European Review for Medical and Pharmacological Sciences 2024; 28: 709-720

Efficacy and safety of keto-supplemented low-protein diet on nutritional status of peritoneal-dialysis patients: a systematic review and meta-analysis of randomized controlled trials

H.-W. ZHANG[1], S.-J. MA[2], Y.-D. YIN[3,4], M.-M. ZHAO[5]

[1]Health Outcomes Division, College of Pharmacy, University of Texas at Austin, Austin, TX, USA
[2]Institute of Basic Theory for Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, China
[3]Postdoctoral Research Station, China Academy of Chinese Medical Sciences, Beijing, China
[4]Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China
[5]Department of Nephrology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Abstract. – OBJECTIVE: The purpose of this meta-analysis is to evaluate the efficacy of a keto-supplemented low-protein diet (sLPD) in enhancing nutritional status among individuals undergoing peritoneal dialysis (PD) compared to a low-protein diet (LPD).

MATERIALS AND METHODS: Studies from PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Data were searched and reviewed up to January 2023. Randomized controlled trials (RCTs) were enrolled and analyzed using STATA MP 17. In this review, serum albumin (Alb), body mass index (BMI), and serum prealbumin (PA) were included for efficacy evaluation and serum calcium (CA) for safety evaluation. Potential heterogeneity was detected using subgroup analyses.

RESULTS: 7 RCTs were included. Compared with LPD, sLPD can improve the Alb [Weighted Mean Difference (WMD)=4.16; 95% CI: 2.50, 5.83; p<0.0001), BMI [WMD=1.35; 95% CI: 0.59, 2.11; p<0.0001] and PA [WMD=0.07; 95% CI: 0.04, 0.10; p<0.0001] level of patients undergoing PD. Subgroup analyses showed that, although Alb had no difference with LPD within 12 months of PD duration, sLPD treatment could improve the levels of Alb and PA regardless of PD duration or course of treatment. sLPD can improve the BMI of patients with a PD duration of more than 24 months, regardless of the duration of treatment.

CONCLUSIONS: A sLPD is an effective intervention for improving the nutritional status of PD patients. It is suggested that patients undergoing PD should initiate sLPD at the beginning of PD to ensure sufficient nutritional intake.

Key Words:
Keto-analogs, Low-protein diet, Nutritional status, Peritoneal dialysis, End-stage renal disease.

Introduction

Chronic kidney disease (CKD), marked by the progressive decline of kidney function, is one of the most important public health concerns in the world that is seeking effective interventions[1,2]. CKD exerts multifaceted harm on the electrolytes status and liver function while leading to a considerable elevation in renin levels[3]. Generally, an individual is diagnosed with End-Stage Renal Disease (ESRD) when their glomerular filtration rate (GFR)[4] falls below 15 mL/min/1.73 m^2. Peritoneal dialysis (PD), as one of the most commonly used treatments for ESRD, has gained widespread recognition and implementation worldwide. Enrolling patients who are grappling with chronic renal failure during PD can effectively enhance treatment satisfaction, extend life expectancy, and improve overall quality of life[5]. Some studies[6-8], however, suggested that PD may harm patients' nutritional status, including wasting protein energy, heightening serum leptin level, and loss of body mass, predisposing patients to malnutrition and an increased mortality rate. On the other hand, CKD patients are often recommended to restrict their protein intake to mitigate subse-

Corresponding Authors: Yundong Yin, Ph.D; e-mail: yyd0030@163.com;
Mingming Zhao, Ph.D; e-mail: XMingYX@163.com

quent kidney damage[9]. This conundrum brings up a debate regarding the feasibility of ensuring adequate nutritional intake for PD patients while preserving residual renal function (RRF).

Recent studies in the literature have investigated the potential of the keto-supplemented low-protein diet (sLPD) as an intervention to slow down the progression of renal function decline in order to confirm its eligibility in clinical practices. One meta-analysis[10] has discussed the effect of sLPD on ESRD patients, and a separate meta-analysis[11] by the same research group examined whether sLPD could delay the progression of CKD in stage 3-5 CKD patients. Both studies[10,11] demonstrated the efficacy of sLPD in alleviating renal function decline, yet neither investigation specifically focused on the impact of sLPD on nutritional status. For studies[12] that did focus on nutritional status, comparisons were usually made between sLPD and a placebo, suggesting that sLPD can delay CKD deterioration while not necessarily leading to malnutrition, as evidenced by measures such as albumin and cholesterol levels. Despite these promising findings, a consensus remains elusive regarding the feasibility of implementing sLPD as a dietary treatment regimen for ESRD patients undergoing PD. Therefore, the primary objective of this meta-analysis is to elucidate whether sLPD stands as a dominant nutritional treatment for PD patients in comparison to the conventional low-protein diet (LPD).

Moreover, according to previous studies[13], α-keto acid typically presents in the form of a calcium salt. Supplementing keto analogs (KA) to daily dietary regimes has been shown[14] to reduce serum phosphorus levels while also potentially elevating serum calcium (CA), leading to the possibility of symptomatic hypercalcemia. In clinical practices, hypocalcemia can be diagnosed when the level is below 2.25 mmol/L, whereas hypercalcemia can be diagnosed with a CA level exceeding 2.58 mmol/L[15]. Therefore, in this review, a CA level of 2.58 mmol/L was applied as a critical threshold for assessing the safety of the treatment approach.

