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Dietary Protein Intake and Kidney Disease in Type 2 Diabetes: A Narrative Review

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Abstract: ***Traditionally, low-protein diet (LPD) is considered an important treatment for chronic kidney disease (CKD), while high-protein diet (HPD) is deemed to exacerbate the progression of CKD. Target dietary protein intake (DPI) for people with diabetes and CKD stages 1-4 should be 0.8 g/kg per day by current guidelines, neither HPD nor LPD appears beneficial. However, data from the NHANES show that the current actually average consumption of protein in the United States is higher than the guidelines recommended amount. We reviewed the current evidences on the relationship between protein intake and renal disease in Type 2 diabetes mellitus (T2DM) patients with different renal function stages and found that in T2DM patients with CKD stages 1-2, HPD was not associated with the risk of renal disease progression, and LPD did not benefit for these patients. Therefore, perhaps we should not emphasize the importance of dietary protein intake intervention in patients with CKD stages 1-2. Besides, LPD may alleviate proteinuria in patients with CKD stages 3-5, despite the risk of malnutrition. This narrow review focuses on the potential consequences of HPD or LPD on kidney diseases, and it may provide a guidance for clinicians to manage protein intake when treating T2DM patients with different stages of CKD.***

Keywords: Dietary protein intake; Type 2 diabetes mellitus; Chronic kidney disease; Renal disease progression.

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1. Introduction

The burden of chronic kidney disease (CKD) in patients with diabetes mellitus (DM) is high and rising. CKD has become the major cause of end-stage kidney disease (ESRD) in people with diabetes worldwide[1, 2]. At present, the management of CKD includes diet, exercise intervention, drug therapy, prevention and treatment of complications. And the regulation of protein intake occupies an important part in diet intervention. Current guidelines recommend a target dietary protein intake (DPI) for people with diabetes and CKD stages 1-4 is 0.8 g/kg per day, and for patients on dialysis should be 1.0-1.2g /kg/d to ensure adequate energy due to high protein consumption[3, 4]. However, recommendations on DPI in guidelines are mainly based on the evidences from researches focused on non-diabetic patients with CKD and animal studies. The appropriate DPI for diabetic patients is still controversial. In this narrow review, we summarized the current evidences on the relationship between protein intake and renal disease in DM, regarding different quantification of protein intake; different sources of protein intake and different CKD stage, in order to provide a guidance for clinicians to manage protein intake when treating patients with CKD.

2. Protein Intake Quantification

At present, quantity and sources of DPI were mainly assessed by indirect ways such as measure urinary urea or nitrogen excretion[5], a food diary, self-reporting food intake via 24-h dietary recall or food frequency questionnaire(FFQ) [6, 7]. However, urinary nitrogen measurement reflects the intake over only a few days before urine collection and provide no information about sources of DPI, and questionnaire-based methods are linked to both random and systematic error. Among them, the FFQ is the most commonly used to investigate food intake over extended periods of time. Although there isn't universal agreement on what constitutes a HPD or a LPD, most definitions state that HPD refers to daily protein providing more than 20% of total energy or DPI > 1.3g/kg per day; LPD refers to DPI < 0.8g/kg per day [3]. Besides, data from the NHANES defined that HPD was > 130 g/d

and > 86g/d in males and females respectively (90th percentile protein intake for males and females in NHANES II data). LPD was defined as 42g/d for males and 28g/d for females based on NHANES II data (10th percentile protein intake for males and females)[8].

3. Quantity of DPI and CKD in patients with T2DM

3.1 HPD and CKD

Studies [9-12] suggest that HPD does not affect renal function in healthy adults, but it impairs non-diabetic adults with CKD [13, 14]. Partial studies were focused on Type 2 diabetes mellitus (T2DM) patients when studied the association of HPD with CKD. We summarized these studies, which was shown in Table 1.

