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SYSTEMATIC REVIEWS

Efficacy and safety of ketoanalogue supplementation combined with protein-restricted diets in advanced chronic kidney disease: a systematic review and meta-analysis

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Abstract

Background The benefits and harms of protein-restricted diets supplemented with ketoanalogues in patients with chronic kidney disease (CKD) remain uncertain. We aimed to evaluate the effects of ketoanalogues supplemented to protein-restricted diets in patients with advanced CKD.

Methods We conducted systematic literature searches of PubMed, Embase, Scopus, and Cochrane Library up to June 3, 2024. Randomized controlled trials comparing ketoanalogue supplementation with a low- or very low-protein diet versus a low-protein diet alone in stages 3–5 CKD patients were selected. Outcomes included glomerular filtration rate (GFR), end-stage kidney disease (ESKD), all-cause mortality, and blood levels of urea nitrogen, calcium, phosphorus, and albumin. Triceps skin fold, mid-arm muscle circumference, lean body mass, and subjective global assessment were also evaluated. The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42023465754).

Results A total of 16 trials comprising 1344 participants were identified, with a median follow-up of 13 months. Compared to a low-protein diet alone, ketoanalogues supplemented to a protein-restricted diet resulted in a significantly higher GFR, decreased levels of urea nitrogen and phosphorus, and increased levels of calcium. Furthermore, ketoanalogues combined with a protein-restricted diet showed a marginally lower risk of ESKD in participants without diabetes. No significant differences were observed in all-cause mortality, albumin, mid-arm muscle circumference, lean body mass, and subjective global assessment.

Conclusions For stages 3–5 CKD patients, ketoanalogues combined with a protein-restricted diet may help postpone initiation of dialysis, improve calcium-phosphate homeostasis, and slow GFR decline, while maintaining a similar nutritional status and survival. Larger, long-term studies are needed to confirm these potential benefits, especially in CKD patients with diabetes.

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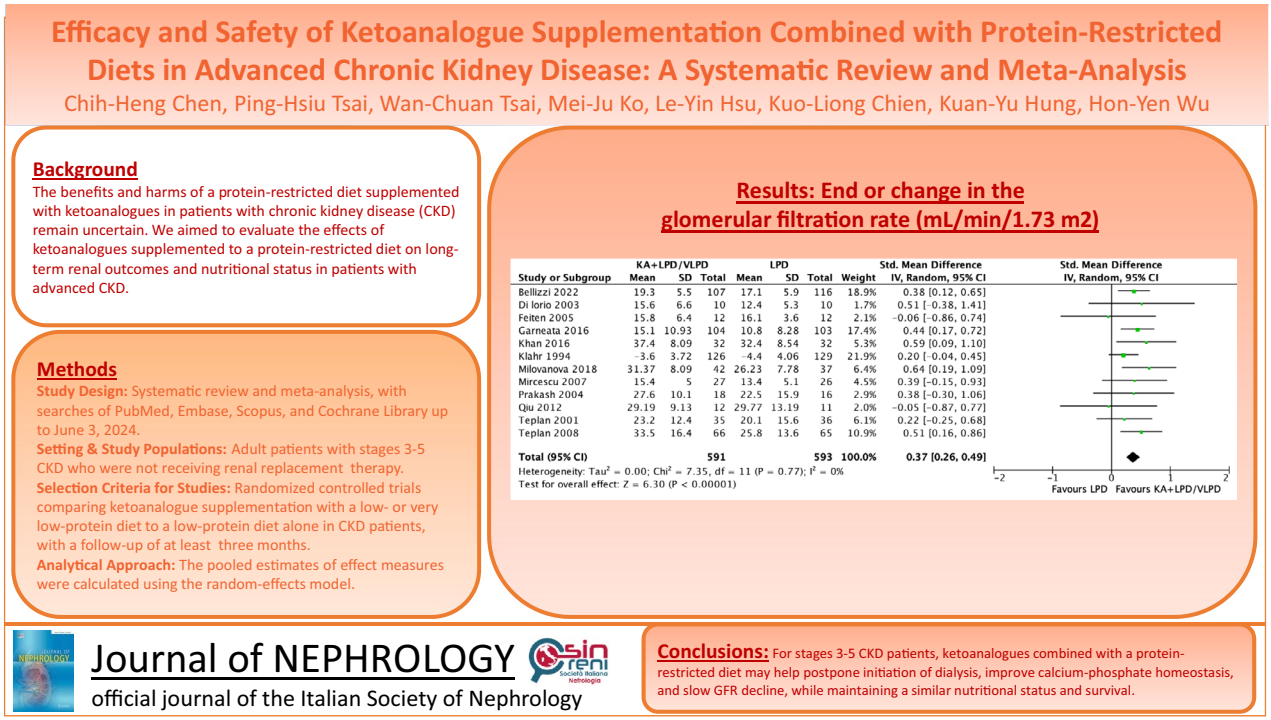
Graphical abstract



Keywords Diet, protein-restricted · Glomerular filtration rate · Ketoanalogues · Renal insufficiency, chronic

Introduction

Chronic kidney disease (CKD), which affects approximately 10% of the global population, is associated with higher risks of cardiovascular events, hospitalization, and mortality [1–5]. The optimal amount of dietary protein for patients with CKD is a topic of ongoing discussion. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend a low-protein diet providing 0.55–0.60 g protein/kg/day or a very low-protein diet providing 0.28–0.43 g protein/kg/day with additional ketoanalogues for CKD patients without diabetes, and a dietary protein intake of 0.6–0.8 g/kg/day for CKD patients with diabetes [6]. In contrast, the latest guidelines by Kidney Disease: Improving Global Outcomes (KDIGO) recommend a dietary protein intake of 0.8 g/kg/day for patients with stage 3–5 CKD, or a very low-protein diet (0.3–0.4 g/kg/day) supplemented with ketoanalogues (up to 0.6 g/kg/day) under close supervision [7].

