Diabetic Kidney Disease Protein Restriction

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Low-protein diets have been recommended as diet therapy for the management of chronic kidney disease. 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.

Keywords: protein restriction ; diabetic kidney disease ; eGFR

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.”

2. Effectiveness and Safety of Low-Protein Diets

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.

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.

Among the 18 studies [3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20], 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. [10] and Teplan et al. [12], who examined the renal protective effects of high-energy diets and supplements such as erythropoietin (EPO) and keto acids. Lindenau et al.'s study [8] 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 [21][22]. 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 m^2) or Ccr (mL/min) Decline per Year in I	GFR (mL/min/1.73 m^2) or Ccr (mL/min) Decline per Year in C	Statistical Significance between Groups
Rosman (1989)	[6]	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)	[7]	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)	[9]	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)	[4]	CKD 3–5, n = 456 non-DM	0.6 g	1.0 g	Ccr−1.8	Ccr−1.0	n.s.
Klahr (1994)	[3]	GFR 25–55 mL/min/1.73 m^2, n = 585 GFR 13–24 mL/min/1.73 m^2, 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)	[11]	GFR < 20, n = 50 non-DM	0.3 g + keto acid	0.65 g	−3.26	−2.89	n.s.
Prakash (2004)	[13]	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)	[15]	CKD 4–5, n = 53 non-DM	0.3 g + keto acids	0.6 g	−3.1	−4.9	n.a.
Cianciaruso (2009)	[16]	CKD 4–5, n = 423 12% was DKD	0.55 g	0.80 g	−2.28	−2.16	n.s.
Garneata (2016)	[20]	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.

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 [23]. 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.

Among the seven studies, four stated that low-protein diets were statistically significantly effective in reducing proteinuria or the albumin excretion rate [24][25][26][27]. Of these, two studies that reported heterogeneity revealed extremely high heterogeneity (87.0% [26] and 90.0% [27]). That is, low-protein diets have not been proven to have unequivocal effects on reducing proteinuria or the albumin excretion rate.

3. Considering the Safety of Low-Protein Diets

With the exclusion of studies consisting solely of rapid decliners, none of the above-mentioned studies indicated the renal protective effects of low-protein diets. Moreover, Locatelli et al. [4] and Valazquez et al. [28] 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 [29]. 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 [30]. Thus, clinicians should always take into consideration the overall renal status of patients prior to recommending diet restrictions without rigorous clinical validation.

Furthermore, Robertson et al. [31] 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.

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