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Dietary therapy to halt the progression of diabetes to diabetic kidney disease†

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Diabetic Kidney Disease (DKD) is a common and serious complication of diabetes, particularly Type 2 Diabetes Mellitus (T2DM), which significantly contributes to patient morbidity and mortality. The limitations of traditional treatments like ACE inhibitors and ARBs in managing DKD progression highlight the need for innovative therapeutic strategies. This review examines the impact of various dietary patterns, such as the Mediterranean diet, ketogenic diet, intermittent fasting, DASH diet, and vegetarian diet, on the management of DKD. Evidence suggests these diets can halt the progression of DKD, although further research is needed to confirm their long-term effectiveness and safety. Personalized dietary approaches tailored to individual needs may enhance outcomes for DKD patients.

1 Introduction

Over the past century, non-communicable diseases (NCDs),[1] including cardiovascular disease, cancer, and diabetes,[2] have emerged as the leading causes of mortality and morbidity worldwide. Among these, diabetes, particularly Type 2 Diabetes Mellitus (T2DM), has become an epidemic, contributing significantly to the global healthcare burden.[3] Diabetic Kidney Disease (DKD) is a common and severe complication of T2DM, characterized by progressive kidney damage that increases the risk of kidney failure and premature death. DKD is not only a major cause of end-stage renal disease (ESRD), but it also exacerbates the comorbidities associated with diabetes, such as cardiovascular diseases, creating a vicious cycle of deterioration in patient health and quality of life.[4]

Despite advancements in treatment options, conventional therapies, such as Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs), have shown limited efficacy in halting or reversing the progression of DKD. These therapies primarily aim to control blood pressure and proteinuria but do not address the root causes or mitigate the long-term impacts of DKD progression. As a result, there remains a critical gap in effective treatments that can prevent the worsening of kidney function in diabetic patients.

Emerging evidence suggests that dietary interventions may offer a promising alternative or adjunct to pharmacological treatments in managing DKD. While various dietary patterns, including the Mediterranean diet, ketogenic diet, intermittent fasting, Dietary Approaches to Stop Hypertension (DASH) diet, and vegetarian diet, have been explored for their potential benefits in managing DKD, the evidence is still inconclusive, particularly regarding their long-term efficacy, safety, and mechanisms of action. This highlights a significant research gap in understanding how different dietary patterns affect DKD progression, and whether these dietary approaches can provide sustained benefits over time. Therefore, this review aims to critically evaluate the current state of knowledge on dietary therapies for DKD, examining their potential to improve patient outcomes and slow disease progression, while identifying areas where further research is urgently needed.

2 Literature search method

To identify relevant studies, we screened publications to date that discussed dietary therapies, such as Mediterranean diet, Ketogenic Diet, and DASH diet, and their role in preventing the progression of diabetes to DKD. We conducted searches in databases including Elsevier, Wiley, Taylor, Francis Online, and Web of Science using keywords such as “diabetes”, “diabetic kidney disease”, “Mediterranean diet”, “Ketogenic Diet”, “fasting”, “Ketogenic Diet”, “DASH diet” and “vegetarian diet”. A total of 281 articles were identified, of which 133 were actually cited.

3 T2DM and diet

Diabetes mellitus (DM) is a prevalent group of NCDs, with over 500 million individuals affected globally, and more than 90%

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of these cases are T2DM.[5] It is well established that weight gain and obesity are associated with the development of T2DM. Additionally, the development of T2DM is accompanied by obesity and insulin resistance, primarily due to the phosphorylation of the insulin receptor substrate (IRS) by receptor tyrosine kinases (RTK), which further contributes to elevated glycemia. Both factors are directly related to food intake.[3]

The etiology of T2DM remains complex and not fully understood. However, evidence indicates that T2DM is characterized by pathophysiological changes, including pancreatic β-cell dysfunction, insulin resistance, and chronic inflammation, which collectively impede glycemic control.[6] Furthermore, T2DM promotes increased cellular and chemokine levels, such as TNF-α and IL-6, and activates pro-fibrotic signaling pathways, including TGF-β and NF-κB, ultimately leading to complications.[7]

Recent studies have highlighted that an unhealthy diet significantly contributes to T2DM development.[8] Diets high in calories, fat, and sugar are associated with weight gain and obesity, particularly central obesity (abdominal fat accumulation), leading to reduced insulin sensitivity and the development of insulin resistance. This impairs the entry of blood glucose into cells for energy production, resulting in elevated blood glucose levels and the onset of T2DM.[9] Additionally, a diet high in fat, particularly saturated fatty acids, has been linked to fat accumulation in visceral organs, such as the liver. This ectopic fat accumulation interferes with insulin signaling, leading to chronic inflammation, insulin resistance, and elevated blood glucose levels.[10]

In addition, diet significantly influences the composition and functionality of the gut microbiome. Disturbed gut microbes have been linked to exacerbated metabolic disorders and chronic inflammation, reducing insulin sensitivity.[11] Therefore, dietary habits play a crucial role in T2DM development. Diets high in calories, fat, and sugar increase the risk of T2DM (Fig. 1). Consequently, adopting a healthy and balanced dietary structure and appropriate nutritional management is paramount in preventing and controlling T2DM.