Previous systematic reviews have shown that, compared to a protein-restricted diet alone, ketoanalogue supplementation combined with a protein-restricted diet could preserve the glomerular filtration rate (GFR) and improve CKD-mineral bone disorders in patients with CKD [8–10]. In a recent systematic review examining the impact of varying degrees of protein restriction among CKD patients without diabetes, a very low-protein diet was found to reduce the risk of end-stage kidney disease (ESKD) but not mortality, and the impact on protein-energy wasting remained uncertain due to limited data [11]. Another systematic review, which focused on patients with diabetic kidney disease, showed that ketoanalogue supplementation to a protein-restricted diet resulted in favorable effects on uremic burden and nutritional status, but outcomes regarding ESKD or mortality were inconclusive due to the scarcity of data [12]. While these systematic reviews assessed various renal and biochemical outcomes, concerns about protein-energy wasting in CKD patients on a very low-protein diet and whether ketoanalogue supplementation in a moderately protein-restricted diet improves long-term outcomes among patients with diabetic kidney disease remain to be determined. Additionally, most of these systematic reviews have incorporated crossover studies or non-randomized studies, and some have combined data from CKD patients with those of dialysis patients, potentially introducing more heterogeneity. The aim of this study was to provide an updated and comprehensive assessment of the effects of combining ketoanalogue supplementation with a protein-restricted diet on renal outcomes and nutritional status in patients with advanced CKD compared with the effects of a protein-restricted diet alone.

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Methods

Data sources and literature searches

We carried out electronic literature searches on databases including PubMed, Embase, Scopus, and the Cochrane Library from the earliest available date of indexing to June 3, 2024. The detailed protocol for the study and search strategies can be found in Supplementary Appendix 1. The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42023465754).

Study selection

We included parallel-design, randomized controlled trials (RCTs) that compared the effects of ketoanalogue supplementation to a low-protein diet or a very low-protein diet against a low-protein diet alone in patients with stages 3–5 CKD. RCTs with an in-trial follow-up duration of less than three months or those enrolling patients younger than 18 years or undergoing renal replacement therapy were excluded. Included studies had to report at least one of the following outcomes: GFR, ESKD, all-cause mortality, blood urea nitrogen (BUN), serum calcium, serum phosphorus, serum albumin, triceps skin fold, mid-arm muscle circumference, lean body mass, and subjective global assessment. Only studies published as full-length articles in peer-reviewed journals were considered eligible.

Data extraction and quality assessment

Two investigators (C-HC and P-HT) independently extracted relevant information from the included trials. The extracted data included study design, patient characteristics, intervention, and outcomes observed during the trial period. For studies that did not report standard deviations, we calculated or imputed the missing standard deviations following the *Cochrane Handbook for Systematic Reviews of Interventions* (Supplementary Appendix 2) [13]. Two investigators (C-HC and P-HT) independently evaluated the methodological quality of eligible trials by using version 2 of the Cochrane risk of bias tool for randomized trials [14]. The domains assessed included bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result [14]. Disagreements between the two investigators were resolved through discussion, and in cases where consensus could not be reached, a senior investigator (H-YW) was consulted to reach a consensus.

Outcomes

Comparing ketoanalogue supplementation to a low-protein diet or a very low-protein diet versus a low-protein diet alone, the primary outcome was the end or change in the GFR. When both the end and change in levels were available in an RCT, the end level was included in the meta-analysis. The secondary outcomes encompassed kidney-related measures, including ESKD, all-cause mortality, and follow-up BUN, serum calcium, and serum phosphorus. We also evaluated nutritional measures, including serum albumin, triceps skin fold, mid-arm muscle circumference, lean body mass, and undernourishment (defined by subjective global assessment category B or C), at follow-up. ESKD was defined as the need for long-term dialysis therapy or kidney transplantation.

Data synthesis and analysis

Categorical variables are reported as frequencies or percentages, while continuous variables are reported as the mean values, unless otherwise specified. The pooled estimates of effect measures and 95% confidence intervals (CIs) for comparisons between ketoanalogue supplementation to a low-protein diet or a very low-protein diet versus a low-protein diet alone were calculated using the DerSimonian and Laird random-effects model. Considering the variations in measurement scales and follow-up durations among the studies, effect sizes of continuous outcomes (end or change in the GFR, BUN, calcium, phosphorus, albumin, triceps skin fold, mid-arm muscle circumference, and lean body mass) were presented as standardized mean differences (SMDs) with 95% CI. SMDs of 0.2, 0.5, and 0.8 are considered to indicate small, moderate, and large effects, respectively [15, 16]. Effect sizes of binary outcomes (ESKD, all-cause mortality, and undernourishment) are presented as risk ratios (RRs) with 95% CIs.

Heterogeneity across studies was assessed using both the I^2 and Chi-squared test. I^2 values of 0%–40%, 30%–60%, 50%–90%, and 75%–100% may represent low, moderate, substantial, and considerable heterogeneity, respectively [13]. Nonreporting bias was evaluated using funnel plots, contour-enhanced funnel plots, and Egger's test for funnel plot asymmetry [17, 18]. Due to the variation in CKD patients' stages and etiologies across the included studies, subgroup analyses were conducted based on baseline renal function (GFR < 20 vs. ≥ 20 mL/min/1.73 m^2) and the presence of diabetes. In addition, subgroup analyses were performed based on the degree of protein restriction in the intervention group (ketoanalogue supplementation

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combined with a very low-protein diet vs. ketoanalogue supplementation combined with a low-protein diet). To evaluate the robustness of our meta-analyses, we performed sensitivity analyses by excluding studies with an in-trial follow-up duration of less than one year. Statistical significance was indicated by a two-sided P value of ≤ 0.05. Statistical analyses were performed using Review Manager (version 5.4, The Cochrane Collaboration, London, United Kingdom) and Stata (version 16, StataCorp LLC, College Station, TX, USA).