A cross-sectional study[15] in 2003 found that higher protein intake [≥ 19% E% (protein energy contribution, the same below)] was not associated with microalbuminuria in diabetes patients (Odds ratio [OR] 2.17; 95% confidence interval[CI], 0.96 - 4.90; $P = 0.09$). Another 5-year follow-up study[16] retrospectively included 144 patients with T2DM (baseline eGFR: 82 ± 20 mL/min/1.73 m^2) and divided them into two groups: LPD (< 0.8 g/kg/d) and HPD (> 1.3 g/kg/d). They found no significant difference in eGFR (0.07 vs -0.41 mL/min/1.73 m^2) or UAE (0.01 vs -0.03 mg/g Cr) between the two groups during the study period. As for randomized controlled trials (RCTs), HPD showed no adverse effects on renal function either among patients with preserved renal function (mean eGFR ≥ 60 mL/min/1.73 m^2). Pomerleau et al. [17] found no significant changes in eGFR (118.2 ± 28.2 vs 118.8 ± 38.4 mL/min/1.73㎡) or urine protein excretion (98 ± 105 vs 100 ± 115 ug/min) in obese T2DM patients (BMI > 27 kg/m^2) after 3 weeks of HPD (2 g/kg/d). Luger et al. [18] enrolled 44 patients with normal renal function treated with insulin. After 12 weeks of dietary intervention with normal protein diet (NPD; 15% E%) and HPD (30% E%), they found that there was no significant difference in urinary protein excretion rate (92.3 ± 299.9 vs 104.3 ± 252.7μg/min) or eGFR (68.5 ± 18.9 vs 73.8 ± 13.9 mL/min/1.73m^2) between the two groups. It is possible that the follow-up period of the trial was insufficient to observe an impact. Therefore, another investigator[19] extended the study time to one year and investigate the effects of HPD (30% E%) and NPD (15% E%) on renal function in obese T2DM patients (BMI: 27-40kg/m^2), there was no difference between the two groups in urinary protein excretion rate (-4.65 vs -4.51 μg/min) or eGFR (1.98 vs 3.2 mL/min/1.73 m^2) either. Besides, another 2-year follow-up RCT [20] of 294 patients with normal renal function found no statistically significant difference in serum creatinine (83.1 ± 23.6 vs 78.5 ± 22.0 μmol/l) or UACR (0.72 vs 0.57 mg/mmol) between the HPD (30% E%) and NPD (15% E%) groups, but only 6% participants in the HPD groups achieved the target protein intake, which may lead to an underestimation of the differences in renal function between the two groups.

In addition, 382 T2DM patients were included in a newly published Dutch prospective study[21] (baseline mean eGFR: 78 ± 24 mL/min/1.73m^2, average protein intake: 91 ± 27g/d), researchers found that DPI was inversely associated with deteriorating renal function (Hazard ratio [HR] 0.62; 95% CI, 0.44 - 0.90) after a median 6 years of follow-up, and patients with an intake >163 g/d had a decreased hazard for renal function deterioration (HR 0.42; 95% CI, 0.18-1.00). Although generally well designed, studies above were limited by their insufficient participant adherence and inconsistent measurements of GFR and proteinuria, which may have a certain impact on the results.

Overall, the populations included above were predominantly T2DM patients with preserved renal function (mean eGFR ≥ 60 mL/min/1.73 m^2), and results shows that the progression of renal disease was not associated with HPD. However, HPD may aggravate the renal burden in patients at higher risk of renal function deterioration. A nested case-control study[22] enrolled 4255 participants (1057 in the ESRD group; 3198 in the control group) with different ethnic backgrounds from American community, they found that individuals in the highest quartile of protein intake (1.96 g/kg/d) had significantly higher odds of having ESRD than those in the lowest quartile (0.47 g/kg/d) (OR=1.76; 95%CI, 1.04 - 2.77; $P < 0.05$) among blacks with diabetes but not among whites with diabetes, suggesting that the effect of protein intake are more likely to be observed among individuals with metabolic disorders. Blacks are more susceptible to be obese and have diabetes, which known to contribute to dysregulated protein metabolism when compared to whites of similar BMI. More studies are needed to explore the association of DPI with people who had a higher risk of deterioration of renal function.

3.2 LPD and CKD

In various studies, 0.6-0.8g/kg/d is the most frequently recommended target for patients who received LPD

intervention. Studies[23, 24] have shown that LPD could slow the progression to ESRD in non-diabetic adults with CKD. Evidences related the potential benefits of a LPD on T2DM patients are inconsistent, which were summarized in Table 2.