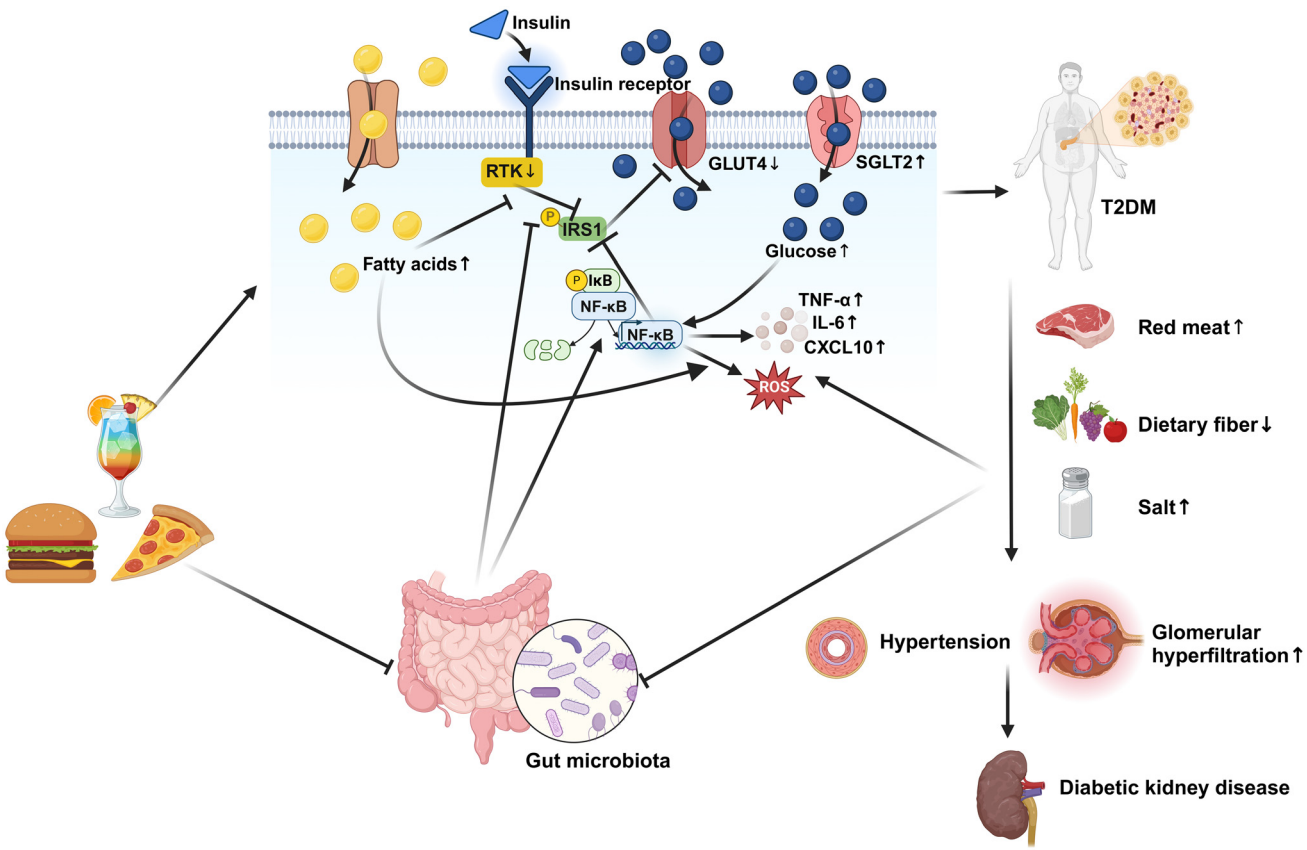

Fig. 1 The role of diet in type 2 diabetes (T2DM) and diabetic kidney disease (DKD). A high-calorie, high-fat, and high-sugar diet is linked to weight gain and central obesity, disrupting insulin signaling, triggering chronic inflammation, and causing insulin resistance. This diet also alters gut microbiota, leading to metabolic disorders and reduced insulin sensitivity, ultimately causing type 2 diabetes (T2DM). In T2DM patients, continued intake of such a diet elevates blood glucose, damages glomerular filtration membranes, and accelerates diabetic kidney disease (DKD). Western diets high in salt and fat increase hypertension risk, worsening glomerular damage and promoting DKD. Excessive red and processed meat consumption burdens kidneys, accelerating dysfunction, while moderate vegetable protein intake offers protection. Low dietary fiber disrupts gut flora, leading to metabolic disorders and inflammation, accelerating DKD. Created with BioRender.com.

4 Diabetic kidney disease (DKD)

As T2DM progresses, an unhealthy diet significantly contributes to the progression of diabetic disease and has been linked to adverse effects on multiple organs, including the heart, retina, liver, and kidneys.[12] DKD is one of the most prevalent and severe complications of diabetes, significantly increasing patient mortality.[4] The role of diet in the progression of T2DM to DKD is complex and multifactorial. A high-glucose, high-fat diet in T2DM patients leads to elevated blood glucose levels, exacerbating insulin resistance and ultimately causing a chronic hyperglycemic state. Persistent hyperglycemia damages the glomerular filtration membrane, leading to glomerular hyperfiltration and accelerating DKD onset and development.

The Western diet, characterized by high salt and fat intake, significantly increases hypertension incidence, exacerbating glomerular damage and promoting DKD development.[13] Excessive consumption of animal protein, particularly red and processed meat, may strain the kidneys and hasten renal function deterioration.[14] Conversely, moderate plant protein intake may protect the kidneys.[15,16] Inadequate dietary fiber consumption may disrupt intestinal flora equilibrium, leading to metabolic imbalances and inflammatory responses, impeding DKD progression (Fig. 1).[17]

In DKD, the kidneys undergo structural and functional alterations, impairing glomerular filtration and tubular reabsorption due to glomerulosclerosis and interstitial fibrosis. The renal damage caused by DKD is irreversible, contributing to disease progression and ultimately leading to end-stage renal disease (ESRD).[18] Current therapeutic strategies, primarily supportive, involve using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs) but have not reversed DKD progression. Thus, there is an urgent need for new therapeutic tools to address this unmet clinical need.[19]

Dietary control is a common and critical treatment strategy for DKD patients. Recent studies have shown that dietary intervention can significantly slow DKD progression.[20] The most commonly prescribed dietary patterns include the Mediterranean, ketogenic, fasting, and DASH diet.[21] These dietary patterns emphasize different food intake priorities and have demonstrated therapeutic potential in DKD management. However, it remains unclear whether food consumption within different dietary patterns affects the efficacy of nutritional supplementation, potentially accelerating disease progression in DKD patients, particularly given the chronic nature of the disease. Therefore, examining the relationship between diet and T2DM and DKD is vital, providing a comprehensive overview of different dietary therapies in DKD and significant advances in understanding the underlying mechanisms. By discussing this topic, we can enhance strategies for preventing and treating DKD and improve DKD prognosis through dietary interventions.