Results

Literature search

Figure 1 shows the process of the literature search. Initially, 1076 articles were retrieved, of which 523 were excluded due to duplicate publications. Subsequently, 376 articles were excluded based on titles, and 146 were excluded based on abstracts. After the full-text review of the remaining 22 articles, 16 articles met the inclusion criteria.

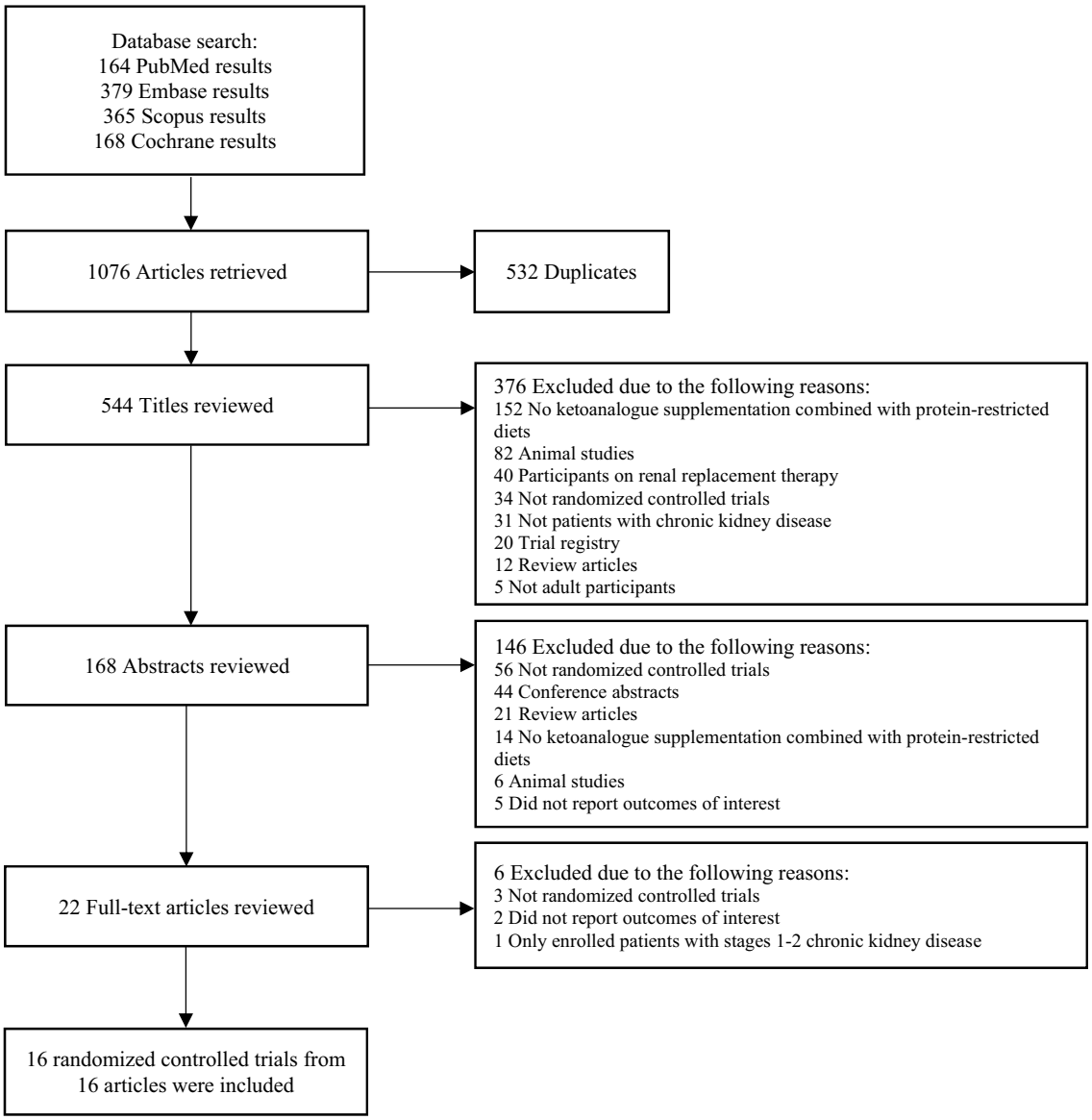

Fig. 1 Summary of study identification and selection

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Study characteristics and quality assessment

There were 16 eligible RCTs, with a total of 1344 participants. Table 1 provides a summary of the clinical and methodological characteristics of each study. Among the participants, the median age was 54 years old, and 60% were male. Six studies did not include patients with diabetes, while two studies specifically excluded patients without diabetes. The median baseline GFR across the included studies was 18.5 mL/min/1.73 m^2. Seven studies enrolled patients with stages 3–4 CKD, seven enrolled patients with stages 4–5, one enrolled patients with stages 3–5, and one enrolled patients with stage 4 CKD. In the intervention arm, eight studies evaluated ketoanalogue supplementation combined with a very low-protein diet, and seven assessed ketoanalogue supplementation combined with a low-protein diet. The median duration of in-trial follow-up was 13 months, with a range of 3 to 44 months. Most of the studies assessed dietary compliance using food diaries or urinary urea excretion. The only two studies that compared compliance rates between the intervention and control groups reported no significant difference [19, 20]. Supplementary Figs. 1 and 2 summarize the risk of bias for the included studies. The primary sources of potential bias include the absence of blinding and inadequate details about the randomization process.