In a prospective study of 6213 patients with T2DM (mean baseline eGFR≥ 60mL /min/1.73 m^2) [25], participants in the lowest tertile of total protein intake (0.36 g/kg/d) had an increased risk of CKD (OR:1.16; 95%CI, 1.05 - 1.30; $P < 0.05$) compared with participants in the highest tertile (0.96 g/kg/d), suggesting that excessive restriction of protein intake is associated with higher risk of CKD. A total of 131 T2DM patients were enrolled in a RCT [26] (baseline eGFR: 82 ± 19 vs 85 ± 23 ml/min/1.73 m^2), after at least 12 months of follow-up, the annual change in eGFR (-4.8 ± 12 vs -6.4 ± 14 ml/min/1.73 m^2, $P = 0.5$) or albuminuria (+1.2 vs +0.1 mg/24h, $P = 0.09$)were not statistically different between LPD (0.8g/kg/d) and NPD (1.15 ± 0.26g/kg/d) groups, but the achieved degree of protein restriction was disappointingly low. Similarly, a RCT [27] included 112 Japanese T2DM patients (baseline eGFR: 61.1 ± 23.7 vs 63.5 ± 26.9 ml/min/1.73m^2) and followed for 5 years, found no statistically difference in annual change of eGFR between NPD (1.2 g/kg/d) and LPD (0.8 g/kg/d) groups (-5.8 ± 5.7 vs -6.1 ± 6.5 ml/min/1.73m^2, $P = 0.93$). Studies above have not confirmed that a LPD favorably impacts CKD trajectory in T2DM patients with preserved renal function (eGFR ≥ 60 mL/min/1.73 m^2).

Conversely, many studies have shown a beneficial impact of LPD upon trajectory of renal function in T2DM patients with reduced renal function (eGFR < 60 mL/min/1.73m^2). A retrospective study [28] enrolled 449 diabetic kidney disease(DKD) patients (stage G4-5) found that patients in LPD group(0.67 ±0.04 g/kg IBW/d) had a lower incidence of renal replacement therapy initiation (HR: 0.4; 95%CI: 0.23, 0.70; $P = 0.001$) compared with NPD group(1.02 ± 0.09 g/kg IBW/d), but it might lead to an increased mortality in patients with malnutrition. In a prospective study[29] of 74 elderly patients (> 65 years old) with DKD (G3b - G4), a significant reduction in decline of creatinine clearance was observed in the LPD group (0.7 g/kg/d) but not in controls (1.1 g/kg/d) over a 36-month follow up (2.4 ±0.2 vs 5.7 ±0.5 mL/min/y, respectively; $P < 0.05$). Besides, a significant reduction in proteinuria, low-grade inflammation, and oxidative stress was observed in the LPD group ($P < 0.05$). A 12-month follow-up RCT [30] showed that LPD (0.6 g/kg/d) combined Ketoacid α could reduce urinary protein level (2.8994 ±1.462 vs 4.77 ±2.12g/d, $P < 0.05$) in DKD patients (G3-4) compared with NPD group but no difference observed in eGFR (29.19 ±9.13 vs 29.77 ±13.19 ml/min/1.73 m^2). Overall, the populations included above were primarily T2DM patients with reduced renal function (mean eGFR < 60 mL/min/1.73 m^2), and results shows that LPD may be beneficial for alleviating the albuminuria in them.

A meta-analysis [31] of 8 RCTs involving 519 diabetic patients and concluded that LPD was not associated with changes of GFR ($P = 0.61$), but a decrease in proteinuria or albuminuria was observed in the LPD group (SMD: -0.69; 95% CI, 1.14-0.23; $P = 0.003$; I^2=81.4%). Another meta-analysis [32] of 13 RCTs involving 779 DKD patients (baseline mean eGFR: 76ml/min/1.73 m^2) found that LPD (0.6-0.8 g/kg/d) was associated with an improvement in GFR (5.82ml/min/1.73m^2; 95%CI, 2.3-9.33; $P < 0.05$) when diet compliance was fair, but proteinuria (-0.14 units; 95%CI, -0.74 - 0.46, $P = 0.65$) were not differed between the LPD and control groups(1-1.6 g/kg/d). Another meta-analysis [33] has shown a differential effect of LPD upon CKD progression according to types of diabetes. Protein intake restriction was beneficial in non-diabetic and type 1 diabetic patients but not in those with T2DM. The subgroup analysis of a meta-analysis published in 2021 [34] found that in DM patients with CKD stages 1–3, there were no statistical differences in GFR decline between the LPD and control groups (weight mean difference [WMD] 7.33 ml/min/1.73 m^2, 95% CI, -1.61-16.27; $P = 0.11$; $I^2 = 94\%$), although LPD group benefited from protein restriction by achieving a decreased proteinuria (standard mean difference [SMD] -0.96 units; 95%CI, -1.81 - -0.11; $P = 0.03$; $I^2 = 90\%$). It is worth noting that the heterogeneities in studies above were substantial for the results.