Materials and Methods

Data Sources and Search Strategy

The literature search was conducted among five online databases: 1) PubMed, 2) EMBASE, 3) Cochrane Library, 4) China National Knowledge Infrastructure (CNKI), and 5) Wanfang Data, up to January 2023. The search strategy incorporated the use of Medical Subject Headings (MeSH) terms, associated free-text terms as provided by the National Center of Biotechnology Information (NCBI), and blurred search. The following keywords were searched: "low protein diet", "protein-restricted diet", "protein restriction", "LPD", "keto acid", "keto analog", "keto supplement", "oxoacid", "keto*", "peritoneal dialysis", "peritoneal dialyzes", "nutritional status", and "nutrition". The full search strategy can be found in **Supplementary Table I**.

Eligibility Criteria

Articles were selected and screened following the PICOS principle: (1) Patients: peritoneal-dialysis patients; (2) Intervention: sLPD and LPD; (3) Comparison: sLPD *vs.* LPD; (4) Outcomes: to ensure data consistency, we compiled nutritional indicators commonly used across different studies. Those indicators that were reported at least four times and had over 100 data observations were deemed as primary outcomes, including serum albumin (Alb), body mass index (BMI), and serum prealbumin (PA); (5) Study design: randomized controlled trials (RCTs). Exclusion criteria were applied as follows: (1) studies involving non-human subjects; (2) studies employing different or inappropriate interventions; (3) studies with duplicated data; (4) studies without full-text accessibility; (5) studies with invalid study type (review, conference abstract, etc.); (6) non-controlled trials; (7) studies with the length of follow-up less than six months.

Data Extraction and Management

All articles were extracted and reviewed by two independent reviewers (Hanwen Zhang and Sijia Ma). Any disagreement would be discussed with a third party (Mingming Zhao). The information extracted from each study included the first author's name, publication year, sample size, baseline characteristics of patients (including age and gender), treatment regime, PD duration, length of follow-up, and baseline data and outcome data of Alb, BMI, PA, and CA. For those clinical trials with missing data, missing information was tried to be obtained by contacting the authors. If data remained missing even after contact attempts, blanks were retained in the table. Following the instructions of the Cochrane Handbook for Systematic Review and Interventions[16], an assessment of methodological bias risk was conducted for each study. 7 criteria were evaluated for this assessment: (1) random sequence generation, (2) allocation concealment, (3) blinding of both participants and personnel, (4) blinding of

outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias.

Statistical Analysis

This meta-analysis was performed using STATA MP (version 17.0), generating all plots, statistical testing results, and estimates. Given that the included clinical indicators in this study were continuous and adjusted to the same unit, Weighted Mean Difference (WMD) was employed. The significance level α=0.05 and the 95% confidence intervals (95% CIs) were utilized for estimations and comparative analyses.

The choice between a random-effect model or a fixed-effect model for calculating the effect sizes of eligible studies was determined by the presence of heterogeneity. Heterogeneity among included studies was assessed through the Chi-square test alone when including 2 studies in comparison, and by both I^2 value and the Chi-square test when including more than 2 studies. According to the Cochrane Handbook for Systematic Reviews and Interventions, in the former scenario, a p-value lower than 0.05 indicated the presence of heterogeneity among studies. In the latter case, if $I^2 \geq 50\%$ and $p<0.05$ were observed, it signified substantial heterogeneity among the selected studies, whereas $I^2<50\%$ and $p>0.05$ indicated negligible heterogeneity16. The calculation of 95% CIs for I^2 followed the guideline established by Higgins and Thompson[17]. Once significant heterogeneity was noted, a random-effect model would be applied. For both fixed-effect and random-effects models, a z-test was conducted to evaluate the overall effect of the comparison.

A sensitivity analysis was performed to evaluate the robustness of the pooled results. Furthermore, multiple subgroup analyses were conducted to discover whether clinical heterogeneity within the collected studies yields divergence in intervention outcomes and to identify potential sources of heterogeneity. Begg's test and Egger's test were utilized to assess the presence of publication bias. We have registered the protocol for the present meta-analysis, with the PROSPERO registration ID number CRD42022361012.

Results

Characteristics and Quality of the Studies

As shown by Figure 1, a total of 54 studies (3 from PubMed, 6 from Embase, 7 from Cochrane Library, 17 from CNKI, and 21 from Wanfang) were identified from literature searching, of which 7 studies[13,18-23] were included in this meta-analysis. All of the studies were designed as RCTs and focused on comparing the effects of a sLPD regimen [daily protein intake (DPI): 0.6-0.8 g/kg/day + KA: 0.12 g/kg/day] against a LPD regimen (DPI: 0.6-0.8 g/kg/day). Specific baseline data of the selected 7 RCTs can be found in Table I. The sample sizes across these trials ranged from 20 to 50 participants. The mean age of the participants ranged from 47.7 to 70.2 years old, with the mean duration of PD spanning from 6 months to 39.18 months. Among these 7 studies, 3 studies[13,19,21] had a follow-up period of 6 months, while the remaining 4 studies[18,20,22,23] had a 12-month follow-up period.

The assessment of risk of bias is shown in Table II. Among the 7 studies[13,18-23] included in this review, 1 study[21] did not report the comprehensive baseline personal and health characteristics of the patients (age and duration of PD). There was one study[20] that did not calculate the mean age of the patients and did not provide baseline information with respect to each group. Additionally, there was another study[22] that had patients withdraw. When assessing risks, these studies were evaluated as "high risk of bias" in the corresponding norm. However, most of the studies included had good quality and a negligible amount of bias.

