



Latest Perspectives of Protein Restriction for Chronic Kidney Disease (CKD) and Diabetic Kidney Disease (DKD)

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Abstract

Various controversies in protein-restriction diet are found for chronic kidney disease (CKD) and diabetic kidney disease (DKD) for years. Historically, the Modification of Diet in Renal Disease (MDRD) study reported changes in eGFR in the 1990s. American Diabetes Association (ADA) guidelines in 2013 showed no effect on kidney function. In contrast, Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative (KDOQI) have still continued protein restriction theory even into the 2020s. The latest report in Jan 2024 showed this debate for pros and cons, suggesting a gradual shift of unnecessary restriction in the future associated with RAS-i and SGLT2-i.

Keywords: Protein-restriction diet; Chronic kidney disease (CKD); American Diabetes Association (ADA); Kidney Disease: Improving Global Outcomes (KDIGO); Japan Low Carbohydrate Diet Promotion Association (JLCDPA)

Commentary Article

Various discussions have been observed regarding protein restriction in dietary therapy for chronic kidney disease (CKD) or diabetic kidney disease (DKD) for years. In the latest report, impressive debate was found in the light of pros and cons for these matters. From historical and renal points of view, important data will be described in this article [1].

Historically, Addis proposed the hypothesis of the protective effect of a protein-restricted diet on CKD in 1948 [2]. Later, Brenner et al. explained the hypothesis that protein intake accelerates the progression of kidney disease [3]. Successively, the Modification of Diet in Renal Disease (MDRD) Study reported changes in eGFR in the 1990s [4]. Further, the Northern Italian Cooperate Study also showed changes in Ccr [5]. In the former, the rate of decline in eGFR in the protein-restricted diet group became slower following the initial drop. This appears to be similar to the action of SGLT2 inhibitors. On the other hand, this situation was not found in the latter.

After that, it has been believed that protein restriction for CKD is probably warranted. However, there were various debates regarding its effectiveness. In the 2000s, the American Diabetes Association (ADA) showed in 2013 guideline that protein-restricted diets have no effect on kidney function, cardiovascular disease, or blood glucose [6]. It also stated that DKD patients should consume the same amount of protein as the general population. This comment has been similarly followed in the guidelines as of 2019 [7]. These comments seem to be related to various debate of low carbohydrate diet (LCD), where authors et al. have been involved in LCD and CKD [8,9]. As the ADA accumulated evidence, it gradually changed its evaluation of CR and LCD. At the same time, discussions about carbohydrate content for diabetes and protein intake for kidney function progressed. From a recent case-control study (T2D & control, n=105 each), the top quartile of the LCD score showed a 71% lower risk of diabetic nephropathy (odds ratio 0.29) [10].

On the other hand, the Kidney Medical Association takes a different position. Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative

(KDOQI) have been discussing the protein restriction theory even into the 2020s [11]. KDIGO weakly recommends protein restriction of 0.8g/kg/day for CKD [12,13]. KDOQI presents a stronger restriction of 0.55 to 0.60g/kg/day [14]. As mentioned above, the current situation shows the discrepancy in the effectiveness of protein restriction for CKD. As for Japan, the Japanese Society of Nephrology (JSN) recommends a protein-restricted diet with moderate evidence (B) in the 2023 edition of the evidence-based CKD treatment guidelines.