A number of factors are assumed to influence the effectiveness of LPD in researches above. Firstly, the results of the RCTs often affected by the compliance of participants to dietary intervention. As Koya et al[27] reported previously, no differences in actual protein intake between NPD and LPD groups during follow-up. And the difference in actual protein intake between LPD and the control group was only 0.08g/kg/d at 6-month follow-up in another RCT[26]. Similarly, no differences were found in actual protein intake between the two groups during the follow-up in the RCT of Dussol et al. [35]. When applied a best-case analysis in patients with good adherence, Dussol et al. observed no statistical difference in changes of renal function between the two groups either. And among patients not receiving antihypertensive treatment, the decrease in GFR is four to five times higher than in patients with antihypertensive treatment, suggesting that antihypertensive treatment may have blunted the putative role of protein restriction on renal disease progression. Besides, Kasiske et al. [36] pointed out that the beneficial effect of a LPD seemed to be significantly greater in smaller trials, suggesting possible publication bias.

Furthermore, the study populations' sizes, as well as durations of intervention and the target of protein restriction were highly variable across the meta-analyses, which may also lead to inconsistent results.

3.3 Mechanisms in protein intake impact kidney function

It was first noted in the isolated perfused frog kidney model that amino acids and peptides could increase blood flow to the kidneys in 1928. And intervention studies indicate that HPD induces short-term up-regulation of GFR[37]. HPD dilates the afferent arteriole, induced by the tubuloglomerular feedback mechanism and nitric oxide synthases at el., resulting in an increased glomerular filtration rate over a short period, which leading to increased TGF-β release and subsequent progressive glomerular fibrosis and renal damage [37, 38]. The adverse impact of HPD on the kidneys in diabetics was also observed. Tuttle et al. [39] found that the renal hemodynamic response to an increase in plasma amino acid concentrations is augmented in diabetic patients with enlarged kidneys. Although acute high protein intake may lead to glomerular hyperfiltration which result in progressive renal damage, the long-term effects of chronic high protein intake still controversial. Lacroix et al. [40] found that there was no difference in renal function between HPD (50% E%) and controls (14% E%)groups in male rats after 6 months of follow-up. More longer-term studies are needed to confirm the association of HPD with renal function in T2DM patients.

Animal studies have shown that LPD could prevent the occurrence and slow down the progression of diabetic nephropathy by improving abnormal metabolic factors and hemodynamics through multiple mechanisms, including improvements in glomerular hypertension and capillary hypertrophy[37, 41]. In animal models of T2DM, researchers demonstrated that an LPD intervention could improve diabetes-induced renal damages by restoring autophagy through the suppression of mTORC1[42]. However, clinical studies have not consistently shown beneficial effects of the dietary intervention with an LPD for the preservation of renal function in diabetic patients, more studies are needed to further confirm the relationship between them.

4. Sources of DPI

Observational studies[43-45] have noted that plant protein (defined as protein from tofu/soybean curd, legumes, vegetables, fruits and whole and refined grains) are beneficial for non-diabetic patients with CKD, while intake of animal protein, especially processed red meat consumption, are associated with the incidence and progression of CKD.

Partial studies were focused on T2DM patients when studied the association of CKD with sources of DPI. Cross-sectional studies found that increased animal protein intake derived from processed meat and red meat were associated with the presence of microalbuminuria [46], while higher intake of vegetable protein was associated with a lower prevalence of renal function impairment among T2DM patients[47]. A large prospective study[45] enrolled 60,198 participants(35% of whom were diabetics) showed that increased red meat intake was strongly associated with ESRD risk in a dose-dependent manner (4th vs.1st quartile HR=1.40 [95% CI, 1.15 - 1.71; P <0.001]) after a mean follow-up of 15.5 years, and replacing red meat with other food sources of protein such as fish may reduce the incidence of ESRD. In another RCT with follow up over 4 years [48], significant improvements were observed in albuminuria (-0.15 ± 0.039 vs 0.02 ± 0.01g/d; P = 0.001) and urinary creatinine (-1.5 ± 0.9 vs 0.6 ± 0.3g/d; P = 0.01) by soy protein intake (35% animal, 35% soy-origin, and 30% vegetable proteins) compared with those in the control group (70% animal and 30% vegetable proteins). And previous studies[49, 50] have shown that compared with intake of plant protein, intake of animal protein causes an imbalance in the composition of the gut microbiome and has a pro-inflammatory profile, which may affect kidney function. Besides, high red meat intake has been linked to increased inflammation and oxidative stress[51]. Thus, Plant and fish protein may be a more reasonable choice than animal protein which from red meat or processed meat for patients with T2DM. Further studies are needed to determine the effect of protein type upon renal function in T2DM patients with different stages of CKD.