5 Role of dietary therapy in DKD

5.1 DKD and mediterranean diet (MED)

The traditional MED originates from the coastal areas of the Mediterranean Sea and is characterized by high consumption of vegetables, fruits, nuts, and olive oil.[22] The MED has garnered considerable research interest in recent years due to its potential to prevent various chronic diseases, including cardiovascular disease, T2DM, metabolic syndrome, certain cancers, and chronic kidney disease.[23,24] A *meta*-analysis of 2 217 404 participants showed that adherence to the MED significantly reduces the risk of developing colorectal cancer.[25] Another *meta*-analysis demonstrated that the MED reduces liver enzymes and liver fat content in patients with non-alcoholic fatty liver disease (NAFLD).[26] Additionally, recent studies have associated the MED with notable improvements in overall cognition and gastrointestinal symptoms.[27]

In diabetes treatment, the MED has yielded noteworthy outcomes. Prospective studies have shown that adherence to the MED is associated with a reduced risk of developing diabetes,[28,29] and significant reductions in glycated hemoglobin levels[30] and inflammation[31] in patients with prediabetes and T2DM. Furthermore, the MED has been shown to diminish the incidence of cardiovascular complications,[32] carotid atherosclerosis,[33] non-alcoholic fatty liver disease,[34] and mortality in patients with T2DM.[35] A recent *post-hoc* analysis from the San Carlos Gestational Prevention Study demonstrated that a nutritional regimen based on the MED before the twelfth week of gestation reduces the incidence of gestational diabetes mellitus at three years postpartum.[36] Moreover, a prospective cohort study found that the MED significantly reduces the risk of DKD in patients with hyperglycemia,[37] with a dose-dependent effect.[38] However, adding extra virgin olive oil to the MED does not prevent DKD in the cohort study.[39] Numerous studies have also substantiated that adherence to the MED is not markedly correlated with cardiovascular risk factors and renal function.[40,41]

From a mechanical perspective, the components of the MED are effective in reversing the progression of T2DM to DKD. The abundance of antioxidants, such as ascorbic acid and β-carotene in MED foods significantly reduces oxidative stress, chronic inflammation, and platelet aggregation.[42,43] Furthermore, adherence to the MED has been linked to lower levels of C-reactive protein (CRP),[44] which correlates with a reduced impact of elevated blood glucose on renal cellular function, thus lowering the risk of developing DKD from T2DM. Recent clinical studies have demonstrated that glucagon-like peptide-1 (GLP-1) can attenuate the progression of T2DM[45] and DKD[46] by promoting insulin production and secretion. Notably, the MED has been shown to promote GLP-1 secretion,[47] enhance endothelial function, and delay DKD progression in T2DM patients.[48]

Moreover, evidence indicates that the MED can correct the imbalance of gut microbial homeostasis in patients with T2DM and DKD.[49] Gut microbes utilize the fiber in the MED to synthesize short-chain fatty acids (SCFAs),[50] which regulate

glucose and lipid metabolism,[51] slowing the progression of T2DM. While the MED emphasizes whole plant foods, excessive consumption of refined carbohydrates (*e.g.*, fruit juices, processed grains) within some MED interpretations may paradoxically elevate insulin resistance risk (Fig. 2).[52] Additionally, individuals with T2DM adhering to the MED may risk protein malnutrition.[53] Therefore, further clinical trials are required to fully understand the benefits and risks of MED in T2DM and DKD.

5.2 DKD and ketogenic diet (KD)

The ketogenic diet (KD) was initially developed in the 1920s and gained popularity for treating epilepsy in children. By mimicking the fasting state (*i.e.*, reducing carbohydrates and increasing fat intake), it effectively reduces the frequency of seizures. However, its use declined with the advent and development of antiepileptic drugs. In recent years, the KD has received attention for its potential benefits beyond epilepsy, including weight loss, T2DM, metabolic syndrome, and other neurological disorders such as Alzheimer's and Parkinson's diseases.[54]

The KD is a high-fat, low-carbohydrate, and moderate-protein diet.[55] It induces a metabolic state called ketosis, characterized by reduced carbohydrate intake and increased fat intake. In this state, the body primarily relies on fats and ketone bodies (produced by the liver) for energy rather than glucose.[56] Since its introduction, the KD has demonstrated benefits such as extending life expectancy,[57] enhancing memory,[58] improving tumor prognosis,[59] facilitating liver metabolism,[60] and inhibiting the progression of polycystic kidney disease.[61]