Effects of ketoanalogue supplementation on renal and nutritional outcomes

Figures 2, 3 and 4 show the pooled estimates of the primary and secondary outcomes. Compared to a low-protein diet alone, ketoanalogue supplementation combined with a low-protein diet or a very low-protein diet resulted in a significantly higher GFR (SMD: 0.37; 95% CI 0.26, 0.49; $P<0.001$; Fig. 2A), decreased BUN (SMD: − 0.99; 95% CI − 1.43, − 0.56; $P<0.001$; Fig. 3A) and serum phosphorus (SMD: − 0.88; 95% CI − 1.19, − 0.56; $P<0.001$; Fig. 3C), as well as elevated serum calcium (SMD: 0.59; 95% CI 0.11, 1.07; $P=0.02$; Fig. 3B) and triceps skin fold (SMD: 0.25; 95% CI 0.04, 0.45; $P=0.02$; Fig. 4B). No significant differences were observed between the two groups in the outcomes of ESKD (RR: 0.79; 95% CI 0.56, 1.10; $P=0.16$; Fig. 2B), all-cause mortality (RR: 1.05; 95% CI 0.77, 1.41; $P=0.77$; Fig. 2C), serum albumin (SMD: 0.28; 95% CI − 0.05, 0.61; $P=0.10$; Fig. 4A), mid-arm muscle circumference (SMD: 0.10; 95% CI − 0.12, 0.32; $P=0.38$; Fig. 4C), lean body mass (SMD: − 0.11; 95% CI − 0.34, 0.12; $P=0.34$; Fig. 4D), and undernourishment (RR: 1.04; 95% CI 0.72, 1.50; $P=0.85$; Fig. 4E). Considerable heterogeneity was observed in the outcomes of BUN, serum calcium, and serum albumin, while the heterogeneity in other outcomes ranged from low to substantial levels. Supplementary Fig. 3 displays the results of funnel plots, contour-enhanced funnel plots, and Egger's tests for each outcome. Nonreporting bias was unlikely for all outcomes except BUN, as indicated by the asymmetry observed in the contour-enhanced funnel plot and the significant result from Egger's test for the BUN outcome (Supplementary Fig. 3D). For the BUN outcome, the study by Di Iorio et al. was unblinded, had the smallest number of participants, and reported a notably large reduction in BUN compared to other studies [21]. As a result, we conducted sensitivity analyses by omitting the Di Iorio et al. study from the BUN outcome; this led to a nonsignificant result in Egger's test ($P=0.52$) and better symmetry in the funnel plots (Supplementary Fig. 3D).

Subgroup analyses and sensitivity analyses

For most outcomes, no significant differences were observed between subgroups based on baseline GFR, presence of diabetes, or degree of protein restriction in the intervention group; furthermore, some subgroup analyses could not be conducted due to the lack of RCTs for certain outcomes in specific subgroups (Supplementary Figs. 4–6). Ketoanalogue supplementation significantly increased serum albumin in patients with a baseline GFR ≥ 20 mL/min/1.73 m^2 (SMD 0.52; 95% CI 0.20, 0.84; $P=0.001$) but not in those with a baseline GFR < 20 mL/min/1.73 m^2 (SMD, − 0.04; 95% CI − 0.41, 0.34; $P=0.85$), and this difference between the subgroups was statistically significant ($P=0.03$; Supplementary Fig. 4G). Ketoanalogue supplementation had a borderline significant effect in lowering the risk of developing ESKD for patients without diabetes (RR: 0.66; 95% CI 0.43 to 1.00; $P=0.05$), but there was no significant difference in effects between the subgroups with and without diabetes ($P=0.37$; Supplementary Fig. 5B). In the subgroup analyses by the degree of protein restriction (very low-protein diet or low-protein diet) in the intervention group, the addition of ketoanalogues to a low-protein diet resulted in a significant increase in serum albumin compared to a low-protein diet alone (SMD: 0.56; 95% CI 0.17, 0.96; $P=0.005$); however, the addition of ketoanalogues to a very low-protein diet did not result in a significant change in serum albumin (SMD: 0.06; 95% CI − 0.32, 0.45; $P=0.74$), and the difference between the subgroups approached statistical significance ($P=0.08$; Supplementary Fig. 6G). Although not significantly different between subgroups, we observed that the addition of ketoanalogues to a very low-protein diet resulted in a significant decrease in serum phosphate (SMD: − 0.93; 95% CI − 1.36, − 0.50; $P<0.001$) and a borderline significant increase in serum calcium (SMD: 0.64; 95% CI − 0.02, 1.29; $P=0.06$), with these changes being more prominent than the addition of ketoanalogues to a low-protein diet (Supplementary Fig. 6E and F). Five studies

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Table 1 Baseline characteristics of the included studies