5. Conclusion

To the best of our knowledge, this is the first review for investigating the correlation between protein intake and renal disease in T2DM patients with different renal function stages, and we summarize the current literature on the potential consequences of HPD or LPD on kidney diseases, which may provide a reference for clinicians when

treating patients.

According to NHANES data[52], the current average protein consumption in the United States is estimated to be approximately 1.2-1.4 g/kg per day, which is higher than the recommended amount. And in our narrow review, we found that HPD was actually not associated with increased renal function deterioration in patients with preserved renal function (eGFR ≥ 60 mL/min/1.73 m^2), and LPD did not provide a significantly benefit for these patients. Thus, among patients with preserved renal function, we need not to emphasize the importance of dietary protein intake intervention, maybe unrestricted DPI was not contraindicated as a part of T2DM management. Besides, DPI under 0.8g/kg/d may be beneficial for alleviating the albuminuria in T2DM patients with reduced renal function (eGFR < 60 mL/min/1.73 m^2), but the risk of malnutrition should be concerned. In addition, maybe it is a more reasonable choice for T2DM patients to intake protein from plant and fish due to processed red meat was associated with renal function impairment. Further studies are needed to investigate the association of DPI with renal disease progression in T2DM patients with different stages of CKD.

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Disclosure

All the authors have declared no competing interest.

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Table1: Summary of studies of high protein intake and kidney disease in type 2 diabetes

Study Reference	Type	Size	Duration	Mean eGFR ($mL/min/1.73m^2$)	Mean proteinuria levels	Protein intake (g/kg/d or % of % of energy)	Variable and Outcome
Wrone et al.[15]	Cross-sectional	4223	-	HPD: Females: 99.8 ±1.1 Males: 84.8 ±0.9	ACR < 300g/mg	HPD: ≥ 19% E% LPD: < 11.7% E%	HPD was not associated with microalbuminuria.
Kaji et al.[16]	Retrospective study	144	5y	82 ±20	UAE: 15(7-38.9mg/gCr)	HPD: >1.3g/kg/d LPD: <0.8g/kg/d	HPD was not associated with changes in eGFR or UAE (P > 0.05 for all comparisons).
Malhotra et al.[22]	nested case-control study	1409	8y	-	-	HPD: 1.96g/kg/d LPD: 0.47 g/kg/d	HPD was associated with increased incidence of ESRD (4th vs. 1st quartile OR=1.76; 95%CI, 1.04 - 2.77; P <0.05) in blacks with diabetes but not in whites with diabetes.
Oosterwijk et al. [21]	Prospective cohort	382	6y	78 ±24	-	1.22±0.33g/kg/d	Increased dietary protein was inversely associated with renal function deterioration (HR: 0.62; 95%CI, 0.44 - 0.90).
Pomerleau et al. [17]	RCT	12	3wk	118. 2 ±28.2	AER: 15-300ug/min	HPD: 2 g/kg/d	HPD was not associated with changes of eGFR(118.2 ±28.2 vs 118.8 ±38.4mL/min/1.73㎡) or albumin excretion rate(98 ±105 vs 100 ±115 ug/min) after HPD for 3 weeks.
Luger et al.[18]	RCT	44	12wk	≥ 90	AER: HPD: 65.9 ±175.4 ug/min NPD: 60.8±195.8 ug/min	HPD: 30%E% NPD: 15%E%	eGFR(68.5 ± 18.9 vs 73.8 ± 13.9 mL/min/1.73㎡) and AER(92.3 ± 299.9 vs 104.3 ± 252.7μg/min) were not different between HPD and NPD groups.
Tay et al.[53]	RCT	115	12mo	HPD: 96 NPD: 92	-	HPD: 28%E% NPD: 15%E%	The changes of eGFR were not different between HPD and NPD groups(-4 vs -2 mL/min/1.73㎡, P = 0.25).
Larsen et al.[19]	RCT	99	12mo	HPD: 70.2 NPD: 72.6	AER: HPD: 30ug/min NPD: 26.2ug/min	HPD: 30% E% NPD: 15%E%	The changes of eGFR(1.98 vs 3.2 mL/min/1.73㎡) or AER(-4.65 vs -4.51μg/min) were not different between groups, although protein intake measured by urea nitrogen was not significantly.
Jesudason et al.[54]	RCT	45	12mo	HPD: 98 ±28 PD: 91 ±30	AER: HPD: 41 ±11ug/min NPD: 82 ±13ug/min	HPD: 30%E%M NPD: 20%E%S	eGFR(97 ±20 vs 90 ±28mL/min/1.73㎡) and AER were not different between HPD and NPD groups.
Krebs et al.[20]	RCT	294	2y	≥60	UACR＞30mg/mmol	HPD: 30%E% NPD: 15%E% (μmol/l)	Serum creatinine (83.1 ± 23.6 vs 78.5 ± 22.0μmol/l) and UACR (0.72 vs 0.57mg/mmol) were not different between HPD and NPD groups.