Similarly, the KD plays an important role in treating T2DM. The KD has been shown to prevent the development of obesity and diabetes[62] and to significantly affect blood glucose levels and insulin sensitivity, reducing glycated hemoglobin levels[30] and body weight[63] in patients with T2DM. A recent 12-week randomized controlled study analyzed 60 overweight patients with newly diagnosed diabetes, comparing a conventional diabetic diet (30 subjects) with a ketogenic diet (30 subjects). The results demonstrated that the KD significantly improved glycated hemoglobin, fasting blood glucose, insulin levels, lipids, weight, and body mass index (BMI)[64] Another recent randomized controlled trial (RCT) (NCT03810378) compared the effects of a ketogenic diet and a low-carbohydrate Mediterranean diet on glycemic and cardiometabolic risk factors in patients with type 2 diabetes or pre-diabetes. The results showed that both diets positively affected glycated hemoglobin, but the KD was more effective in lowering triglycerides and body weight and increasing HDL cholesterol.[30]

Typically, the body obtains energy from glucose in carbohydrates. In contrast, the KD emphasizes strict carbohydrate restriction, significantly reducing intestinal monosaccharide absorption and thus lowering blood glucose levels.[65] Additionally, the KD regulates hepatic glycogen breakdown, affecting basal glucose metabolism and reducing blood glucose levels.[66,67] The KD also alters the gut microbiome composition, increasing the proportion of anabolic bacteria, promoting digestive processes, and facilitating weight loss.[68] Moreover, the KD influences gut microbes to produce short-chain fatty acids, which regulate blood glucose, stimulate GLP-1 secretion,[51] and alleviate insulin resistance.[69] The KD has also demonstrated anti-inflammatory,[70] anti-hepatic fibrosis,[71] antioxidant,[72] and mitochondrial function effects (Fig. 2).[73] Additionally, studies observed that patients could significantly reduce or discontinue their diabetes medications during KD treatment.[74]

This evidence collectively indicates that the KD can markedly impede the progression of T2DM to DKD. However, the role of the KD in DKD development remains debated in the scientific community. Animal studies have provided compelling evidence that the KD can effectively reverse mitochondrial energy metabolism,[75] proteinuria,[76] and oxidative stress[77] in animal models of T2DM (db/db mice). Furthermore, clinical studies have substantiated that the KD enhances glomerular filtration indexes, diabetic status, and risk factors for kidney disease progression in DKD patients.[78] Currently, there is limited direct research on the KD and DKD.

It is important to note that not all observed beneficial effects are attributable to the KD; some effects are associated with overall carbohydrate intake rather than ketosis. A high protein intake may also increase renal burden, particularly in patients with pre-existing renal impairment.[79] Although the KD emphasizes fat intake, protein intake may increase in practice.[80] The KD may initially cause electrolyte imbalances, including potassium, sodium, and magnesium, which are particularly important in patients with renal insufficiency[81] Furthermore, the KD carries the risk of triggering ketoacidosis, a life-threatening condition.[82]

Given the potential benefits and risks associated with KD in managing DKD, its implementation must be undertaken with caution and under the guidance of medical professionals and dietitians. Additional clinical studies and long-term follow-up data will clarify the efficacy and safety of KD in managing DKD.

5.3 DKD and fasting

Fasting has recently gained considerable attention as a potential strategy for managing health and disease. Fasting is the complete abstinence from food or a significant reduction in calorie intake over a specified period. The fundamental premise is to induce a shift in the body's metabolic state by temporarily reducing or halting food intake to achieve health benefits. The principal categories of fasting include intermittent fasting, exemplified by the 16 : 8 diet (eating and drinking are limited to 8 hours of the day and fasting for the remaining 16 hours), the 5 : 2 diet (5 days of a normal diet and 2 days of a low-calorie diet), alternate-day fasting, 24-hour fasting, extended fasting (fasting for more than 24 hours, usually ranging from 48 hours to several days), and time-restricted diets (eating is limited to a certain window of time each day, usually 8–12 hours).[83] Fasting is typically considered safe and has significantly prevented disease progression.[84]

