Review

First, Do No Harm: Critical Appraisal of Protein Restriction for Diabetic Kidney Disease

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Abstract: Low-protein diets have been recommended as diet therapy for the management of chronic kidney disease; however, its effect on chronic kidney disease has not been scientifically proven. Although several studies have reported significantly more favorable results with low-protein diet than with normal-protein diet, the renal protective effects of low-protein diets are still unclear in diabetic patients with chronic kidney disease. Moreover, some studies have reported that extremely low-protein diets may increase the risk of mortality. Thus, this paper describes the effectiveness and safety of low-protein diets for patients with diabetic kidney disease by reviewing the historical background of different low-protein diets that were critically examined in several studies.

Keywords: protein restriction; diabetic kidney disease; eGFR; hyperfiltration theory

1. Introduction

Low-protein diets are typically recommended as diet therapy for the management of chronic kidney disease (CKD) regardless of its type (i.e., diabetic kidney disease (DKD) or non-diabetic chronic kidney disease (non-DM-CKD)). A review article by Kalantar-Zadeh et al. [1] published in the *New England Journal of Medicine* in 2017 and the clinical practice recommendation for DKD by the 2020 Kidney Disease: Improving Global Outcomes (KDIGO) (KDIGO 2020) [2] both recommend low-protein diets for CKD. Kalantar-Zadeh et al. [1] stated that protein reduction should be prioritized over other nutrients, such as sodium, potassium, and phosphorus. However, its effects on CKD are yet to be proven scientifically as Kalantar-Zadeh et al. [1] stated, "It is possible, though not yet unequivocally proved, that nutritional interventions slow disease progression," and the KDIGO 2020 [2] stated that "the certainty of the evidence" is "low" or "very low." In fact, the American Diabetes Association [3] recommended the following nutrition recommendations until 2008: (1) diet with 0.8–1.0 g/kg protein for diabetic patients with microalbuminuria, and (2) 0.8 g/kg protein for diabetic patients with macroalbuminuria. However, this recommendation was retracted in 2013 as these low-protein diets did not have renal protective effects. Since then, the same level of protein intake has been recommended for diabetic patients with DKD as that for healthy adults (1.0–1.5 g/kg) [3–5]. Given the uncertainties involved with low-protein diets for diabetic patients with CKD, this review discusses the effectiveness and safety of low-protein diets for DKD. This study reviewed the historical background of different low-protein diets, which were critically examined in several studies that were used by Kalantar-Zadeh et al. [1] and the KDIGO 2020 [2].

2. Historical Background of Low-Protein Diet Recommendations

Low-protein diets were first recommended for patients with kidney disease by Addis [6], specifically for glomerulonephritis, because the urinary excretion of urea loads the kidneys. Thereafter, Brenner et al. [7] reported that excessive protein intake causes an increase in both glomerular filtration and glomerular pressure, and recommended low-protein diets for patients with age-related renal dysfunction and DKD. Furthermore, partial loss of glomerular function irrespective of the cause leads to compensatory hyperfiltration

and subsequent increased injury of the remaining glomeruli. This was referred to as the "hyperfiltration theory." Researchers, since then, considered that low-protein diets and renin-angiotensin system (RAS) inhibition were effective in protecting renal function [8]. It can be said that the glomerular hyperfiltration theory per se has been proven by the renal protective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors, which occur potentially via tubuloglomerular feedback in chronic kidney disease [9–11]. SGLT2 inhibitors have been found to decrease the estimated glomerular filtration rate (eGFR) at an early stage; however, the rate of decrease lowers subsequently. As compared to the control group, the eGFR of patients receiving SGLT2 inhibitors was maintained at a higher level after administering these drugs for approximately one year. These findings suggest that SGLT2 inhibitors help reduce glomerular hypertension and hyperfiltration. In fact, one hypothesis stated that high-protein diets might lead to a decrease in the renal protective effects of SGLT2 inhibitors [12]. However, hyperfiltration attributed to high-protein or normal-protein diets is yet to be verified. The Modification of Diet in Renal Disease (MDRD) study (Study 1) found that eGFR changes in the low-protein diet group were similar to those in patients receiving SGLT2 inhibitors [13]. This is potential evidence that high-protein intake leads to hyperfiltration, which is used as a rationale for the significance of low-protein diets [1]. In contrast, the Northern Italian Cooperative Study reported contradictory results [14]. The study found that the remaining renal function in a subgroup, which included patients with the highest baseline blood creatinine levels, decreased rapidly at an early stage as the patients received normal-protein diets. Similarly, the rate of decrease was slower in this group at a later stage than in the group receiving low-protein diets. That is, the association between a normal protein intake level and hyperfiltration has not been verified. Meanwhile, a follow-up study of the MDRD study (Study 1) found that the progression of renal dysfunction was faster in the low-protein diet group at six years or later, although no statistically significant difference was observed [15]. Thus, the hypothesis that protein intake leads to hyperfiltration could not be verified by this study (Study 1). Therefore, further research is needed to evaluate whether normal-protein diets with a protein intake of 1.0–1.5 g/kg cause glomerular hyperfiltration in injured kidneys [16]; it could not be determined whether such protein diets lead to hyperfiltration before data are obtained, indicating that low-protein diets are effective in protecting the kidneys of patients with CKD. Hostetter et al. [17] used rats with one kidney removed and those with one kidney and one-third of the contralateral kidney removed, and histologically found that high-protein diets with protein accounting for 40% of the total energy intake (all casein) led to nephrosclerosis. Consequently, low-protein diets were recommended; however, their findings did not go beyond the experimental level where high-protein diets were quantitatively and qualitatively examined in experimental disease conditions. For a protein diet accounting for 40% of the total energy intake, a 50 kg woman with a 2000 kcal daily energy intake would need to eat 4.0 g/kg of protein. Meanwhile, young men attempting to increase their musculature typically consume up to 3.0 g/kg of protein [18], which accounts for only 30% of the total energy intake [19]. The hyperfiltration theory proposed by Brenner et al. [7,8] has not been supported by any clinical study on normal protein intake in CKD patients. Findings from animal experiments (preclinical studies) should not be directly applied to any human clinical decision making. The decision of clinician should always be determined based on the results of clinical studies. Hence, this review examined the clinical studies that were used as rationales for recommendations by Kalantar-Zadeh et al. [1] and the KDIGO 2020 [2].