T2DM, type 2 diabetes mellitus; ACR, urinary albumin-creatinine ratio; UAE, urinary albumin excretion; UACR, urine albumin: creatinine ratio; AER, albumin excretion rate; HPD, high protein intake; NPD, normal-protein intake; RCT, randomized controlled trial.

Table 2: Summary of studies of low protein intake and kidney disease in type 2 diabetes

Study Reference	Type	Size	Duration	Mean eGFR(mL/min/1.73m^2)	Mean proteinuria levels	Protein intake (g/kg/d or % of % of energy)	Variable and Outcome
Tauchi et al. [28]	Retrospective study	449	1.7y	LPD: 19.7 ±10.9 NPD: 29.1 ±20.9	UACR≥ 300mg/g	LPD: 0.67 ±0.04 g/kg IBW/d NPD: 1.02 ±0.09 g/kg IBW/d	LPD group had a lower incidence of renal replacement therapy initiation (HR:0.4; 95%CI, 0.23 - 0.70; P =0.001) compared with NPD group, but might lead to increased mortality in patients with malnutrition.
Dunkler et al. [25]	Prospective cohort	6213	5.5y	71.61	UACR: 9.31 mg/mmol	VLPD: 0.36 g/kg/d NPD: 0.96 g/kg/d	VLPD had greater risk of incident CKD (HR:1.16; 95%CI: 1.05,1.30; P <0.05) when compared with NPD group.
Giordand et al. [29]	Prospective cohort	74	36mo	15≤ eGFR<45	Proteinuria: LPD: 2.4 ±0.5g/d NPD: 2.3 ±0.9g/d	LPD: 0.7 g/kg/d(6 days a week) NPD: 1.1 g/kg/d	Compared with NPD, LPD was beneficial to improve the creatinine clearance(2.4 ±0.2 vs 5.7 ±0.5 ml/min/y, P< 0.05) and proteinuria(1.1 ±0.2 vs 2.4 ±0.8g/d, P< 0.05).
Qiu et al. [30]	RCT	23	12mo	LPD: 31.3 ±10.41 NPD: 36.75 ±13.25	AER>300 mg/d	LPD:0.6 g/kg/d NPD: 0.8 g/kg/d	LPD combined Ketoacid α could alleviate albumin excretion rate (2.8994 ±1.462 vs 4.77 ±2.12g/d, P < 0.05) compared with NPD group but no difference observed in eGFR(29.19 ±9.13 vs 29.77 ± 13.19 ml/min/1.73 m2).
Koya et al. [27]	RCT	112	5y	LPD: 63.5±26.9 NPD: 61.1±23.7	-	LPD: 0.8g/kg/d NPD: 1.2 g/kg/d	The annual changes in eGFR were not different between NPD and LPD groups (-5.8 ±5.7 vs-6.1 ±6.5 ml/min/1.73 m2, P =0.93).
Dussol et al. [35]	RCT	47 (37 with T2DM)	2y	LPD: 89 ±27 NPD: 82 ±21	AER: >30mg/d	LPD: 0.8g/kg/d NPD: 1.2 g/kg/d	The changes in eGFR (-5 ±15 vs -7 ±11 ml/min/1.73 m^2) and AER (+114 ±364 vs +156 ±486mg/d) were not different between NPD and LPD groups with strict blood pressure control.
Meloni et al. [55]	RCT	69 (37 with T2DM)	12mo	LPD: 43.9 ±4.7 NPD: 45 ±5.1	-	LPD: 0.68 ± 0.21g/kg/d NPD: 1.39 ±0.28 g/kg/d	The changes in eGFR were not different between LPD and NPD groups (6.15 ±1.61 vs 6.26 ±1.84ml/min/1.73 m2) with strict blood pressure and glycemic control, and it may induce malnutrition.
Meloni et al. [56]	RCT	80 (56 with T2DM)	12mo	LPD: 43.9 ±4.7 NPD: 45 ±5.1	-	LPD: 0.8 g/kg/d NPD: 1.24 g/kg/d	There were no statistically significant differences in eGFR (5.78 ± 1.5 vs 6.03 ±1.3 ml/min/1.73 m^2) between the LPD and NPD groups.
Barsotti et al. [57]	RCT	32(10 with T2DM)	3.7y	creatinine clearance(ml/min) VLPD: 8.9 ±5.6 LPD: 44.6 ±12.8	-	VLPD: 0.3 g/kg/d LPD: 0.7g/kg/d NPD: No restriction	LPD group had a lower decline in creatinine clearance(-0.22 ±0.21 vs -0.9 ±0.62 ml/min, P<0.001) per month compared with NPD group.
Pijlis et al. [26]	RCT	131	28mo	LPD: 82 ±19 NPD: 85 ±23	albuminuria: LPD: 21.2mg/d NPD: 20.5mg/d	LPD: 0.8g/kg/d NPD: 1.15 ± 0.26g/kg/d	After at least 12 months of follow-up, the annual change in eGFR (-4.8 ±12 vs -6.4 ±14 ml/min/1.73 m2, P = 0.5) and albuminuria (+1.2 vs +0.1 mg/24h, P = 0.09) were not statistically different between LPD and NPD groups, but poor patient compliance.
Pan et al. [31]	Meta-analysis	519(8 RCT and 4 including T2DM)	12 ~24mo	LPD: 43.9 ±4.7 ~ 82 ±21 NPD: 45 ±5.1 ~ 89 ±27	-	LPD: 0.6 - 0.8 g/kg/d NPD: 1.27 g/kg/d	LPD was not associated with changes in GFR but may slightly improve proteinuria (SMD: -0.69; 95%CI, -1.14 - -0.23; P = 0.003; I2 = 81.4%).
Li et al. [34]	Meta-analysis	506(9 RCTs and 4 including T2DM)	4.5 ~60mo	-	-	LPD: 0.6 - 0.8 g/kg/d NPD: 1.29 g/kg/d	The subgroup analysis of patients with CKD stages 1–3 found no statistical differences in GFR decline between the LPD and NPD groups (WMD:7.33mL/min/1.73m2,95%CI, -1.61 - 16.27; P = 0.11;