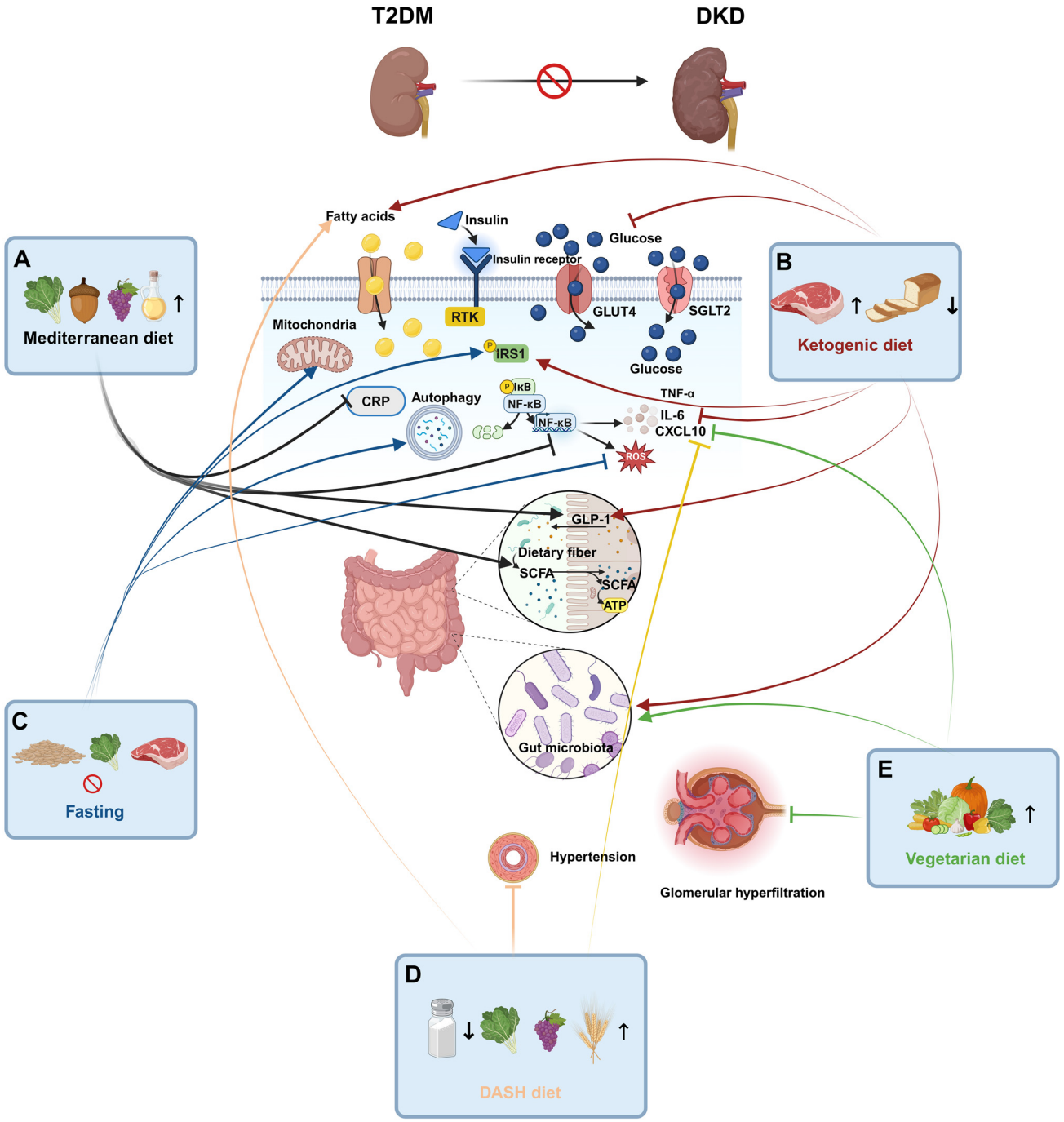

Fig. 2 Molecular mechanisms of dietary therapy and their metabolites in in diabetic kidney disease. (A) The Mediterranean diet (MED) has been demonstrated to impede the progression of Type 2 diabetes mellitus (T2DM) to diabetic kidney disease (DKD) through the reduction of inflammatory responses and oxidative stress, the stimulation of glucagon-like peptide 1 (GLP-1) secretion, and the modulation of the gut microbiota. (B) The ketogenic diet (KD) has been demonstrated to impede the progression of T2DM to DKD through the regulation of the body's metabolic state, the influence of gut microbiota homeostasis, the promotion of GLP-1 secretion, and the exertion of anti-inflammatory and antioxidant effects. (C) Fasting has been demonstrated to delay renal cell damage and loss of function. This is achieved by improving insulin sensitivity, reducing inflammation and oxidative stress, and promoting mitochondrial function and autophagy processes. (D) The DASH diet has been demonstrated to safeguard kidney function by regulating blood pressure and reducing inflammation, lipid levels and kidney burden. (E) The vegetarian diet has been demonstrated to impede the progression of T2DM to DKD through a number of mechanisms. These include antioxidant and anti-inflammatory effects, modulation of gut microbiota, reduction of proteinuria and improved nutritional status. Created with BioRender.com.

Animal studies have confirmed that 5 : 2 or 16 : 8 intermittent fasting improves non-alcoholic steatohepatitis (NASH) and its transition to hepatocellular carcinoma (HCC),[85,86] and reduces body weight.[87] Fasting has also been demonstrated to slow the aging process,[88,89] reduce blood pressure and cardiovascular risk, and lower blood pressure and cardiovascular risk.[90,91] Furthermore, fasting plays a significant role in managing T2DM. Intermittent fasting has been shown to significantly reduce body weight,[92] improve lipid and glucose metabolism,[93] and reduce inflammatory and oxidative stress levels in patients with T2DM (Fig. 2).[94] A recent RCT (ChiCTR2000040656) of Chinese adults with early-stage type 2 diabetes found that the 5 : 2 diet reduced body weight and blood glucose levels in the short term compared to metformin or empagliflozin. These findings suggest that the 5 : 2 diet may be a promising approach for the initial intervention and early management of T2DM.[95] Furthermore, a fasting protocol alleviated gut microbial disorders and prevented complications in db/db mice.[96] Animal studies demonstrate that fasting remodels mitochondrial networks, though human data remain limited.[97]

Nevertheless, the potential benefits of fasting in the context of DKD warrant further investigation. Currently, there is a lack of conclusive evidence from clinical and animal studies confirming the role of fasting in the progression of T2DM to DKD and the progression of DKD itself. However, based on the available evidence, it can be hypothesized that fasting may have a beneficial impact on the progression of T2DM to DKD by enhancing mitochondrial function in renal tubular cells,[98] promoting mitophagy,[99] and promoting ketone body production,[100] among other mechanisms to exert renoprotective effects.

Given the unique and complex nature of DKD, prolonged fasting may potentially lead to malnutrition and further increase the renal burden in patients with DKD. Therefore, it is essential to exercise caution when implementing fasting. One potential approach could be to gradually extend the duration of fasting and ensure adequate intake of essential nutrients, including vitamins, minerals, and dietary fiber, during the feeding period. Furthermore, additional clinical studies and long-term follow-up data will undoubtedly contribute to a better understanding of the effectiveness and safety of fasting in managing DKD.