3. Effectiveness and Safety of Low-Protein Diets

3.1. Effectiveness of Low-Protein Diets in 18 Studies Cited by Kalantar-Zadeh et al.

Kalantar-Zadeh et al. [1] recommended low-protein diets (Table 1). In their article, they emphasized their preference for low-protein diet over diet recommendations on sodium, potassium, phosphorus, calcium, fibers, alkali, plant-based foods, energy, and fats. Low-protein diets with a protein intake of <1.0 g/kg are recommended for people

without CKD but with risk for CKD, such as those with diabetes or hypertension. Although Kalantar-Zadeh et al.'s study [1] is not a review on DKD, further verification is necessary for its low-protein diet recommendation for diabetic patients without CKD. In particular, it is necessary to validate whether there is any rationale for restricting normal-protein diets (1.0–1.5 g/kg) in all diabetic patients. Kalantar-Zadeh et al. Reference [1] cited 18 papers as references. These papers were selected because they reported on controlled trials consisting of greater than 30 participants that have examined the effects of low-protein or very low-protein diets on various outcome measures in patients with CKD (Table 2).

Table 1. Recommended daily protein intake in a review article by Kalantar-Zadeh et al.'s paper.

CKD Stage	Normal Kidney Function with Increased CKD Risk	Mild-to-Moderate CKD	Advanced CKD	Transition to Dialysis	Ongoing Dialysis	Any Stage with PEW
CKD stage (mL/min/1.73 m^2)	eGFR ≥ 60 with CKD risk	60 > eGFR ≥ 30	30 > eGFR or proteinuria > 0.3 g/day			
Daily protein intake (g/kg)	<1.0	<1.0	0.6–0.8 including 50% HBV, or <0.6 with EAA or KA	0.6–0.8 on non-dialysis days and > 1.0 on dialysis days	1.2–1.4	>1.5
Other considerations	Increased proportion of plant-based protein	Consider 0.6–0.8 if eGFR < 45				

CKD, chronic kidney disease; PEW, protein-energy wasting; HBV, high biologic value; EAA, essential amino acids; KA, ketoacids. Reprinted with permission from ref. [1]. Copyright 2017 Massachusetts Medical Society.

Table 2. Abstracts of 18 papers from Kalantar-Zadeh et al.'s paper.

First Author	Reference Numbers	Patients	Intervention (Daily Protein Intake)	Comparison	Outcome	Results
Rosman	[20]	Ccr 10–60 mL/min *n* = 228 non-DM	0.6 g (CKD3), 0.4 g (CKD4–5)	Usual Protein	SCr10% elevation at 2 years	○ 40% vs. 75% (CKD 3) ○ 50% vs. 97% (CKD 4–5)
Rosman	[21]	Ccr 10–60 mL/min *n* = 248 non-DM	0.6 g (CKD3), 0.4 g (CKD4–5)	Usual Protein	Ccr decline	▲ −0.28 vs. −0.31 (CKD 3) ○ −0.16 vs. −0.20 (CKD 4–5)
Ihle	[22]	Cr 4–11 mL/min CKD, *n* = 64 non-DM	0.4 g	Usual Protein	ESRD	○ 2/31 vs. 9/33
Lindenau	[23]	Ccr < 15 mL/min, *n* = 40 no description of primary renal disease	0.4 g + keto acids	0.6 g	Bone biopsy	○ keto acids reduce bone fibrotic change
Williams	[24]	SCr > 1.70 (Male), > 1.47 (Female) mg/dL, *n* = 95 12/95 (12.6%) were DKD	0.6 g	0.8 g	Ccr decline	▲ −0.56 vs. −0.69