Efficacy of sLPD vs. LPD among PD patients

Serum albumin (Alb)

When conducting an analysis of the comparison between Alb levels in patients following sLPD and LPD, all 7 RCTs[13,18-23] were included in the synthesis of the data. A significant degree of heterogeneity in the data was observed (I^2=70.90%; 95% CI: 36.46-86.63; $p<0.0001$), so a random-effect model was employed to perform the comparative analysis. The results suggested that the Alb level of the sLPD group was 4.16 g/L (95% CI: 2.50-5.83; $p<0.0001$) higher than those in the LPD group. This finding suggests that, in comparison to LPD, the sLPD regimen appears to have a positive impact on improving the Alb levels in patients undergoing PD (Figure 2).

Body Mass Index (BMI)

4 studies[19,21-23] were included to assess the impact of sLPD *vs.* LPD on BMI levels. Given an insignificant degree of heterogeneity (I^2=0%; 95% CI: 0-46.36; p=0.98), a fixed-effect model was employed, and it suggested the sLPD cohort

Table I. Summary of the included studies and the baseline data.

Studies	N		Age		Intervention		PD Duration (month)		Follow-up (month)
	T (M:F)	C (M:F)	T	C	T	C	T	C	
Wang[18] 2021	35 (19:16)	35 (18:17)	70.16±5.20	70.21±5.23	LPD (0.8 g/kg/day) + KA (0.12 g/kg/day)	LPD (0.8 g/kg/day)	34.30±10.04	34.34±10.03	12
Hu et al[19], 2019	50 (25:25)	50 (28:22)	51.94±13.97	47.70±14.86	LPD (0.8 g/kg/day) + KA (0.12 g/kg/day)	LPD (0.8 g/kg/day)	39.18±15.21	34.08±14.34	6
Yang et al[13], 2017	30 (18:12)	30 (20:10)	54.90±6.50	54.30±6.20	LPD (0.8 g/kg/day) + KA (0.12 g/kg/day)	LPD (0.8 g/kg/day)	19.40±3.20	20.10±3.50	6
Guo and He[20], 2015	21	21	NR	NR	LPD (0.6-0.8 g/kg/day) + KA (0.12 g/kg/day)	LPD (0.6-0.8 g/kg/day)	18.90±5.20		12
Yuan[21], 2013	20	20	NR	NR	LPD (0.8 g/kg/day) + KA (0.12 g/kg/day)	LPD (0.8 g/kg/day)	NR	NR	6
Jiang et al[22], 2009	20 (11:9)	20 (7:13)	56.30±11.60	51.40±13.80	LPD (0.6-0.8 g/kg/day) + KA (0.12 g/kg/day)	LPD (0.6-0.8 g/kg/day)	10.60	6.00	12
Chen et al[23], 2008	31 (18:13)	26 (15:11)	67.20±12.50	64.10±10.70	LPD (0.8 g/kg/day) + KA (0.12 g/kg/day)	LPD (0.8 g/kg/day)	31.30±24.80	29.50±20.10	12

LPD: low-protein diet; KA: keto analogs; NR: Not reported.

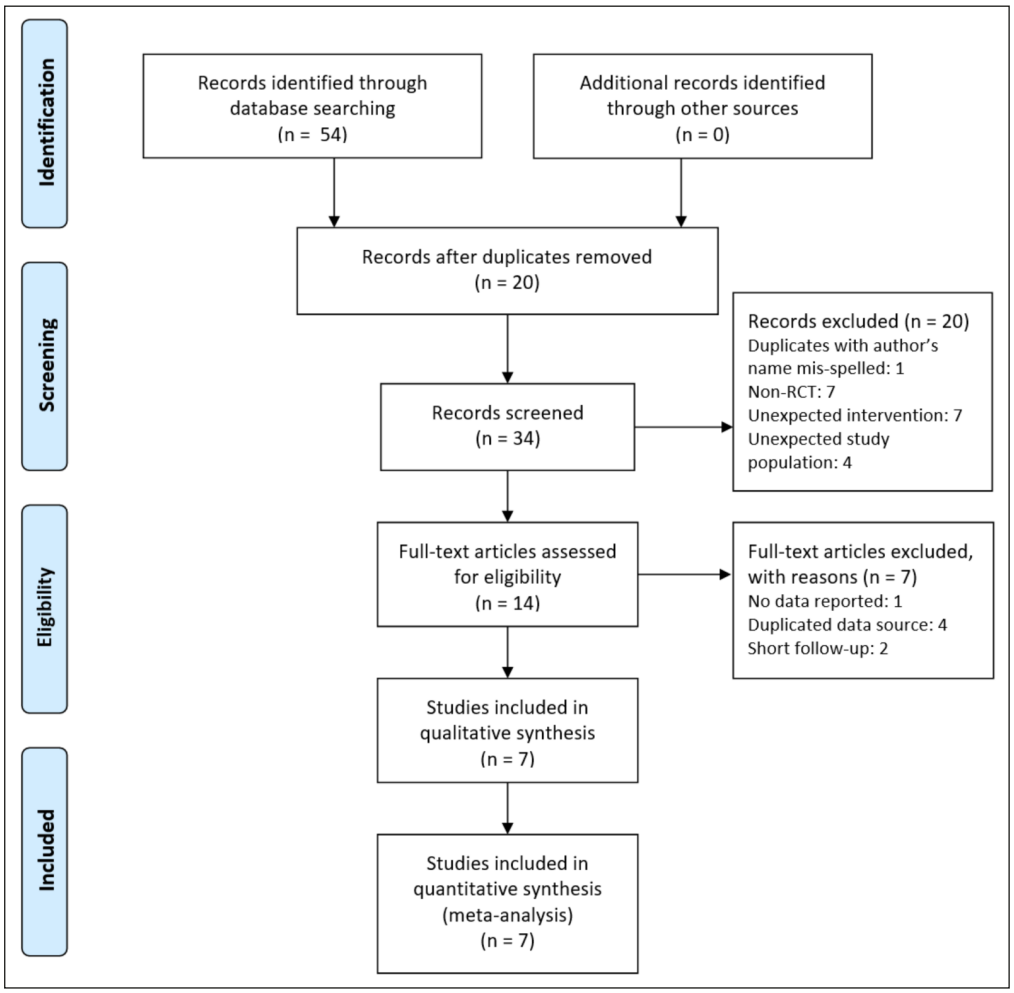

Figure 1. Flow diagram of searching for eligible studies.