5.4 DKD and DASH diet

The National Heart, Lung, and Blood Institute (NHLBI) developed the DASH diet with the original intention of helping individuals reduce high blood pressure. Additionally, it is a dietary pattern conducive to promoting overall health. The DASH diet is rich in fruits, vegetables, and low-fat dairy products and includes whole grains and legumes. It emphasizes nutrient-rich foods that have been shown to benefit blood pressure, such as potassium, calcium, and magnesium while encouraging the limitation of sodium, saturated fats, and sugar intake.[101]

The DASH diet has demonstrated considerable success in managing hypertension. A recent randomized controlled trial (RCT) (IRCT20180201038585N12) involving 60 subjects with metabolic syndrome showed that the DASH diet effectively managed hypertension.[102] Another RCT (ChiCTR2300069393) found that combining an 8-hour time-limited diet with the DASH diet resulted in a more pronounced reduction in blood pressure compared to DASH alone in stage 1 hypertension patients.[103] Mechanistically, the DASH diet controls blood pressure by increasing potassium and sodium intake. The increased dietary fiber in the DASH diet indirectly controls blood pressure by lowering cholesterol, thereby slowing the progression of hypertension and cardiovascular events.[101,104]

Furthermore, the DASH diet has been demonstrated to reduce the risk of chronic kidney disease (CKD).[105] Recent studies have shown that the DASH diet is associated with a reduced risk of developing T2DM,[106] increased insulin sensitivity,[107] and better control of blood pressure[108] and body weight[109] in T2DM patients (Fig. 2). The DASH diet's low protein intake and antioxidant-rich foods (*e.g.*, vegetables and fruits) reduce kidney burden[110] and decrease the inflammatory response.[111] Additionally, the DASH diet helps reduce LDL cholesterol and triglycerides while increasing HDL cholesterol, safeguarding the cardiovascular system and, indirectly, the kidneys.[112] Recent clinical studies also corroborate that the DASH diet mitigates the likelihood of progression to DKD in T2DM patients.[38,113]

In conclusion, the DASH diet represents a scientifically backed and effective dietary pattern particularly suited to preventing and controlling hypertension. Moreover, it effectively inhibits the progression of T2DM to DKD and promotes overall health. However, it is important to note that although the DASH diet recommends lean meat and fish, patients with kidney disease may require further protein intake reduction. Due to impaired renal function, DKD patients must also restrict foods rich in potassium and phosphorus. Despite the DASH diet's emphasis on fruits and vegetables, adjustments may be necessary due to the potassium content of these foods. Additionally, while the DASH diet is inherently low in sodium, DKD patients must rigorously monitor their sodium intake to prevent hypertension and fluid retention.

Overall, implementing the DASH diet requires a gradual transition and long-term adherence. For optimal results, it is recommended that this diet be followed under the guidance of a healthcare professional.

5.5 DKD and vegetarian diet

A vegetarian diet is based on plant-based foods, excluding all animal products, including red and white meat and fish. The classification of vegetarian diets includes strict vegetarian, egg-lacto-vegetarian, lacto-vegetarian, egg-vegetarian, and fish-vegetarian diets.[114] Prospective epidemiological studies indicate that a vegetarian diet may have a preventive effect against obesity,[115] hypertension,[116] cancer,[117] and cognitive decline.[118] A recent meta-analysis indicates that adherence to a plant-based diet for a minimum of 14 days is associated with improved insulin resistance in individuals with a BMI above the healthy range.[119] Furthermore, a vegetarian diet has been demonstrated to diminish the likelihood of developing T2DM.[120]

Recent animal studies have suggested that a vegetarian diet may impede the progression of T2DM to DKD by enhancing insulin sensitivity,[121] preventing oxidative stress, and reducing inflammation (Fig. 2).[122] Recent clinical studies have also demonstrated that vegetarian diet plant proteins significantly reduce CKD risk in diabetic patients compared to animal proteins.[123] These diets have been shown to significantly reduce albuminuria and improve nutritional status in patients with DKD.[124]

It is important to note that patients with DKD must control their protein intake while ensuring sufficient high-quality plant protein intake. Additionally, certain plant foods are high in phosphorus and potassium, and intake must be monitored according to renal function to prevent the accumulation of these minerals in the body.

In conclusion, a vegetarian diet may benefit individuals with DKD, but it must be planned and managed appropriately to ensure adequate nutritional intake and avoid potential risks.

6 Comparison of different dietary therapies in DKD

Dietary therapies represent a pivotal intervention in the management of DKD. The complex relationship between diet and the progression of DKD indicates that no single dietary approach can exert optimal therapeutic effects on its own (Fig. S1†). Instead, a multifaceted approach may be required to address the various metabolic demands and complications associated with DKD.

Each dietary strategy has distinctive benefits and mechanisms of action. The Mediterranean diet (MED) is characterized by a high content of antioxidants and anti-inflammatory components, which may contribute to reducing oxidative stress and chronic inflammation, both considered key factors in the progression of DKD. The vegetarian and DASH diets emphasize the consumption of fruits and vegetables and the reduction of sodium intake, demonstrating efficacy in managing blood pressure and overall cardiovascular health. Additionally, these diets confer indirect benefits to kidney function.

Although there is evidence that ketogenic diets (KD) and intermittent fasting regimens may provide metabolic benefits, such as improved insulin sensitivity and reduced oxidative stress essential for managing DKD, it is unclear to what extent fasting can slow the progression of DKD in T2DM patients. Furthermore, ensuring that patients with diet-restricted DKD consume adequate amounts of essential nutrients (*e.g.*, proteins, vitamins, and minerals) remains challenging. The inherent risks associated with KD and fasting, such as electrolyte imbalances, ketoacidosis from KD, and nutritional deficiencies from prolonged fasting, necessitate close monitoring and professional guidance.