Table 2. *Cont.*

First Author	Reference Numbers	Patients	Intervention (Daily Protein Intake)	Comparison	Outcome	Results
Locatelli	[14]	CKD 3–5, *n* = 456 non-DM GFR 25–55 mL/min/1.73 m²	0.6 g	1.0 g	SCr doubling or HD	▲ 27/226 vs. 42/230
Klahr	[13]	*n* = 585 GFR 13–24 mL/min/1.73 m², *n* = 255 3% was DKD	0.58 g in study 1 0.28 g + keto acid in study 2	1.3 g study 1 0.58 g study 2	GFR decline	−3.6 vs. −4.0 −4.4 vs. −3.6
Montes-Delgado	[25]	CRF, *n* = 33 9/33 (27.3%) were DKD	0.6 g + high energy	0.6 g	Ccr decline	○ 11 → 10.7 vs. 18.3 → 13.8
Malvy	[26]	GFR < 20 mL/min/1.73 m², *n* = 50 non-DM	0.3 g + keto acid	0.65 g	GFR < 5 mL/min/1.73 m²	▲ 100% vs. 100%
Teplan	[27]	Ccr 22–36 mL/min, *n* = 105 non-DM	0.6 g + EPO + keto acid 0.6 g + EPO	0.6 g	Ccr decline	○ −0.672 (EPO + keto acid) vs. −2.124 (control) ▲ −1.512 (EPO) vs. −2.124 (control)
Prakash	[28]	Ccr 20–50, *n* = 34 20/34 (58.8%) were DKD	0.3 g + keto acids	0.6 g + placebo	eGFR decline	n.a. 28.1 → 27.6 vs. 28.6 → 22.5
Brunori	[29]	CKD 5, *n* = 56 non-DM	0.3 g + keto acids	1.2 g + HD start	Mortality	▲ 12.7% vs. 16.3%
Mircescu	[30]	CKD 4–5, *n* = 53 non-DM	0.3 g + keto acids	0.6 g	Urea	▲ Urea nitrogen 73.3 → 56.5 vs. 63.0 → 67.2
Cianciaruso	[31] *	CKD 4–5, *n* = 423 12% was DKD	0.55 g	0.80 g	PEM, HD, GFR decline	▲ PEM2 vs. 1, HD41 vs.42, GFR −0.19 vs. −0.18
Di Lorio	[32]	CKD moderate-advanced, *n* = 32 20/32 (62.5%) were DKD	0.3 g + keto acids	Low protein	Proteinuria	○ 58% reduce
Jiang	[33] *	PD, *n* = 34 2/34 (5.9%) were DKD	0.6–0.8 g/kg IBW With or without Keto acids	1.0−1.2	GFR decline	Without keto acids 4.0 → 2.3 vs. 4.3 → 2.6 With keto acids 3.8 → 3.4 vs. 4.3 → 2.6
Jiang	[34]	PD, *n* = 60 3/60 (5.0%) were DKD	0.6–0.8 g/kg IBW With or without Keto acids	1.0−1.2	Peritoneal function	▲ without keto acids ○ with keto acids
Garneata	[35]	CKD 4–5, *n* = 207 non-DM	0.3–0.4 g + keto acids + vegetarian	0.6 g	HD start or GFR 50% loss	○ 13% vs. 42%

* The two papers were originally proceedings of a scientific meeting. In this review, the author selected articles from other medical journals whose titles were similar. Abbreviations: Ccr, creatinine clearance; Cr, creatinine; SCr, serum creatinine; GFR, glomerular filtration rate; CKD, chronic kidney disease; EPO, erythropoietin; PD, peritoneal dialysis; ESRD, end-stage renal disease; HD, hemodialysis; CRF, chronic renal failure; n.a., not available; IBW, ideal body weight. ○ indicates that intervention was statistically superior to control. ▲ indicates that there was not statistically significant difference between intervention and control. Reprinted with permission from ref. [1]. Copyright 2017 Massachusetts Medical Society.

Among the 18 studies [13,14,20–35], eight had significantly more favorable results in the intervention group (low-protein diet) than in the control group (normal-protein diet) in terms of study outcomes. However, these studies did not necessarily examine the renal protective effects of low-protein diets. For example, the amount of protein intake was the same between the intervention and control groups, as reported by Montes-Delgado et al. [25] and Teplan et al. [27], who examined the renal protective effects of high-energy diets and supplements such as erythropoietin (EPO) and keto acids. Lindenau et al.'s study [23] did not report on renal function; however, it provided bone biopsy results. In

recent years, there has been an increase in the use of eGFR changes as a surrogate marker when examining outcomes in studies on the kidneys [36,37]. Table 3 presents ten articles that reported changes in renal function as outcomes in genuine intervention studies of low-protein diets for patients with predialysis renal failure.