Table II. Risk of bias summary.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Wang[18], 2021	+	+	+	+	+	+	+
Hu et al[19], 2019	+	+	+	+	+	+	+
Yang et al[13], 2017	+	+	+	+	+	+	+
Guo and He[20], 2015	+	?	+	+	-	?	?
Yuan[21], 2013	+	?	+	+	-	?	?
Jiang et al[22], 2009	+	+	+	+	+	+	-
Chen et al[23], 2008	+	+	?	?	+	+	+

"+": low risk of bias; "-": high risk of bias; "?": the level of bias could not be determined.

exhibiting a 1.35 kg/m^2 (95% CI: 0.59-2.11; p<0.0001) higher in BMI compared to the LPD cohort. This result suggests that sLPD offers a favorable improvement in BMI for individuals undergoing PD (Figure 3).

Serum Prealbumin (PA)

A total of 5 studies[13,18,19,21,23] was included in the comparison between sLPD and LPD on PA levels. To ensure consistency, we standardized the unit of measurement to g/L before conducting the analysis. The random-effect model (I^2=75.00%; 95% CI: 38.41-89.86; p=0.003) suggested a significant improvement of 0.07 g/L (95% CI: 0.04-0.10; p<0.0001) in PA levels among patients undergoing PD when utilizing sLPD in comparison to LPD (Figure 4).

Safety of sLPD vs. LPD Among PD Patients

Two studies[19,22] were included in the comparison between sLPD and LPD on the CA levels. A fixed-effect model was applied, given the insignificant heterogeneity between studies (χ^2=0.52; p=0.47). The results demonstrated that the sLPD intervention had a statistically significant effect of leveraging the CA levels by 0.21 mmol/L (95% CI: 0.14-0.28; p<0.0001) within the sLPD cohort when compared to the LPD cohort (Figure 5). However, this increase did not exceed 2.58 mmol/L, which means no evidence of hypercalcemia was observed.

Sensitivity Analysis

A sensitivity analysis was performed to evaluate the robustness and ensure the reliability of the present meta-analysis **(Supplementary Table II)**. Although there were minor fluctuations in the results when excluding studies by Guo and He[20] and Yuan[21], respectively, the overall stability of the individual studies remained strong. Therefore, these results reinforce the credibility and validity of our synthesized findings.

Subgroup Analysis

In the included literature, various authors employed distinct designs for their clinical trials, including differences in PD duration, length of follow-up, and the dosage of intervention administered to the enrolled patients. Only 2 of these studies[19,22] incorporated CA as one of their clinical indicators, and these 2 studies exhibited disparities across the aforementioned three conditions. Despite these variations, our analysis did not reveal any significant heterogeneity among the studies. Therefore, it is reasonable to postulate that the

