, the expression of HMGCS2 was significantly elevated in the kidneys, leading to enhanced production of ketone bodies, particularly BHB. In vitro experiments involving the application of BHB to renal proximal tubular cells (RPTC) demonstrated an increase in the protein expression of TGF-β1 and collagen. These findings suggest that BHB may exacerbate the progression of DKD [101].

Despite these recent findings, preclinical trials of KD remain limited and contentious, underscoring the need for comprehensive research to elucidate the mechanisms by which KD may be employed to prevent and treat DKD.

Conclusions and prospects

KD improves body weight, glucose and lipid metabolism, alleviates oxidative stress, regulates autophagy, inhibits inflammation and fibrosis, benefits patients with T2D, and helps prevent DKD. However, KD may also lead to side effects such as diarrhea, vitamin deficiencies, increased urinary calcium levels, and kidney stones. There is concern that the relatively high protein content in KD could accelerate the decline in renal function, precipitate cardiovascular events, and that weight loss may contribute to osteoporosis and fractures, as well as adversely affect renal function. Additionally, KD should not be used in conjunction with SGLT2 inhibitors, as this combination may lead to the development of ketoacidosis. Furthermore, the poor palatability of KD often results in low compliance among patients with DM. It remains unclear how much or how long KD can maintain an appropriate blood concentration of ketones. Therefore, ongoing and timely evaluations of adverse reactions and side effects are necessary to further explore the efficacy and safety of KD [127].

The metabolic benefits and organ-protective functions of KD are primarily mediated by BHB. As the principal component of ketone bodies, BHB directly or indirectly regulates epigenetic mechanisms, engaging in histone methylation, acetylation, and β-hydroxybutyrylation modifications, which in turn influence various pathological and physiological processes. At the same time, BHB plays a crucial role in various signaling pathways, such as the activation of GPR109A and GPR41, which contribute to its anti-inflammatory effects. However, high concentrations of BHB can easily lead to ketoacidosis. Currently,

there is a lack of clinical data directly supporting the use of BHB as a treatment. Thus, further basic science research and well-designed clinical studies are essential to determine whether BHB, or other precursor substances that promote BHB synthesis, can serve as alternatives to KD. Additionally, it is warranted to investigate the pharmacological effects and molecular mechanisms of KD or BHB in the prevention and treatment of DKD.

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Authors' contributions
L.C and W.H were responsible for the conception and design of the study. J.L,W.H and Q.W were responsible for data collection analysis, and image processing. J.L,W.H and Q.W wrote the manuscript, and C.L,Z.D,Y.Q,P.Y revised the manuscript. J.L,W.H and Q.W were responsible for the final approval of the version to be submitted. All authors conceived the manuscript structure and contributed to the writing and editing, All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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