Table 3. Abstracts of ten articles selected from Kalantar-Zadeh et al.'s paper that evaluated the renal protective effect of protein restriction intervention.

First Author (Year Published)	Reference Numbers	Patients	Intervention (I) (Daily Protein Intake)	Comparison (C)	GFR (mL/min/1.73 m²) or Ccr (mL/min) Decline per Year in I	GFR (mL/min/1.73 m²) or Ccr (mL/min) Decline per Year in C	Statistical Significance between Groups
Rosman (1989)	[21]	Ccr 10–60 mL/min $n = 248$ non-DM	0.6 g (CKD 3), 0.4 g (CKD 4–5)	Usual Protein	Ccr−3.36(CKD 3) Ccr−1.92 (CKD 4–5)	Ccr−3.72 (CKD 3) Ccr−2.40 (CKD 4–5)	n.s. (CKD 3) ○ (CKD 4)
Ihle (1989)	[22]	SCr 4–11 mg/dL, $n = 64$ non-DM	0.4 g	Usual Protein	Ccr−1.8 mL/min	Ccr−6.0 mL/min	○
Williams (1991)	[24]	SCr > 1.70 (Male), > 1.47 (Female) mg/dL, $n = 95$ 12/95 (12.6%) were DKD	0.6 g	0.8 g	Ccr−6.72	Ccr−8.28	n.s.
Locatelli (1991)	[14]	CKD 3–5, $n = 456$ non-DM	0.6 g	1.0 g	Ccr−1.8	Ccr−1.0	n.s.
Klahr (1994)	[13]	GFR 25–55 mL/min/1.73 m², $n = 585$ GFR 13–24 mL/min/1.73 m², $n = 255$ 3% was DKD	0.58 g study 1 0.28 g + keto acid study 2	1.3 g study 1 0.58 g study 2	−3.6 −3.6	−4.0 −4.4	n.s. n.s.
Malvy (1999)	[26]	GFR < 20, $n = 50$ non-DM	0.3 g + keto acid	0.65 g	−3.26	−2.89	n.s.
Prakash (2004)	[28]	Ccr 20–50 mL/min, $n = 34$ 20/34 (58.8%) were DKD	0.3 g + keto acid	0.6 g + placebo	−2.0	−8.1	○
Mircescu (2007)	[30]	CKD 4–5, $n = 53$ non-DM	0.3 g + keto acids	0.6 g	−3.1	−4.9	n.a.
Cianciaruso (2009)	[31]	CKD 4–5, $n = 423$ 12% was DKD	0.55 g	0.80 g	−2.28	−2.16	n.s.
Garneata (2016)	[35]	CKD 4–5, $n = 207$ non-DM	0.3–0.4 g + keto acids + vegetarian	0.6 g	−2.9	−7.1	○

Abbreviations: Ccr, creatinine clearance; Cr, creatinine; SCr, serum creatinine; GFR, glomerular filtration rate; CKD, chronic kidney disease; EPO, erythropoietin; PD, peritoneal dialysis; ESRD, end-stage renal disease; HD, hemodialysis; CRF, chronic renal failure; n.a., not available; n.s., not significant. ○ indicates that intervention was statistically superior to control. Adapted with permission from ref. [1]. Copyright 2017 Massachusetts Medical Society.

None of these studies used a protein intake of <1.0 g/kg or 0.6–0.8 g/kg, which was recommended by Kalantar-Zadeh et al. [1]. In addition, four of the 10 studies (one of them only examined patients with CKD 4–5) reported that low-protein diets protected renal function (Table 3). All four studies used extremely low-protein diets with a protein intake of 0.3 g/kg or 0.4 g/kg. However, in three of the four studies [22,28,35], the eGFR in the control group decreased by 5 mL/min/1.73 m² annually. Patients experiencing a decrease in the eGFR at a rate faster than 5 mL/min/1.73 m² annually were referred to as rapid decliners or rapid progressors, who have a special clinical condition [38]. It would be difficult to generalize data from a study that solely examines rapid decliners. The remaining study [21] observed significant differences in the rate of decrease in Ccr levels in patients with CKD 4–5. However, it is intriguing that the rate of decrease in Ccr levels in patients with CKD 4–5 in the normal-protein diet group (control group) was slower than that in patients with CKD 3 in the low-protein diet group. The results of the study completely overturned the hyperfiltration hypothesis. Hence, the articles cited by Kalantar-Zadeh et al. [1] cannot be used as a rationale for recommending low-protein diets, regardless of the following recommended amount of intake: <1.0 g/kg, 0.6–0.8 g/kg, or 0.3–0.4 g/kg.