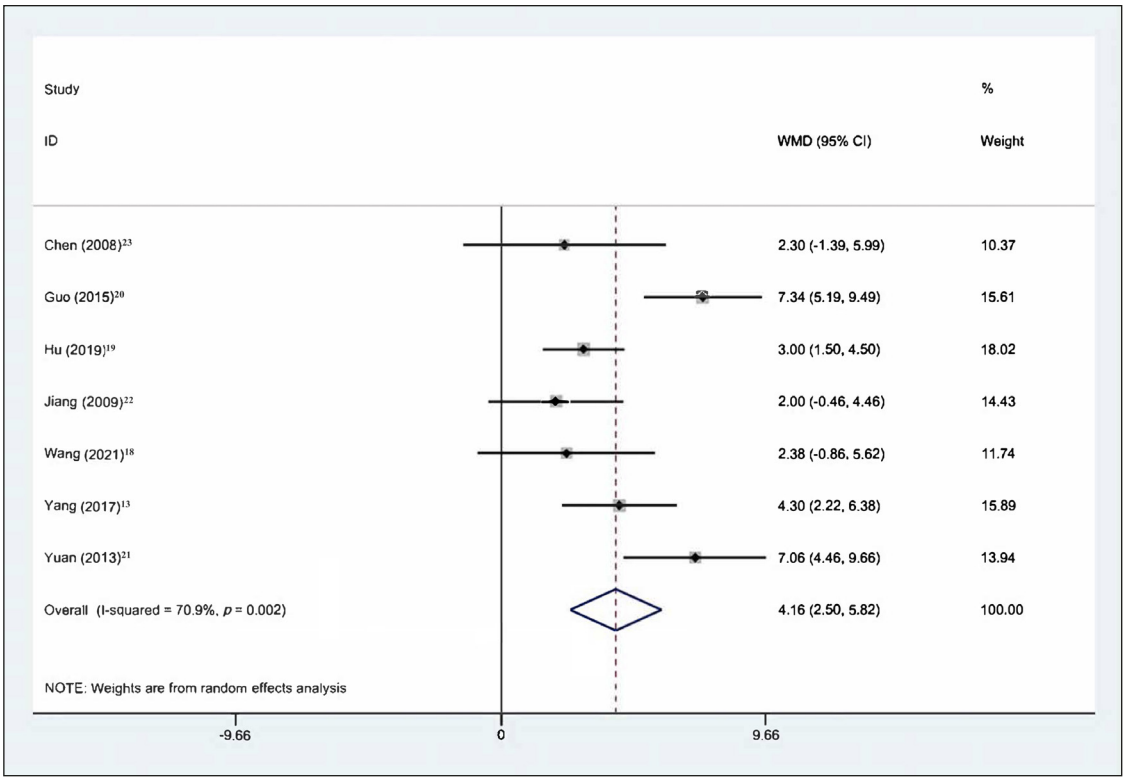

Figure 2. Comparison of effects of sLPD *vs.* LPD on Alb levels among PD patients.

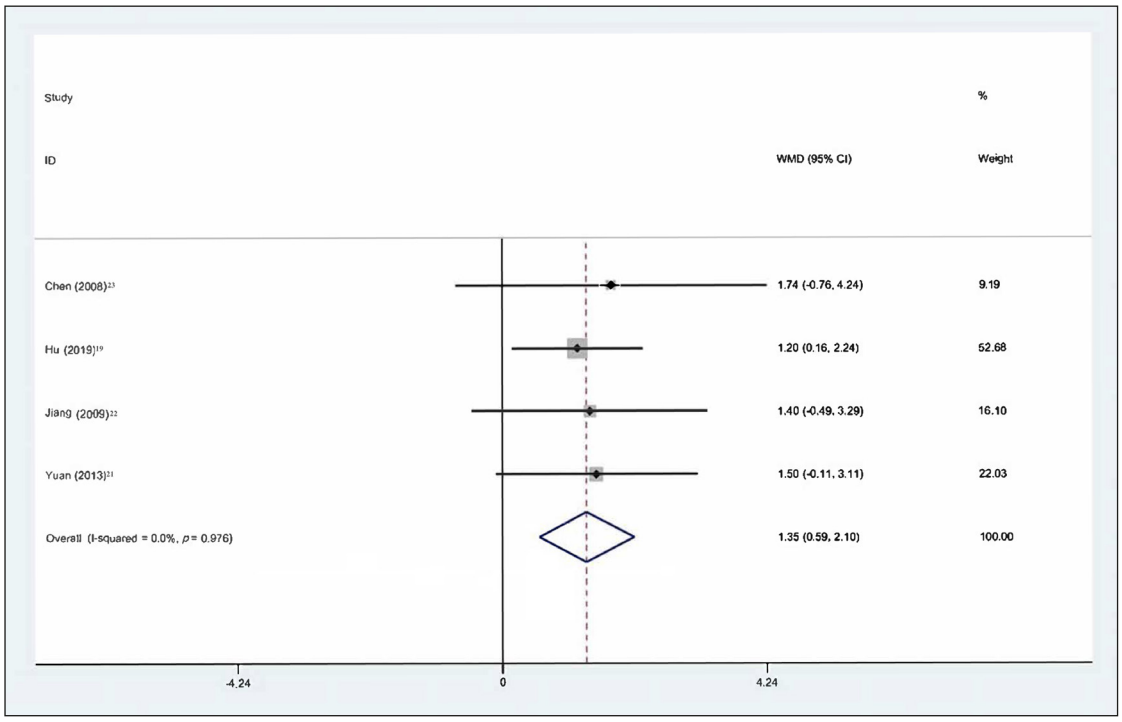

Figure 3. Comparison of effects of sLPD *vs.* LPD on BMI levels among PD patients.