							I2 = 94%), but LPD could improve proteinuria (WMD: -0.96 units,95%CI, -1.81 - -0.11; P = 0.03).
Zhu et al. [58]	Meta-analysis	687(11 RCTs and 6including T2DM)	2~60mo	LPD: 31.1 ±10.41 ~ 131 ± 34 NPD: 36.75 ±5.1 ~ 122 ± 26	-	LPD: 0.6-0.8 g/kg/d	Intake of LPD demonstrated no protective effect on diabetic nephropathy neither on improving GFR (1.59ml/min/1.73m2, 95%CI, -0.57 - 3.75; P = 0.15) nor proteinuria (SMD: -0.48, 95%CI, -1.7 - 0.74; P = 0.44) when compared with NPD.
Nezu et al. [32]	Meta-analysis	779(13 RCTs and 5 including T2DM)	3 ~60mo	76	-	LPD: 0.6–0.8 g/kg/d control group: 1–1.6 g/kg/d	LPD was not associated with changes in proteinuria (-0.14, 95%CI, -0.74 - 0.46; P = 0.65) but had a higher eGFR (5.82ml/min/1.73m2; 95%CI, 2.3 - 9.33; P < 0.05) compared with control groups.

T2DM, type 2 diabetes mellitus; LPD, low-protein intake; VLPD, low-protein intake; NPD, normal-protein intake; UACR, urinary albumin-creatinine ratio; AER, albumin excretion rate; UAER, urinary albumin excretion rate; IBM, ideal body weight; RCT, randomized controlled trial; WMD, weight mean difference; SMD, standard mean difference.