3.2. Effectiveness of Low-Protein Diets in Nine Studies Cited in the KDIGO 2020

The KDIGO 2020 recommends low-protein diets with 0.8 g/kg and 1.0–1.2 g/kg of protein for diabetic patients with CKD and dialysis patients, respectively [5]. This systematic review consisting of 11 articles was used as a rationale for these recommendations. However, the certainties of the evidence for all-cause mortality and end-stage kidney disease were low, and those for doubling of serum creatinine levels and changes in eGFR were very low. The KDIGO 2020 report stated in its Table S12, "we are uncertain whether low-protein diet improves or worsens change in eGFR." It is intriguing that the article recommended low-protein diets although worsening of the eGFR could not be ruled out. For example, a systematic review of all-cause mortality included only two studies (this cannot be considered a systematic review). Based on the review, a decrease in mortality by 21 per 1000 people can be expected in low-protein diet groups during a mean follow-up period of 4.5 years [5,39,40]. A summary of the results of the abovementioned studies is presented in Table 4, which included the following causes of death: myocardial infarction, heart failure, and sepsis. However, the basis of the KDIGO Diabetes Work Group's claims remains questionable. Even if there were statistically significant differences, it can be concluded that low-protein diets are not effective in reducing all-cause mortality. Meanwhile, the KDIGO Diabetes Work Group examined changes in eGFR from eight studies [39,41–47], which are summarized in Table 5. Among the eight studies, only two observed significant differences in eGFR changes [41,42]. Both the studies reported that low-protein diets were effective for patients with type 1 diabetes. In these studies, patients with type 1 diabetes received interventions consisting of low-protein diets with a protein intake of 0.6 g/kg, and rapid progression was observed in the control group with a decrease in the eGFR at an annual rate of 12.7–25 mL/min/1.73 m^2. However, the annual rates of eGFR decrease are 2.7 mL/min/1.73 m^2 in patients with CKD stage G3 (30 mL/min/1.73 m^2 < eGFR < 60 mL/min/1.73 m^2) type 1 diabetes and 3.7 mL/min/1.73 m^2 in those with CKD stage G4 (15 mL/min/1.73 m^2 < eGFR < 30 mL/min/1.73 m^2) type 1 diabetes [48]. Studies that discuss extreme conditions in which the eGFR decreases at an annual rate of 12.7–25 mL/min/1.73 m^2 cannot be used as references for everyday practice. There are no rationales for low-protein diets with a protein intake of 0.8 g/kg, which was recommended by the KDIGO 2020. Moreover, no studies proving the effectiveness of low-protein diets for type 2 diabetes have been cited. Type 2 diabetes accounts for approximately 90% of all diabetes cases. Hence, studies cited in the KDIGO 2020 cannot be used as a rationale for recommending low-protein diets, regardless of whether the recommended amount of intake is 0.8 g/kg or 0.6 g/kg.

Table 4. Abstracts of two studies from the KDIGO 2020 that evaluated all-cause mortality.

First Author (Year Published)	Reference Number	Patients	Intervention	Comparison	Mortality	Cause of Death
Hansen (2002)	[39]	T1DM, AER > 300 mg/day, eGFR 68 ± 31 mL/min/1.73 m^2, $n = 82$	0.6 g/kg	Usual protein	○ 2/41 vs. 7/41	Heart failure, 4; myocardial infarction, 5
Koya (2009)	[40]	T2DM, proteinuria > 1 g/day, eGFR 62.3 ± 25.3 mL/min/1.73 m^2, $n = 112$	0.8 g/kg	1.2 g/kg	n.s. 1/56 vs. 1/56	Sepsis, 1; myocardial infarction, 1

TIDM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; AER, albumin excretion rate; KDIGO, Kidney Disease: Improving Global Outcomes. n.s., not significant. ○ indicates that intervention was statistically superior to control.

Table 5. Abstracts of nine studies from the KDIGO 2020 that evaluated the renal protective effect of protein restriction.