Author (year)	Country	Total number	Age (years)	Male (%)	DM (%)	CKD stage	Baseline GFR (ml/min/1.73 m^2)	Intervention	Control	Assessment of dietary compliance	Follow-up (months)
Aghwana et al. [26] (2023)	Nigeria	60	47.5	60	10	3–5	NR	LPD (0.6 g/kg/d) + Nocid® (4 tablets/day)	LPD (0.6 g/kg/d)	NR	4
Bellizzi et al. [20] (2022)	Italy	223	63.8	61	35	4–5	17.7	VLPD (0.3 g/kg/d) + Ketosteril® (0.125 g/kg/d)	LPD (0.6 g/kg/d)	24-h urinary urea, 3-d food diary	36
Bernhard et al. [27] (2001)	France	12	44.3	83	NR	4	NR	LPD (0.71 g/kg/d) + Cetolog® (1 tablet/5 kg/d)	LPD (0.71 g/kg/d)	24-h urinary urea, 3-d food diary	3
Di lorio et al. [21] (2003)	Italy	20	54.5	60	30	4–5	16.4	VLPD (0.3 g/kg/d) + Alfa Kappa® (1 tablet/5 kg/d)	LPD (0.6 g/kg/d)	24-h urinary urea, food diary	24
Feiten et al. [28] (2005)	Brazil	24	46.8	63	0	4–5	17.3	VLPD (0.3 g/kg/d) + Ketosteril® (1 tablet/5 kg/d)	LPD (0.6 g/kg/d)	24-h urinary urea, 3-d food diary	4
Garneata et al. [19] (2016)	Romania	207	54.4	61	0	4–5	18.0	VLPD (0.3 g/kg/d) + Ketosteril® (1 tablet/5 kg/d)	LPD (0.6 g/kg/d)	Urinary urea, 3-d food diary	15
Khan et al. [29] (2016)	India	64	45	56	100	3–4	29.1	Conservative treatment + EAAs/KAs (1800 mg/d)	Conservative treatment	NR	3
Klahr et al. [25] (1994)	USA	255	50.8	59	5.1	4–5	18.5	VLPD (0.28 g/kg/d) + EAAs/KAs (0.28 g/kg/d)	LPD (0.58 g/kg/d)	Urinary urea, food diary	44
Malvy et al. [30] (1999)	France	50	54.9	58	0	4–5	14.4	VLPD (0.3 g/kg/d) + EAAs/KAs (0.17 g/kg/d)	LPD (0.65 g/kg/d)	Urinary urea	40
Milovanova et al. [31] (2018)	Russia	79	41.5	52	0	3B-4	35.0	LPD (0.6 g/kg/d) + EAAs/KAs (0.1 g/kg/d) or Ketosteril® (1 tablet/5 kg/d)	LPD (0.6 g/kg/d)	NR	14
Mircescu et al. [32] (2007)	Romania	53	54.3	61	0	4–5	17.0	VLPD (0.3 g/kg/d) + Ketosteril® (1 tablet/5 kg/d)	LPD (0.6 g/kg/d)	Urinary urea, 3-d food diary	12
Prakash et al. [33] (2004)	India	34	54.3	50	59	3–4	28.3	VLPD (0.3 g/kg/d) + Ketosteril® (1 tablet/5 kg/d)	LPD (0.6 g/kg/d)	3-d food diary	9

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Table 1 (continued)

Author (year)	Country	Total number	Age (years)	Male (%)	DM (%)	CKD stage	Baseline GFR (ml/min/1.73 m^2)	Intervention	Control	Assessment of dietary compliance	Follow-up (months)
Qiu et al. [34] (2012)	China	23	62.2	NR	100	3–4	33.9	LPD (0.6 g/kg/d) + Ketosteril® (1 tablet/5 kg/d)	Diabetic (0.8 g/kg/d)	3-d food diary	12
Teplan et al. [35] (2001)	Czech Republic	71	54.0	48	NR	3–4	26.2	LPD (0.6 g/kg/d) + rHuEPO (80U/kg/week) + Ketosteril® (0.1 g/kg/d)	Low (0.6 g/kg/d) + rHuEPO (80U/kg/week)	24-h urinary urea	36
Teplan et al. [36] (2008)	Czech Republic	111	52.0	49	34	3–4	32.8	LPD (0.6 g/kg/d) + Ketosteril® (0.1 g/kg/d)	LPD (0.6 g/kg/d)	NR	36
Zhang et al. [37] (2022)	China	58	55.3	67	0	3–4	NR	LPD (0.6 g/kg/d) + Ketosteril® (1 tablet/5 kg/d)	LPD (0.6 g/kg/d)	NR	12

CKD chronic kidney disease; *DM* diabetes mellitus; *EAAs* essential amino acids; *GFR* glomerular filtration rate; *KAs* ketoanalogues; *LPD* low-protein diet; *NR* not reported; *rHuEPO* recombinant human erythropoietin; *USA* United States of America; *VLPD* very low-protein diet

(31%) had an in-trial follow-up duration of less than one year. Sensitivity analyses that excluded these studies yielded results similar to the main analysis, except that the difference in triceps skin fold between the intervention and control arms was no longer significant (Supplementary Fig. 7).

Discussion

In this systematic review and meta-analysis of non-dialysis CKD patients who underwent protein-restricted diets, ketoanalogue supplementation was associated with a slower decline in the GFR over a median follow-up period of 13 months. Additionally, ketoanalogue supplementation improved the balance of calcium and phosphate without adversely affecting nutritional status or increasing the risk of dialysis or death. These findings were largely consistent in the sensitivity analyses of RCTs with a follow-up of more than one year and in subgroup analyses based on baseline GFR, presence of diabetes, or the degree of protein restriction. When ketoanalogues were added to protein-restricted diets, serum albumin levels improved in patients with a baseline GFR of ≥ 20 mL/min/1.73 m^2. In addition, ketoanalogue supplementation combined with protein-restricted diets showed a marginally significant effect in reducing the risk of developing ESKD in patients without diabetes.

Several systematic reviews have assessed the effects of ketoanalogue supplementation on renal function and various outcomes in patients with CKD. In a systematic review conducted by Jiang et al. which included seven RCTs and one non-randomized study, a protein-restricted diet supplemented with ketoanalogues delayed the deterioration of GFR and ameliorated hyperphosphatemia without causing malnutrition [8]. In a systematic review of ten RCTs and two non-randomized studies, Li et al. found that a protein-restricted diet combined with ketoanalogue supplementation not only slowed renal function decline—especially in patients with an estimated GFR > 18 mL/min/1.73 m^2—but also reduced serum phosphorus levels without affecting calcium and albumin levels in the overall meta-analysis [9]. Chewcharact et al. conducted a systematic review that included RCTs involving dialysis, late-stage CKD, and stages 1–2 CKD patients [10]. Their findings demonstrated that a protein-restricted diet supplemented with ketoanalogues could preserve the GFR and reduce serum phosphorus, while only a low-protein diet with ketoanalogue supplementation was effective in raising serum levels of albumin and calcium [10]. These systematic reviews primarily emphasized short-term outcomes and often combined non-randomized studies, crossover RCTs, and parallel RCTs, or pooled data from RCTs involving dialysis patients, early-stage CKD, and late-stage CKD patients. This could potentially affect the quality