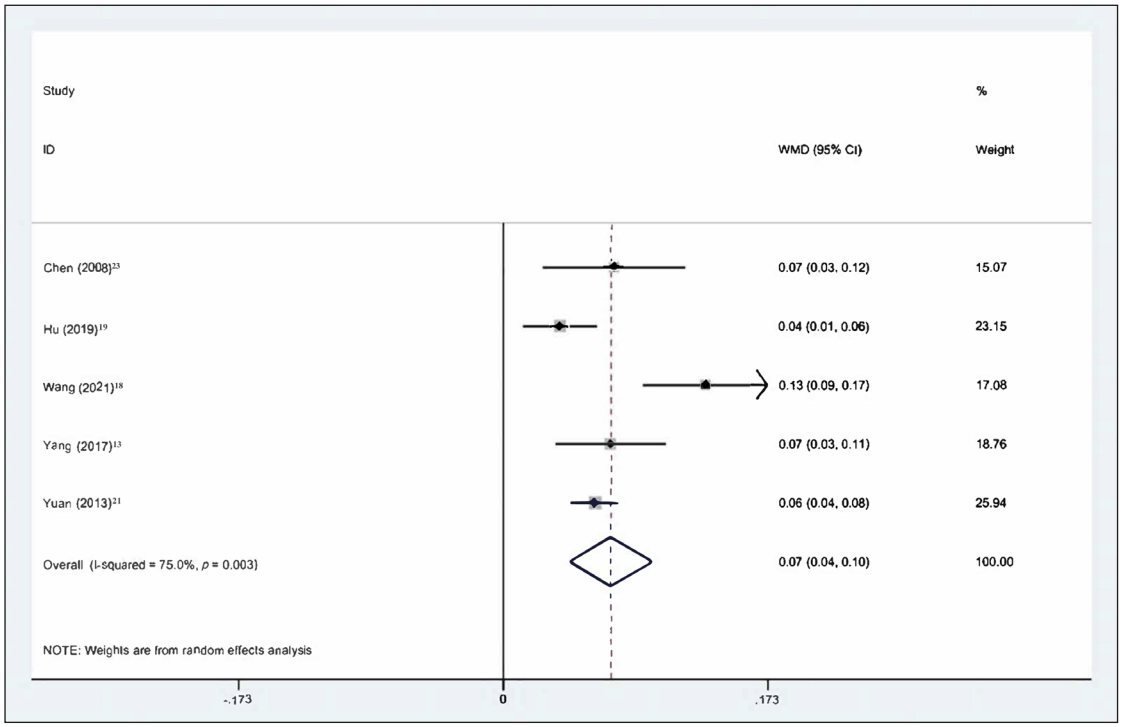

Figure 4. Comparison of effects of sLPD *vs.* LPD on PA levels among PD patients.

efficacy of sLPD on CA levels remains unaffected by differences in PD duration, length of follow-up, or intervention dosage. Based on the baseline analysis, subsequent analyses would focus on Alb, BMI, and PA, especially for Alb and PA, which were observed to have significant heterogeneity.

Graphs generated by subgroup analysis can be accessed in the supplementary materials. The first potential source of heterogeneity was the mean duration of PD. Dialysis treatment can consume nutrients in the body, leading to protein-energy wasting (PEW) and malnutrition. Patients undergoing longer-term PD often exhibit more severe symptoms, making it potentially more challenging for them to obtain sufficient protein from their diets. As a result, we hypothesized that the mean duration of PD could affect the levels of Alb when comparing the effects of sLPD and LPD. Yuan[21]'s study did not provide data on PD duration, making it impossible to determine which subgroup it should belong to. Therefore, we excluded this study from this part of the subgroup analysis. As the test was being conducted, we identified three subgroups based on mean PD duration: those with a mean PD duration of less than 12 months, those between 12 and 24 months, and those over 24 months. The length of follow-up was considered as the second potential source of heterogeneity. In the synthesized data, the length of follow-up was treated as a binary variable, with values of 12 months and 6 months. Additionally, although the majority of the included studies used LPD (0.8 g/kg/day) + KA (0.12 g/kg/day) and LPD (0.8 g/kg/day) as their intervention and control, respectively, studies conducted by Guo and He[20] and Jiang et al[22] employed LPD (0.6-0.8 g/kg/day) + KA (0.12 g/kg/day) and LPD (0.6-0.8 g/kg/day). Therefore, dosage of intervention was considered as the third source of heterogeneity to be examined.

We observed significant heterogeneity in Alb levels related to the duration of PD, both when discarding non-reported cases (p=0.004) and accounting for them (p=0.001). In the subgroup with patients undergoing more than 24 months of PD, the sLPD cohort demonstrated a 2.82 g/L (95% CI: 1.54-4.10) increase in Alb levels compared to the LPD cohort. This trend was consistent with the 2.00 g/L difference (95% CI: -0.64-4.46) observed in patients with less than 12 months of PD. However, the difference between sLPD and LPD observed in the subgroup with patients undergoing PD between 12 and 24 months is substantially shifted - the sLPD cohort demonstrated a 5.77 g/L (95% CI: 4.27-7.26) higher in Alb levels compared to the LPD cohort (**Supplementary Figures 1, 2**). The analysis also revealed a significant relationship between the heterogeneity of PA and the duration of PD when excluding (p=0.001) and including (p=0.003) non-reported cases (**Supplementary Figure 3, 4**). In the subgroup of patients with a PD duration of less than 12 months, the weighted mean difference between the sLPD group and the LPD group in the subgroup was 0.13 g/L (95% CI: 0.09-0.17). However, this value diverged from those observed in the subgroups of patients undergoing PD for more than 24 months and between 12