First Author (Year Published)	Reference Number	Patients	Intervention	Comparison	GFR Decline per Year in I	GFR Decline per Year in C	Statistical Significance between Groups
Zeller (1991)	[41]	T1DM, proteinuria > 500 mg/day, eGFR 47.4 ± 5.8 mL/min/1.73 m², n = 35	0.6 g/kg	Usual protein	−3.0	−12.7	○
Brouhard (1990)	[42]	T1DM, albuminuria >4 3.2 mg/day, eGFR 81.1 ± 31.5 mL/min/1.73 m², n = 15	0.6 g/kg	Usual protein	−18	−25	○
Ciavarella (1987)	[43]	T1DM, Proteinuria > 500 mg/day, CCr 100.6 ± 29.6 mL/min, n = 16	0.71 ± 0.12 g/kg	Normal protein (1.44 ± 0.12 g/kg)	39.6	−10.8	n.s.
Dullaart (1993)	[44]	T1DM without DKD, proteinuria < 500 mg/day, GFR > 90 mL/min/1.73 m², n = 30	0.79 ± 0.16 g/kg	Usual protein	−9	−5	n.s. (both groups showed significant reduction within group)
Dussol (2005)	[45]	T1DM and T2DM, Micro- or macroalbuminuria, GFR 80 ± 20 mL/min/1.73 m², n = 47 (T1DM, 10; T2DM, 37)	0.8 g/kg	Usual protein	−3.5	−2.5	n.s.
Hansen (2002)	[39]	T1DM, Albuminuria > 300 mg/day, eGFR 68 ± 31 mL/min/1.73 m², n = 82	0.6 g/kg	Usual protein	−3.8	−3.9	n.s.
Meloni (2002)	[46]	T1DM and T2DM, Nephropathy and HT, GFR 44.8 ± 5.7 mL/min/1.73 m², n = 69 (T1DM, 32; T2DM, 37)	0.6 g/kg	Usual protein	−6.15	−6.26	n.s.
Raal (1994)	[47]	T1DM, proteinuria dipstick positive, GFR 58 ± 23 mL/min/1.73 m², n = 22	0.8 g/kg	>1.6 g/kg	6	−16	n.a.

Ccr, creatinine clearance; TIDM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; DKD, diabetic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes, HT; hypertension, n.s.; not significant, n.a.; not available. ○ indicates that intervention was statistically superior to control.

3.3. Reviewing Randomized Clinical Trial Meta-Analyses

A meta-analysis provides the benefit of having a higher statistical power and a more robust point estimate than any individual study. Hence, the author searched PubMed using the following keywords: "diabetic kidney disease," "protein restriction," "randomized controlled trial," and "meta-analysis" (search equation is shown in the Appendix A). This search resulted in nine articles [49–57], from which the following were excluded: (1) one that only reported on non-diabetic CKD [50], and (2) another without a meta-analysis [51]. The results of the remaining seven meta-analyses are presented in Table 6. Among the seven studies, three stated that low-protein diets were statistically significantly effective in slowing eGFR decrease [49,54,57]. Of these three studies, two reported statistical heterogeneity. Extremely high heterogeneity was observed in studies by Nezu et al. [54] and Li et al. [57], with I^2 values of 92% and 89%, respectively. Generally, it is not determined whether overall effectiveness is observed when there is high heterogeneity ($I^2 > 75\%$). Thus, it is recommended that subgroup analysis be performed to examine the groups' effectiveness if high heterogeneity is observed. Nezu et al. [54] stated that effectiveness was observed in groups with high compliance. If so, it is necessary for researchers to develop a method of low-protein diet education to help patients maintain a high level of compliance. In fact, the meta-analysis by Nezu et al. [54] included four randomized comparative studies

that indicated the eGFR preservation effects of low-protein diets (studies reporting a shift toward favoring low-protein diets without overlapping the vertical line, indicating a mean difference of 0 in their forest plot). From these four studies, three [41,43,47] examined patients with type 1 diabetes in whom the rates of eGFR decrease were extremely high among those in the control groups (annual rates were as follows: -12.7 mL/min/1.73 m^2 relative to a baseline eGFR of 47.4 ± 5.8 mL/min/1.73 m^2 [41]; -25 mL/min/1.73 m^2 relative to a baseline Ccr of 100.6 ± 29.6 mL/min [43]; and -16 mL/min/1.73 m^2 relative to a baseline GFR of 58 mL/min/1.73 m^2 [47]). The remaining randomized comparative study of patients with type 2 diabetes [58] found that the GFR in patients with type 2 diabetes and macroalbuminuria who received normal-protein diets decreased from a baseline of 74.4 ± 31.4 mL/min/1.73 m^2 to 65.1 ± 25.5 mL/min/1.73 m^2 in four months. This can be translated to an extremely fast annual decrease of 27.9 mL/min/1.73 m^2. It is surprising that the GFR in the low-protein diet group increased from a baseline of 56.3 ± 29.0 mL/min/1.73 m^2 to 74.2 ± 40.4 mL/min/1.73 m^2 in four months [58]. These changes indicated that low-protein diets led to hyperfiltration. In addition, Li et al. [57] stated that a dietary protein intake of <0.8 g/kg was highly effective. However, this statement corresponded with only two studies [41,43]. As mentioned above, the two studies examined patients with type 1 diabetes, and the rates of eGFR decrease were extremely high in the control groups, as did those in the study of Nezu et al. [41,43,54]. The effectiveness of low-protein diets with a protein intake of 0.8 g/kg, recommended by the KDIGO 2020, could not be verified. Moreover, the hyperfiltration theory was completely rejected based on these data.