The latest debate concerning protein-restricted diets for CKD was reported in January 2024 [1]. The outline included the debate on the pros and cons of a case study. There are several reasons for recommending a protein-restricted diet. a) KDOQI recommends 0.55-0.60 g/kg/day of protein restriction or a strong restriction diet of 0.28-0.43 g/kg/day with supplements such as essential amino acids for CKD (stage 3-5) [14]. Other guidelines also recommend restricted <0.8g/kg/day [15]. b) Previous studies showed that high-protein diets dilate afferent arterioles, leading to glomerular hyperfiltration and CKD progression. Conversely, lower protein intake contributes to reducing intraglomerular pressure and glomerular damage [15]. c) RAS inhibitors and SGLT2 inhibitors reduce glomerular hyperfiltration, and a protein-restricted diet is synchronized. This is consistent with data showing that low protein intake reduces the risk of progression to renal failure and all-cause mortality in CKD patients [16]. d) MDRD study verified the inhibition of CKD progression by a protein-restricted diet [4]. Comparing the two groups (1.3g vs 0.58g/kg/day), the latter seemed to show a lower rate of eGFR decline in the early stage. e) From three international clinical trial reports, protein-restricted diets seem to suppress end-stage renal disease and death [14]. f) Extremely protein-restricted vegetarian diets with supplements, were less likely to develop end-stage renal disease (ESRD) or cause a 50% decrease in GFR than normal diets [17]. g) Among patients on protein-restricted diets, there was no significant difference in the incidence of malnutrition between low-protein diets and regular diets [16].

On the other hand, important reasons for unnecessary protein restriction would be as follows. They are a) there are various theories for the clinical efficacy of protein-restricted diets in meta-analyses of randomized controlled trials (RCTs). The existence of bias cannot be ruled out, even if positive results can be obtained in small or methodologically questionable validity [18]. b) By the Cochrane review, protein-restricted diets had little effect on preventing in CKD patients without diabetes [19]. Extremely protein-restricted diets might slow the progression of renal failure, but it is important to examine adverse events and quality of life. c) Previous studies showing the effectiveness of protein-restricted diets seem to be old and differ from the current medical situation. Blood pressure control was not satisfactory, RAS inhibitors are rarely used, and SGLT2-i was not yet

introduced. For example, MDRD Study 1 indicated that ACE inhibitor use was 34% (normal diet group) and 54% (protein-restricted diet group) [4]. Therefore, clinical effects were not apparent under previous situations, associated with various biases. In fact, protein-restricted diets have been known to be extremely difficult to continue. Its adherence is very low, in which a study found a compliance rate of 15% [20]. d) Safety issues are important for daily lives. The World Health Organization (WHO) has set the recommended minimum amount as 0.83 g/kg/day [21]. e) When we consider a case of eGFR 35 mL/min/1.73 m² and assume the annual decline rate of eGFR (about 1 mL/min/1.73 m² per year), dialysis therapy will be not required for more than 20 years. Furthermore, there is solid evidence nowadays that RAS inhibitors and SGLT2 inhibitors can suppress the decline in eGFR. Consequently, the first matter to do would be to provide these meds properly.

A variety of discussions have continued for long around the world regarding protein restriction for CKD and DKD. In 2013, the ADA declared that protein restrictions were invalid. However, specialized kidney societies such as KDIGO and KDOQI have continued to recommend protein-restricted diets. Furthermore, the Japanese Society of Nephrology (JSN) has strongly recommended (level 1) the protein-restricted diet with moderate confidence (B) in both its 2018 and 2023 guidelines. In addition, some changes would be observed in the presentations of N Engl J Med. In 2017, Kalantar-Zadeh et al. found that a protein-restricted diet is effective in suppressing the progression of CKD [22]. In this report, the meaningful comments were described as follows: "It is possible, though not yet unequivocally proven, that nutritional interventions slow disease progression." Based on this perspective, new clinical studies have been expected to be conducted over the past seven years. However, such a clinical protocol and actual study seemed to be difficult. Recently, in 2024, Chang et al. presented the novel opinions of pros and cons [1]. It contributed to giving meaning to the effectiveness of protein-restricted diets as a reference for readers to judge. Thus, the first-class journal N Engl J Med even suggests the probable gradual shift in recognition that protein-restricted diets are not necessarily recommended at present and also future period.

In summary, there have been no effective drugs for CKD until now, and it may be important to discuss whether or not to restrict protein intake. Currently, RAS inhibitors and SGLT2 inhibitors exist as effective medical agents for CKD. For present and/or future CKD studies, can we set up the clinical research to verify clinical efficacy, associated with the situation where CKD patients are already provided RAS-i and SGLT2-i?.

Conflict of Interest

The authors declare no conflict of interest.

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