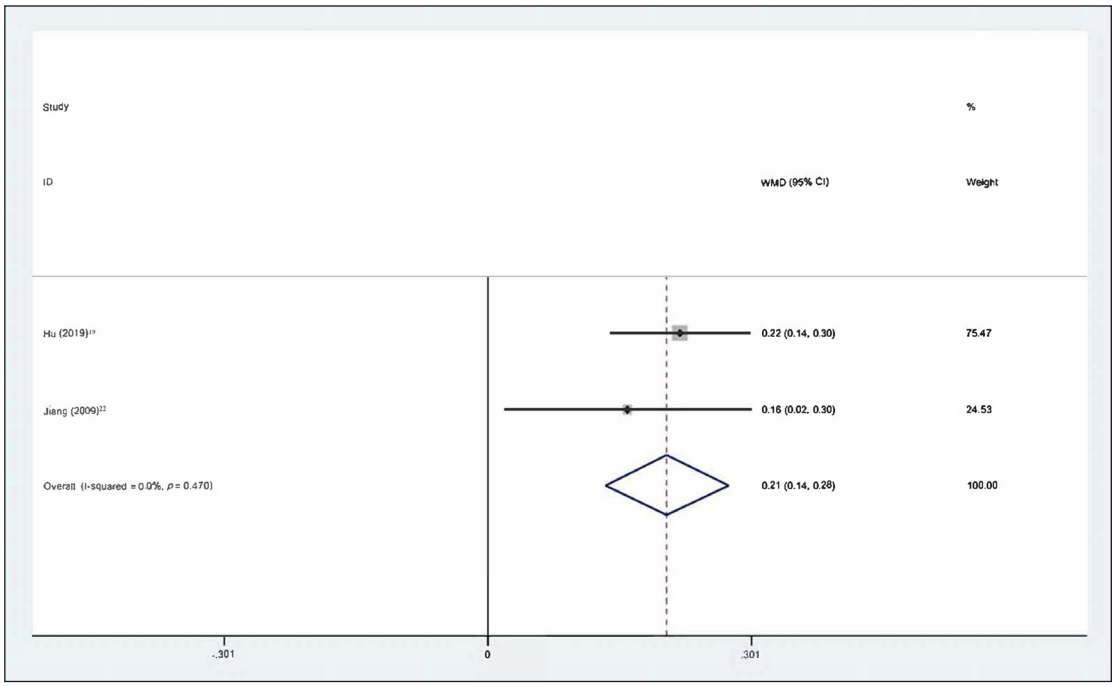

Figure 5. Comparison of effects of sLPD *vs.* LPD on CA levels among PD patients.

and 24 months, where the differences in PA levels between the sLPD and LPD groups were 0.04 g/L (95% CI: 0.02-0.07) and 0.07 g/L (95% CI: 0.03-0.11), respectively. Additionally, PA levels were also affected by the length of follow-up. During trials with a 6-month follow-up period, a comparison was made between the sLPD group and the LPD group regarding their PA levels. It was observed that the weighted mean difference between the two groups was 0.06 g/L (95% CI: 0.04-0.07). However, in the subgroup, including trials with a 12-month follow-up, a higher value was observed. The weighted mean difference between the sLPD group and LPD group regarding PA levels observed within that subgroup was 0.11 g/L (95% CI: 0.08-0.14) (**Supplementary Figure 5**).

Furthermore, Alb remained unaffected by both the length of follow-up (p=0.90) and the dosage of intervention (p=0.20) (**Supplementary Figures 6, 7**). When evaluating PA levels, all the included trials used LPD (0.8 g/kg/day) + KA (0.12 g/kg/day) and LPD (0.8 g/kg/day) as their intervention and control, respectively, but the effect of the dosage of the intervention on PA was not assessed. Additionally, we observed that BMI was not affected by either PD duration (p=0.97), the length of follow-up (p=0.79), or the dosage of intervention (p=0.95) (**Supplementary Figures 8, 9, 10**).

Publication Bias

Publication bias assessment was conducted using Egger's test, focusing on the primary nutritional outcomes from the selected trials. The findings indicate that there is no significant publication bias for Alb (p=0.11) and BMI (p=0.66). However, there is a susceptibility to publication bias observed for PA (p=0.05).

Discussion

The prevalence of CKD is gradually rising on a global scale. In the United States, it is estimated that approximately 15% of adults, equivalent to approximately 37 million individuals, are affected by CKD[24]. As advancements in dialysis technology continue to unfold, PD has emerged as a prominent choice for renal replacement therapy among individuals with ESRD[25,26]. Globally, it accounts for 11% of the dialysis population and is experiencing an annual growth rate of 7%[27].

PD operates on the principle of utilizing the peritoneum, a semi-permeable membrane within the abdominal cavity, to facilitate the exchange of solutes and water. This exchange occurs between the dialysate introduced into the abdomen and the plasma components in the capillaries on the other side of the peritoneum, involving processes such as diffusion and convection. Through this mechanism, excess bodily water, retained metabolites, and toxins are efficiently removed, ultimately achieving blood purification[28]. However, PD carries the risk of inducing malnutrition, specifically a condition known as PEW. PEW, in turn, substantially elevates the morbidity and mortality rates among patients. Among patients undergoing continuous ambulatory peritoneal dialysis (CAPD), PEW is prevalent, affecting approximately 80% to 85% of patients to varying degrees of protein-energy consumption[29]. Studies have shown that during daily PD sessions, patients can lose approximately 5 g to 15 g of protein through the peritoneal dialysate[27].

The gradual decline in immunity due to protein loss in the body raises the risk of infections during dialysis and contributes to higher mortality rates among PD patients[30,31]. Therefore, it is important to focus on preventing and addressing malnutrition resulting from PD, as it plays a vital role in enhancing both the efficacy of the treatment and the survival rates of PD patients[32]. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition[33] in CKD, dialysis patients are recommended to consume a DPI of 1.2-1.3 g/kg. However, due to structural and functional damage to the kidneys, dialysis patients often cannot meet this protein requirement. Numerous studies[34] have investigated the optimal DPI for dialysis patients. Dong et al[34] discovered that a DPI range of 0.73 g/kg/day to 0.94 g/kg/day is associated with favorable nutritional status among PD patients. Nonetheless, other research[35] has indicated that maintaining a stable nitrogen balance in dialysis patients occurs when DPI ≥1.0 g/kg/day. Therefore, the discussion shifts with an additional dimension, from "how to prevent and improve the nutritional status of PD patients" to the more nuanced question of "how to prevent and enhance the nutritional status of PD patients without overburdening renal function".