Among the seven studies, four stated that low-protein diets were statistically significantly effective in reducing proteinuria or the albumin excretion rate [49,53,56,57]. Of these, two studies that reported heterogeneity revealed extremely high heterogeneity (87.0% [56] and 90.0% [57]). That is, low-protein diets have not been proven to have unequivocal effects on reducing proteinuria or the albumin excretion rate.

Table 6. List of meta-analyses of randomized protein restriction studies for diabetic kidney disease.

First Author (Year Published)	Reference Number	Trial Number	Type of Diabetes	eGFR Decline Results	Heterogeneity	Proteinuria or the Albumin Excretion Rate Results	Heterogeneity	Conclusion of the Paper
Pedrini (1996)	[49]	5 (including 2 non-randomized study)	T1DM, n = 3 T2DM, n = 0 Mix, n = 0 Total n = 3	Significant reduction, RR = 0.56	n.a.	Significant reduction, RR = 0.56	n.a.	Protein restriction is effective for slowing the progression of DKD
Robertson (2007)	[52]	12 (including 3 non-randomized study)	T1DM n = 7, T2DM n = 2, Mix n = 0, Total n = 9	n.s. n.s. n.s. n.s.	not applicable	Not reported	Not reoprted	Protein restriction appears to slightly slow the progression of DKD
Pan (2008)	[53]	8	T1DM n = 4, T2DM n = 2, Mix n = 2, Total n = 8	n.s. n.s. n.s. n.s.	not applicable	n.a. n.a. n.a. significant reduction (SMD −0.69)	n.a.	Protein restriction is not associated with improvement of renal function
Nezu (2013)	[54]	13	T1DM n = 6, T2DM n = 5, Mix n = 2 Total n = 13	n.s. n.s. n.s. significant improvement 5.82 mL/min/1.73 m^2	I^2 = 92%	n.s.	not applicable	Protein restriction is significantly associated with improvement of diabetic nephropathy
Zhu (2018)	[55]	11	T1DM n = 5, T2DM n = 4, Mix n = 2, Total n = 11	n.s. n.s. n.s. n.s.	not applicable	n.s.	not applicable	Protein restriction is not significantly associated with improvement of renal function
Li (2019)	[56]	20 (including 11 for eGFR evaluation)	T1DM n = 5, T2DM n = 5, Mix n = 1, Total n = 11	n.a. n.a. n.a. n.s.	not applicable	n.a. n.a. n.a. significant reduction (SMD −0.62)	I^2 = 87.0%	No statistical difference was found in GFR between the two groups.
Li (2020)	[57]	9	T1DM n = 5, T2DM n = 2, Mix n = 2, Total n = 9	n.a. n.a. n.a. significant improvement 3.86 mL/min/1.73 m^2	I^2 = 89%	n.a. n.a. n.a. significant reduction (SMD −0.88)	I^2 = 90.0%	Dietary protein intake of < 0.8 g/kg was strongly associated with a slow decline in eGFR.

DKD, diabetic kidney disease; TIDM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; Mix, type 1 and type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; RR, relative risk; n.a., not available; n.s., not significant.

3.4. Considering the Safety of Low-Protein Diets

With the exclusion of studies consisting solely of rapid decliners, none of the abovementioned studies indicated the renal protective effects of low-protein diets. Moreover, Locatelli et al. [14] and Valazquez et al. [58] reported that the hyperfiltration theory was not valid in terms of protein intake. Several studies may indicate statistically significant differences. However, it is clear from a clinical perspective that the effectiveness of low-protein diets remains unproven. In fact, a case report found that patient education on low-carbohydrate and high-protein diets (a carbohydrate intake of 80–90 g/day with protein accounting for 30% of the total energy intake) helped protect renal function [59]. Furthermore, one randomized controlled study reported that a low-carbohydrate, high-protein diet with low-iron and polyphenol-rich foods improved renal and overall survival than a low-protein diet [60]. The author and my colleague have also previously reported that patient education on low-carbohydrate diet (with an average protein intake of 1.6 g/kg) helped maintain the rate of decrease in the eGFR at 2.3 mL/min/1.73 m^2 over the course of three years (a decrease of 0.8 mL/min/1.73 m^2 annually), which was equivalent to that in healthy adults [61]. Thus, clinicians should always take into consideration the overall renal status of patients prior to recommending diet restrictions without rigorous clinical validation. Additionally, it is surprising that Kalantar-Zadeh et al.'s study [1] and the KDIGO 2020 still recommend low-protein diets. Given that such diets are recommended before their effectiveness is thoroughly validated, it can be assumed that their safety has barely been validated.