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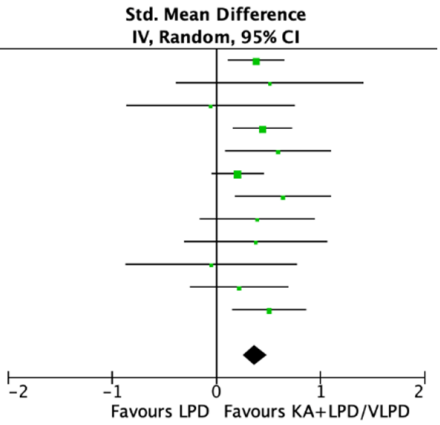
(A) End or change in the glomerular filtration rate (mL/min/1.73 m^2)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellizzi 2022	19.3	5.5	107	17.1	5.9	116	18.9%	0.38 [0.12, 0.65]
Di Iorio 2003	15.6	6.6	10	12.4	5.3	10	1.7%	0.51 [−0.38, 1.41]
Feiten 2005	15.8	6.4	12	16.1	3.6	12	2.1%	−0.06 [−0.86, 0.74]
Garneata 2016	15.1	10.93	104	10.8	8.28	103	17.4%	0.44 [0.17, 0.72]
Khan 2016	37.4	8.09	32	32.4	8.54	32	5.3%	0.59 [0.09, 1.10]
Klahr 1994	−3.6	3.72	126	−4.4	4.06	129	21.9%	0.20 [−0.04, 0.45]
Milovanova 2018	31.37	8.09	42	26.23	7.78	37	6.4%	0.64 [0.19, 1.09]
Mircescu 2007	15.4	5	27	13.4	5.1	26	4.5%	0.39 [−0.15, 0.93]
Prakash 2004	27.6	10.1	18	22.5	15.9	16	2.9%	0.38 [−0.30, 1.06]
Qiu 2012	29.19	9.13	12	29.77	13.19	11	2.0%	−0.05 [−0.87, 0.77]
Teplan 2001	23.2	12.4	35	20.1	15.6	36	6.1%	0.22 [−0.25, 0.68]
Teplan 2008	33.5	16.4	66	25.8	13.6	65	10.9%	0.51 [0.16, 0.86]
Total (95% CI)			**591**			**593**	**100.0%**	**0.37 [0.26, 0.49]**

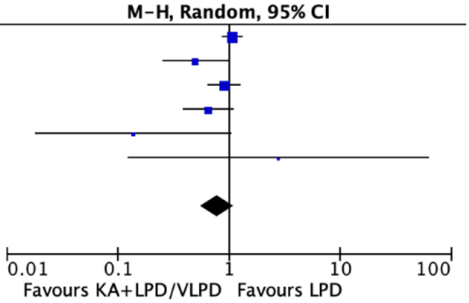
Heterogeneity: Tau^2 = 0.00; Chi^2 = 7.35, df = 11 (P = 0.77); I^2 = 0%
Test for overall effect: Z = 6.30 (P < 0.00001)



(B) End-stage kidney disease

Study or Subgroup	KA+LPD/VLPD Events	Total	LPD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bellizzi 2022	70	107	71	116	33.1%	1.07 [0.88, 1.31]
Garneata 2016	11	104	22	103	15.2%	0.50 [0.25, 0.97]
Klahr 1994	44	126	50	129	28.0%	0.90 [0.65, 1.24]
Malvy 1999	11	25	17	25	20.0%	0.65 [0.39, 1.09]
Mircescu 2007	1	27	7	26	2.6%	0.14 [0.02, 1.04]
Qiu 2012	1	12	0	11	1.2%	2.77 [0.12, 61.65]
Total (95% CI)		**401**		**410**	**100.0%**	**0.79 [0.56, 1.10]**
Total events	138		167			

Heterogeneity: Tau^2 = 0.08; Chi^2 = 12.01, df = 5 (P = 0.03); I^2 = 58%
Test for overall effect: Z = 1.39 (P = 0.16)



(C) All-cause mortality

Study or Subgroup	KA+LPD/VLPD Events	Total	LPD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bellizzi 2022	43	107	46	116	87.1%	1.01 [0.73, 1.40]
Garneata 2016	0	104	0	103		Not estimable
Klahr 1994	10	126	6	129	9.4%	1.71 [0.64, 4.56]
Malvy 1999	2	25	2	25	2.6%	1.00 [0.15, 6.55]
Mircescu 2007	0	27	2	26	1.0%	0.19 [0.01, 3.84]
Total (95% CI)		**389**		**399**	**100.0%**	**1.05 [0.77, 1.41]**
Total events	55		56			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.22, df = 3 (P = 0.53); I^2 = 0%
Test for overall effect: Z = 0.29 (P = 0.77)

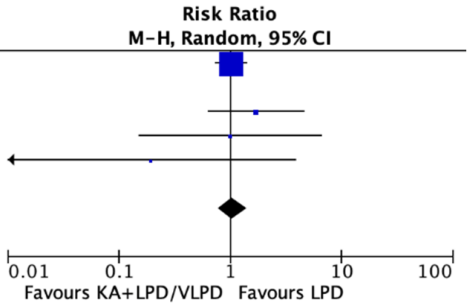


Fig. 2 Pooled estimates comparing ketoanalogue supplementation combined with a low-protein diet or very low-protein diet versus a low-protein diet alone on outcomes of **A** end or change in the glomerular filtration rate, **B** end-stage kidney disease, and **C** all-cause mortality. For study outcome (**A**), "Klahr 1994" reported the change in the glomerular filtration rate, and other studies reported the glomerular filtration rate at the end of follow-up. *CI* confidence interval; *IV* inverse variance; *KA + LPD/VLPD* ketoanalogue supplementation combined with a low-protein diet or very low-protein diet; *LPD* low-protein diet; *M–H* Mantel−Haenszel; *SD* standard deviation

of the evidence concerning the effects of ketoanalogue supplementation on protein-restricted diets in advanced CKD patients.