Different dietary patterns exhibit varying degrees of risk. In MED, the consumption of certain foods, such as full-fat cheeses and proteins, may require individual adjustments.[125] KD, high in saturated fat, increases the risk of cardiovascular disease, and its long-term effects on renal function are unclear, necessitating caution in patients with pre-existing renal impairment.[126] The DASH diet's high potassium intake may be risky for patients with impaired renal function and requires individualized adjustment.[127] Fasting diets may result in nutritional imbalances and glycemic fluctuations, particularly in insulin-dependent patients, necessitating caution and professional guidance.[128] Vegetarian diets must ensure sufficient plant protein intake and micronutrient supplementation, such as vitamin B12, iron, and calcium, to prevent nutritional deficiencies.[129]

Implementing these dietary patterns in managing DKD must consider the individual's health status, nutritional requirements, and personal preferences (Table 1). Therefore, it is recommended that dietary plans be developed under the guidance of healthcare professionals to ensure the safety and efficacy of the dietary regimen. Several clinical trials (NCT05495451, NCT05984459, NCT05589467, and NCT06152588) aim to improve outcomes for T2DM or DKD patients by combining dietary therapy (Table S1†).

7 Current challenges and future directions

7.1 Limitations and challenges

7.1.1 Complexity of dietary interventions. One of the primary challenges is the complexity of dietary interventions and their varying impacts on individuals with DKD. While the Mediterranean diet, DASH diet, and ketogenic diet, among others, have demonstrated potential benefits, individual responses can vary considerably due to genetic susceptibility, coexisting conditions, and lifestyle choices. This variation complicates the development of universal dietary guidelines and necessitates a more individualized approach.

7.1.2 Adherence and sustainability. Long-term adherence to prescribed dietary therapies represents a significant challenge. Many patients encounter difficulties adhering to dietary changes over the long term due to cultural preferences, socioeconomic factors, or a lack of understanding of the diet's benefits. Ensuring the sustainability of these dietary interventions requires implementing strategies to enhance patient education and support.

7.1.3 Lack of comprehensive guidelines. The absence of standardized dietary guidelines specific to DKD represents a significant challenge. Current recommendations frequently vary by healthcare provider, resulting in inconsistent dietary advice. This inconsistency can cause patient concern and reduce the effectiveness of dietary interventions.

7.1.4 Integration with medication. It is imperative to enhance the integration of dietary therapies with existing pharmacological treatments for DKD. While certain dietary components may augment medication efficacy, others may impede drug metabolism or exacerbate adverse effects. A com-

Table 1 Comparison of different dietary therapies in DKD

Dietary pattern	Advantages	Disadvantages	Research conclusions
Mediterranean diet	Rich in healthy fats (olive oil), antioxidants (fruits and vegetables), and fiber (whole grains); associated with reduced inflammation, improved glycemic control, and cardiovascular health benefits.[7,31–43]	May be difficult to adhere to in the long term due to dietary restrictions and availability of specific foods; can be more expensive compared to standard diets.[60,61,133]	Shows potential in reducing the risk of DKD progression, improving glycemic control, reducing cardiovascular risk, and enhancing overall health outcomes. Widely supported by numerous studies.[31–43]
Ketogenic diet	Low carbohydrate intake forces the body to use fat as a primary energy source, which can improve glycemic control, promote weight loss, and potentially improve insulin sensitivity.[38,62–71]	May lead to nutrient deficiencies (fiber, vitamins, and minerals) and is not suitable for everyone, especially those with kidney issues due to the high protein and fat content.[88–90]	Mixed results; some studies show benefits in weight loss and glycemic control, while others highlight potential risks, especially for kidney health. Long-term safety and effects need further research.[38,62–71]
Fasting	Flexible approach with various fasting schedules; can promote weight loss, improve insulin sensitivity, and reduce oxidative stress and inflammation.[91–105]	Can be difficult to maintain; potential for overeating during feeding periods, which might negate the benefits; initial adaptation phase can be challenging.	Emerging evidence suggests benefits for metabolic health, weight loss, and reduction in inflammation and oxidative stress. Long-term effects and optimal fasting protocols require further investigation.[91–105]
DASH diet	Emphasizes fruits, vegetables, whole grains, and low-fat dairy; associated with lower blood pressure, improved heart health, reduced risk of cardiovascular diseases, and better glycemic control.[109–121]	May be difficult to adhere to due to dietary restrictions and the need for significant changes in eating habits; requires careful planning to meet nutritional needs.[121]	Associated with improved kidney function, lower blood pressure, and reduced cardiovascular risk. Adherence can be challenging, but the health benefits are well-supported by research.[109–121]
Vegetarian diet	High in fiber (fruits, vegetables, legumes) and low in saturated fats; associated with reduced risk of chronic diseases (heart disease, hypertension), improved kidney function, and potential weight management benefits.[122–132]	Requires careful planning to ensure adequate nutrient intake, especially protein, vitamin B12, iron, and omega-3 fatty acids; potential for nutrient deficiencies if not well-planned.	Generally beneficial for kidney function and overall health; reduces risk of chronic diseases and supports weight management. Nutrient deficiencies need to be managed through careful dietary planning.[122–132]

prehensive understanding of these interactions is essential to optimize treatment regimens.

7.1.5 Impact of comorbidities. A significant proportion of individuals with DKD also present with comorbidities such as cardiovascular disease or hypertension. This necessitates considering additional dietary factors. Managing DKD through diet is further complicated by the need to balance the dietary demands of multiple conditions.

7.2 Strategies to overcome challenges and improve clinical translation

7.2.1 Personalized nutrition. Advances in nutrigenomics and metabolomics offer the potential for developing personalized nutrition plans based on an individual's genetic and metabolic profile. By understanding how specific nutrients interact with a patient's unique biological makeup, healthcare providers can design more effective dietary interventions.