In terms of low-protein diet safety, the KDIGO 2020 mentioned a critical issue. That is, the World Health Organization (WHO) recommended a daily protein intake of 0.8 g/kg for healthy people. The KDIGO's recommendation was based on the WHO's recommendation for protein intake for the general population. The WHO Technical Report 2007 [18] indicated a safe lower limit of protein intake at 0.83 g/kg, which was considered to satisfy the required amount of protein in 97.5% of a given group. It should be noted that the report did not recommend a protein intake of 0.8 g/kg. Indeed, a safe lower limit that satisfies the required amount in 97.5% of a given group is referred to as the "recommended dietary allowance (RDA)." However, the RDA should never be confused with the optimal recommended amount. The RDA indicates the minimum amount that limits the risk of deficiency. Hence, the author is wary of the possibility that the authors of the KDIGO 2020 were confused between the RDA and recommended amounts. Meanwhile, the WHO Technical Report did not mention any definitive figures for the safe upper limit. However, it is certainly safe to consume up to 1.66 g/kg of protein, which is twice the RDA amount. The report stated that caution was required with amounts 3–4 times greater than the RDA (2.49–3.32 g/kg), as it is not guaranteed that such amounts do not cause harm to health [18]. The KDIGO 2020 recommended that a protein intake of 0.8 g/kg be maintained for DKD patients. However, given that the KDIGO 2020 drew on recommendations by the WHO, it should assure the safety for a protein intake of up to 1.66 g/kg even for DKD patients. In addition, Kalantar-Zadeh et al. [1] recommended low-protein diets with a protein intake of <1.0 g/kg for diabetic patients without CKD. They also recommended a protein intake of 0.6–0.8 g/kg for those with an eGFR of <45 mL/min/1.73 m^2. Rather, Kalantar-Zadeh et al. [1] should indicate that the RDA for a group with an eGFR of <45 mL/min/1.73 m^2 is not 0.83 g/kg but 0.6 g/kg. The RDA refers to the minimum amount that helps a given group to avoid the risk of deficiency. Recommending low-protein diets without indicating that the RDA is reduced to 0.6 g/kg imposes a risk on patients. Furthermore, the benefits of low-protein diets and the protection of renal function by such diets were not assured. Certain researchers claimed the effectiveness of limiting phosphate loads through low-protein diets [62]. In contrast, Shinaberger et al. [63] warned against recommending low-protein diets that are aimed at reducing phosphate loads by suggesting that low-protein diets lead to increased mortality despite phosphate intake reduction [63]. Particularly, clinicians should be reminded that extremely low-protein diets may increase the risk of mortality [62,64].

Furthermore, Robertson et al. [52] reported that there was no data on the effects of low-protein diet on health-related quality of life and costs. Further study evaluating quality-adjusted life-years associated with low-protein diet is required prior to its recommendation.

4. Conclusions

The renal protective effects of low-protein diets are still unclear in diabetic patients with CKD. Moreover, some studies have reported that extremely low-protein diets may increase the risk of mortality. Thus, the author discourages the recommendation of low-protein diet to diabetic patients with CKD at any stage, until scientific evidence unequivocally proves its renal protective effects.

Those who recommend low-protein diets at levels less than the RDA may need to review their clinical practice by respecting the principle of medicine: "First, Do No Harm."

Appendix A

31 December 2020: ("diabetic kidney disease" [All Fields] OR "diabetic nephropathy" [All Fields]) AND ("protein restriction" [All Fields] OR "low protein" [All Fields]) AND ("random allocation" [MeSH Terms] OR ("random" [All Fields] AND "allocation" [All Fields]) OR "random allocation" [All Fields] OR "random" [All Fields] OR "randomization" [All Fields] OR "randomized" [All Fields] OR "randomisation" [All Fields] OR "randomisations" [All Fields] OR "randomise" [All Fields] OR "randomised" [All Fields] OR "randomising" [All Fields] OR "randomizations" [All Fields] OR "randomize" [All Fields] OR "randomizes" [All Fields] OR "randomizing" [All Fields] OR "randomness" [All Fields] OR "randoms" [All Fields] OR ("random allocation" [MeSH Terms] OR ("random" [All Fields] AND "allocation" [All Fields]) OR "random allocation" [All Fields] OR "random" [All Fields] OR "randomization" [All Fields] OR "randomized" [All Fields] OR "randomisation" [All Fields] OR "randomisations" [All Fields] OR "randomise" [All Fields] OR "randomised" [All Fields] OR "randomising" [All Fields] OR "randomizations" [All Fields] OR "randomize" [All Fields] OR "randomizes" [All Fields] OR "randomizing" [All Fields] OR "randomness" [All Fields] OR "randoms" [All Fields])) AND ("meta analysis") [Publication Type] OR "meta analysis as topic" [MeSH Terms] OR "meta analysis" [All Fields].

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