Consistent with the findings from previous systematic reviews, our study found that the addition of ketoanalogues to protein-restricted diets slowed the decline in the GFR, reduced BUN and serum phosphorus levels, and increased serum calcium levels. Ketoanalogues are synthesized as calcium salts, which not only raise serum calcium levels but also act as phosphate binders [22]. In our subgroup analysis, we noted that effects of ketoanalogue supplementation on serum phosphate and calcium were more pronounced in patients on a very low-protein diet than those on a low-protein diet, which may be attributed to the stricter phosphate

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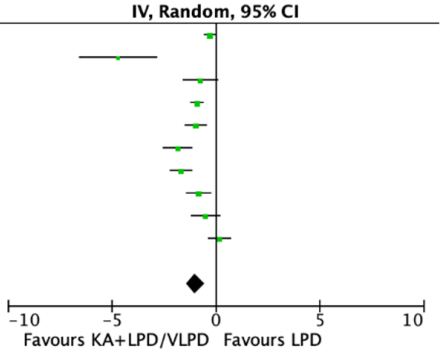
(A) Blood urea nitrogen (mg/dL)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellizzi 2022	49.5	16.3	107	55.5	21.5	116	12.3%	−0.31 [−0.58, −0.05]
Di Iorio 2003	42	8	10	84	9	10	3.9%	−4.72 [−6.58, −2.87]
Feiten 2005	43.6	14.9	12	56.8	18.2	12	8.8%	−0.77 [−1.60, 0.07]
Garneata 2016	56.9	15.8	104	105.5	73.7	103	12.2%	−0.91 [−1.20, −0.62]
Khan 2016	21.6	5.69	32	27.8	6.77	32	10.9%	−0.98 [−1.50, −0.46]
Malvy 1999	51.89	18.79	25	96.48	27.77	25	9.9%	−1.85 [−2.52, −1.18]
Milovanova 2018	23	3.1	42	35.3	10	37	10.9%	−1.69 [−2.21, −1.17]
Mircescu 2007	56.47	13.07	27	67.2	12.13	26	10.6%	−0.84 [−1.40, −0.27]
Prakash 2004	30.4	11.2	18	46.71	44.4	16	9.8%	−0.51 [−1.19, 0.18]
Zhang 2022	34.61	26.8	30	30.64	21.8	28	10.9%	0.16 [−0.36, 0.68]
Total (95% CI)			**407**			**405**	**100.0%**	**−0.99 [−1.43, −0.56]**

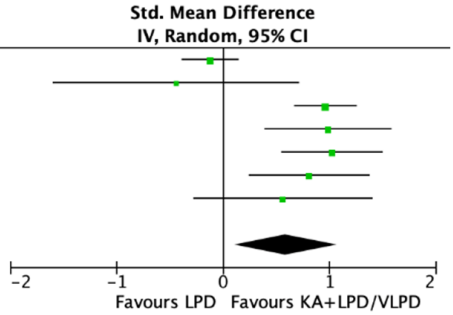
Heterogeneity: Tau² = 0.39; Chi² = 65.71, df = 9 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.45 (P < 0.00001)



(B) Serum calcium (mg/dL)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellizzi 2022	9.5	0.8	107	9.6	0.8	116	17.4%	−0.12 [−0.39, 0.14]
Bernhard 2001	9.1	0.2	6	9.38	0.8	6	8.9%	−0.44 [−1.60, 0.71]
Garneata 2016	8.8	1.04	104	7.8	1.04	103	17.2%	0.96 [0.67, 1.25]
Malvy 1999	9.7	0.68	25	9.02	0.68	25	14.4%	0.98 [0.39, 1.57]
Milovanova 2018	9.7	0.68	42	8.5	1.54	37	15.6%	1.02 [0.55, 1.49]
Mircescu 2007	8.8	1.4	27	7.8	1	26	14.7%	0.81 [0.25, 1.37]
Qiu 2012	11.9	7.98	12	8.54	0.56	11	11.8%	0.56 [−0.28, 1.40]
Total (95% CI)			**323**			**324**	**100.0%**	**0.59 [0.11, 1.07]**

Heterogeneity: Tau² = 0.32; Chi² = 42.39, df = 6 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.41 (P = 0.02)



(C) Serum phosphorus (mg/dL)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellizzi 2022	4	0.7	107	4.5	1.2	116	17.3%	−0.50 [−0.77, −0.24]
Bernhard 2001	3.87	0.84	6	4.06	0.5	6	5.6%	−0.25 [−1.39, 0.88]
Di Iorio 2003	3.2	0.3	10	4.1	0.5	10	5.6%	−2.09 [−3.23, −0.95]
Feiten 2005	4	1.1	12	4.6	1.4	12	8.6%	−0.46 [−1.27, 0.35]
Garneata 2016	4.4	0.52	104	6.2	1.81	103	16.7%	−1.35 [−1.65, −1.05]
Malvy 1999	4.3	0.93	25	5.57	2.01	25	11.9%	−0.80 [−1.38, −0.22]
Milovanova 2018	3.84	0.8	42	4.8	1.1	37	13.8%	−1.00 [−1.47, −0.53]
Mircescu 2007	4.5	1.7	27	6	1.9	26	12.2%	−0.82 [−1.38, −0.26]
Qiu 2012	3.68	0.15	12	4.12	0.84	11	8.2%	−0.72 [−1.57, 0.13]
Total (95% CI)			**345**			**346**	**100.0%**	**−0.88 [−1.19, −0.56]**

Heterogeneity: Tau² = 0.13; Chi² = 23.99, df = 8 (P = 0.002); I² = 67%
Test for overall effect: Z = 5.39 (P < 0.00001)