7.2.2 Long-term clinical trials. Large-scale, long-term clinical trials are imperative to assess the efficacy and safety of various dietary patterns in treating DKD. These studies must encompass diverse populations to account for genetic and environmental differences and aim to elucidate the mechanisms by which diet affects kidney function.

7.2.3 Role of the gut microbiota. Recent studies have demonstrated that the gut microbiota plays a pivotal role in mediating the effects of dietary interventions in DKD. The underlying mechanism involves multifaceted interactions, including the production of short-chain fatty acids (SCFAs, *e.g.*, butyric acid, propionic acid) by GM fermentation of dietary fiber. These SCFAs have been shown to reduce renal inflammation and maintain intestinal barrier integrity by inhibiting histone deacetylase (HDAC) and activating G-protein-coupled receptors (*e.g.*, GPR43/41), which can reduce the intestinal-derived accumulation of uremic toxins (*e.g.*, indophenol sulphate, paracresol) and alleviate renal tubulointerstitial fibrosis.[130] Secondly, intestinal-derived lipopolysaccharide (LPS) translocation caused by GM dysregulation can activate the Toll-like receptor 4 (TLR4) signaling pathway, promote the release of inflammatory factors (*e.g.*, IL-6, TNF-α) from glomerular mesangial cells, and accelerate the progression of DKD.[131] Clinical studies have further revealed a direct association between GM composition and renal function indices. A cohort study of 432 DM patients found that the relative abundance of butyric acid-producing bacteria in the gut (*e.g.*, Faecalibacterium prausnitzii, Roseburia spp.) was positively correlated with estimated glomerular filtration rate (eGFR) (β = 0.34, $P < 0.01$). Furthermore, the annual rate of decline in eGFR increased by 0.82 mL min^{-1} per 1.73 m^2 for each log unit decrease in its abundance.[132] Furthermore, elevated levels of the GM metabolite trimethylamine-*N*-oxide (TMAO) induced apoptosis in renal tubular epithelial cells, which was independently associated with the urinary albumin/creatinine ratio (UACR) in DKD patients (OR = 1.52, 95%CI 1.18–1.96).[133] The aforementioned mechanisms provide the foundation for dietary modification strategies. The first strategy involves the implementation of a high-fiber/resistant starch diet (≥30 g per

day) to enhance uremic toxin clearance through the enrichment of SCFAs-producing bacteria. The second strategy focuses on the incorporation of Mediterranean dietary polyphenols (*e.g.*, olive oil hydroxytyrosol) to selectively promote *Akkermansia muciniphila* and other beneficial bacteria and inhibit the overgrowth of pathogenic Proteobacteria. In addition, prebiotic/prebiotic combination interventions (*e.g.*, oligofructose + *bifidobacteria*) restored GM diversity and lowered TMAO levels. Future studies must further elucidate the profile of flora characteristics and personalized dietary targets at different DKD stages to optimize the precise GM-based nutritional treatment strategy.

7.2.4 Develop comprehensive guidelines. Researchers, clinicians, and policymakers must collaborate to develop comprehensive dietary guidelines for DKD. These guidelines must be evidence-based, culturally sensitive, and adaptable to patients' individual needs.

7.2.5 Patient education and support. Enhanced patient education and support are essential for improving adherence to dietary interventions. This may involve creating digital tools and resources, such as mobile apps or online platforms, to provide personalized dietary advice, track progress, and offer motivational support.

7.2.6 Integration with digital health technologies. Integrating diet management with digital health technologies, such as wearables and mobile health apps, can provide real-time feedback and support to patients, enhancing adherence and treatment outcomes. These technologies can also enable remote monitoring and counseling, improving the accessibility of diet management.

7.2.7 Interdisciplinary research. Encouraging interdisciplinary research and drawing insights from nutritional sciences, nephrology, genomics, and behavioral sciences can facilitate a more comprehensive approach to managing DKD. Collaborative research programs can foster innovation and accelerate the translation of research findings into clinical practice.

8 Conclusion

In summary, dietary therapies show great promise in treating DKD. However, their use must be individualized and closely monitored to maximize benefits and minimize risks. Future research should focus on large-scale, long-term clinical trials to further elucidate the efficacy and safety of these dietary approaches in different DKD patient populations. Combining dietary therapies with pharmacological treatments could pave the way for a comprehensive and effective DKD management strategy, ultimately improving patients' prognosis and quality of life.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
BMI	Body mass index
CKD	Chronic kidney disease
CRP	C-reactive protein
DASH	Dietary approaches to stop hypertension
DKD	Diabetic kidney disease
DPP-4	Dipeptidyl peptidase 4
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GLP-1	Glucagon-like peptide 1
HbA1c	Hemoglobin A1c
HDAC	Histone deacetylase
IL-6	Interleukin 6
LPS	Lipopolysaccharide
KD	Ketogenic diet
MED	Mediterranean diet
MODY	Maturity onset diabetes of the young
NAFLD	Non-alcoholic fatty liver disease
NCD	Non-communicable disease
RCT	Randomized controlled trial
RAAS	Renin–angiotensin-aldosterone system
SCFA	Short-chain fatty acid
SGLT2	Sodium-glucose co-transporter 2
SMBG	Self-monitoring of blood glucose
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor alpha
TMAO	Trimethylamine-*N*-oxide
UACR	Urinary albumin/creatinine ratio

Author contributions

Hongtu Hu and Wei Liang were involved in the conception and design. Hongtu Hu and Wei Liang drafted of the manuscript. Wei Liang and Guohua Ding revised the manuscript critically for intellectual content. Hongtu Hu, Wei Liang and Guohua Ding approved the final version to be published. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Data availability

No datasets were generated or analyzed during the current study.

Conflicts of interest

The authors declare no competing interests.

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