The compound α-keto acid contains a variety of essential amino acids for PD patients, such as leucine and histidine. Supplementation with keto acids has shown[36] promise in enhancing the amino acid profile and increasing protein synthesis among PD patients, thereby augmenting their nutritional levels. Therefore, this review focused on RCTs that compare sLPD with the

traditional LPD. All the included studies[13,18-23] have their participants selected from those who had undergone PD for a duration over 6 months, with an observation period extending beyond 6 months. Apart from differences in individual patient conditions, the only difference between the two groups was that, under the same DPI, the sLPD group administered an additional 0.12 g/kg/day of keto analogs as compared to the LPD group. 7 studies had been selected for this meta-analysis and the mean difference indicators such as Alb, BMI, and PA were analyzed. Our results suggest that sLPD can lead to improvements in Alb, BMI, and PA levels in PD patients. The combination of LPD with essential amino acids and keto analog supplementation appears to slow down the progression of CKD both in well-designed clinical trials and in real-world nephrology practice[37]. In animal studies[38], keto-analogs have demonstrated a protective effect on ischemia-reperfusion-induced renal injury and fibrosis by reducing inflammatory infiltration and apoptosis via inhibition of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. The sLPD has the potential to maintain a stable nutritional status among dialysis patients and provide additional beneficial effects[39]. Both LPD of 0.8 g/kg/day and LPD of 0.6-0.8 g/kg/day have proved to improve the nutritional status of PD patients. Further research is needed to determine whether a more aggressive protein intake restriction yields additional benefits.

The timing of the initiation of sLPD is an important problem to be considered in clinical practices. The results of the subgroup analysis have demonstrated that, although there was no significant difference in the Alb levels between sLPD and LPD within the first 12 months of PD, sLPD treatment consistently improves the Alb and PA levels regardless of the length of PD or the course of treatment. The sLPD can also improve the BMI of patients who have been undergoing PD for more than 24 months, regardless of the treatment duration. This suggests that initiating sLPD early in the course of PD is advisable to combat protein malnutrition effectively.

In terms of safety assessment, an analysis of changes in CA levels before and after treatment, as reported in two[19,22] of the 7 collected articles, indicated that sLPD did result in increased CA levels compared to LPD. However, this increase did not exceed 2.58 mmol/L, which means no evidence of hypercalcemia was observed. Therefore, sLPD can be considered a safe treatment in clinical practice.

Limitations

This review had some limitations that should be addressed for future improvements. First, this meta-analysis was based on a relatively small number of included studies. Only 7 groups of trials were included for data synthesis. 2 of these trials lacked complete baseline data, potentially increasing the risk of bias. In future reviews, as more such long-term, large-sample RCTs become available, we anticipate a broader range of data observations and more accurate results.

Moreover, it is important to acknowledge that the studies included in this review used different nutritional indicators to assess the nutritional status of PD patients. This review focused on the three indicators that were most commonly used among included studies, which were Alb, BMI, and PA. Unfortunately, due to the limited availability of data, we were unable to incorporate other indicators such as hemoglobin (Hb), mid-arm circumference (MAC), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC), transferrin (TRF), total cholesterol (TC), and triglycerides (TG) into our analysis. This limitation could compromise the comprehensiveness of the study since we could not reveal the difference between sLPD and LPD regarding their impacts on all possible clinical indicators related to malnutrition, and may miss out on valuable insights regarding the specific aspects that sLPD excels in improving compared to PD.

Similarly, the impact of sLPD on alleviating inflammation compared to LPD was not discussed due to the lack of relevant data. This comparison has been considered crucial. Studies[11] have shown that there is an interaction between malnutrition and inflammation among PD patients. Malnutrition can exacerbate the production of inflammatory factors, and the exacerbation of inflammation can, in turn, lead to a decline in nutritional levels. Therefore, the ability of sLPD to inhibit inflammatory factors by sLPD is essential for the nutritional well-being of patients.

Finally, the purpose of sLPD, incorporating keto acid into LPD, is to obtain enough amino acids required by a patient's body functions while preventing damage to kidney function from an excess of proteins. The ultimate goal of this treatment is to fill the gap in amino acid intake between LPD and a normal protein diet (NPD) with a DPI of 1.2 g/kg/day. The nutritional status of patients after sLPD treatment is expected to be equivalent to that of ordinary people with NPD. Therefore, it is essential to explore further whether sLPD can effectively assist PD patients in regaining nutrition levels considered

standard for the general population. In addition, the Global Leadership Initiative on Malnutrition (GLIM)[40] recently established diagnostic criteria for malnutrition based on phenotypic and etiologic criteria such as weight loss, BMI, reduced muscle mass, reduced food intake, and inflammation. We suggest future studies incorporating the criteria outlined in the GLIM guidelines to better understand the efficacy of sLPD in addressing malnutrition among PD patients.

Conclusions

In summary, based on the existing data from RCTs, it is evident that sLPD offers a more effective and safer intervention in enhancing the nutritional status of patients undergoing PD when compared to LPD. Specifically, sLPD has demonstrated significant improvements regarding multiple clinical indicators, including Alb, BMI, and PA. This approach combines the benefits of LPD in managing overall protein intake to prevent further kidney damage, while also supplementing with keto acids to provide essential amino acids required by the body. As a result, it can be concluded that this intervention holds significant clinical value.

Funding
This work was supported by the National Natural Science Foundation of China [grant number 81873300]; the Capital Health Research and Development of Special [grant number 2018-2-4173]; the Fundamental Research Funds for the Central Public Welfare Research Institutes [grant number ZZ11-023]; and the Beijing Municipal of Science and Technology Major Project [grant number Z191100006619063].

Authors' Contributions
Research idea and study design: HZ, MZ; data acquisition: HZ, SM; data analysis/interpretation: HZ, SM; statistical analysis: HZ, SM; supervision or mentorship: HZ, YY, MZ; revision: HZ, YY, MZ. All authors read and approved the final manuscript.

Conflict of Interest
The authors declare that there are no conflicts of interest.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

Data Availability
All data generated or analyzed during this study are included in this published article and its supplementary information files.

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