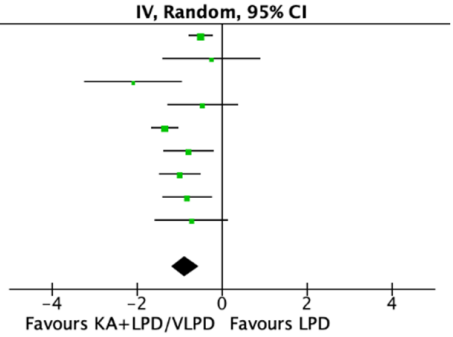


Fig. 3 Pooled estimates comparing ketoanalogue supplementation combined with a low-protein or very low-protein diet versus a low-protein diet alone on outcomes of **A** blood urea nitrogen, **B** serum calcium, and **C** serum phosphorus. *CI* confidence interval; *IV* inverse variance; *KA + LPD/VLPD* ketoanalogue supplementation combined with a low-protein diet or very low-protein diet; *LPD* low-protein diet; *M–H* Mantel−Haenszel; *SD* standard deviation

restriction in the very low-protein diet. Our study showed that the addition of ketoanalogues to protein-restricted diets resulted in an increase in triceps skin fold in the primary analyses and revealed an elevation in serum albumin levels in patients with a baseline GFR ≥ 20 mL/min/1.73 m^2. Among patients with advanced CKD, chronic metabolic acidosis and inflammation from comorbid diseases can influence albumin synthesis, resulting in hypoalbuminemia unrelated to dietary factors [23]. This may explain why ketoanalogue supplementation did not increase serum albumin in patients with a GFR < 20 mL/min/1.73 m^2. Furthermore, we evaluated the effects of ketoanalogue supplementation on long-term outcomes such as ESKD and all-cause mortality and conducted sensitivity analyses for RCTs with a

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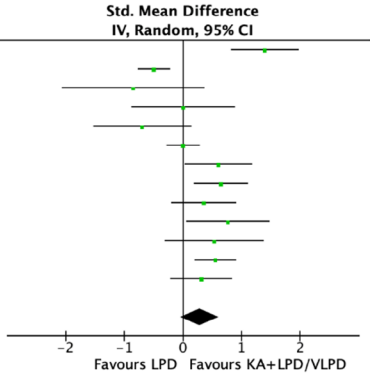
(A) Serum albumin (g/dL)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aghwana 2023	3.4	0.4	30	2.9	0.3	30	8.0%	1.40 [0.83, 1.96]
Bellizzi 2022	4.2	0.4	107	4.4	0.4	116	9.8%	−0.50 [−0.77, −0.23]
Bernhard 2001	4.03	0.46	6	4.45	0.45	6	4.3%	−0.85 [−2.06, 0.35]
Di Iorio 2003	4	0.2	10	4	0.2	10	6.0%	0.00 [−0.88, 0.88]
Feiten 2005	4.1	0.45	12	4.9	1.5	12	6.3%	−0.70 [−1.53, 0.13]
Garneata 2016	4.1	0.26	104	4.1	0.26	103	9.8%	0.00 [−0.27, 0.27]
Malvy 1999	4.37	0.38	25	4.15	0.34	25	8.0%	0.60 [0.03, 1.17]
Milovanova 2018	3.8	0.33	42	3.61	0.24	37	8.7%	0.65 [0.19, 1.10]
Mircescu 2007	4.2	0.6	27	4	0.5	26	8.1%	0.36 [−0.19, 0.90]
Prakash 2004	4.01	0.63	18	3.53	0.59	16	7.1%	0.77 [0.07, 1.47]
Qiu 2012	4.01	0.39	12	3.75	0.55	11	6.2%	0.53 [−0.31, 1.37]
Teplan 2008	3.42	0.65	66	3.12	0.4	65	9.4%	0.55 [0.20, 0.90]
Zhang 2022	4.24	0.44	30	4.1	0.45	28	8.3%	0.31 [−0.21, 0.83]
Total (95% CI)			**489**			**485**	**100.0%**	**0.28 [−0.05, 0.61]**

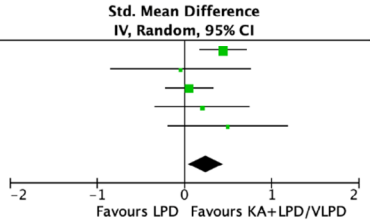
Heterogeneity: Tau² = 0.27; Chi² = 65.83, df = 12 (P < 0.00001); I² = 82%
Test for overall effect: Z = 1.67 (P = 0.10)



(B) Triceps skin fold (mm)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellizzi 2022	13.1	7.1	107	10.5	4.4	116	36.9%	0.44 [0.18, 0.71]
Feiten 2005	103.4	41.1	12	105.7	49.6	12	6.3%	−0.05 [−0.85, 0.75]
Garneata 2016	19.8	2.08	104	19.7	1.55	103	35.8%	0.05 [−0.22, 0.33]
Mircescu 2007	20.1	3	27	19.3	4.6	26	12.7%	0.20 [−0.34, 0.74]
Prakash 2004	28.3	7.2	18	24.8	6.5	16	8.3%	0.50 [−0.19, 1.18]
Total (95% CI)			**268**			**273**	**100.0%**	**0.25 [0.04, 0.45]**

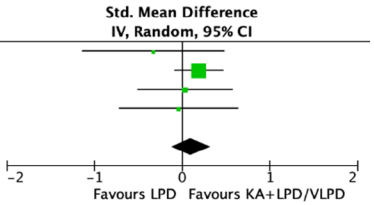
Heterogeneity: Tau² = 0.01; Chi² = 5.06, df = 4 (P = 0.28); I² = 21%
Test for overall effect: Z = 2.34 (P = 0.02)



(C) Mid-arm muscle circumference (cm)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Feiten 2005	93	11	12	96.2	7.4	12	7.5%	−0.33 [−1.14, 0.48]
Garneata 2016	23.1	1.82	104	22.8	1.29	103	65.1%	0.19 [−0.08, 0.46]
Mircescu 2007	23.1	2.5	27	23	4	26	16.7%	0.03 [−0.51, 0.57]
Prakash 2004	27.1	4.6	18	27.3	4.8	16	10.7%	−0.04 [−0.72, 0.63]
Total (95% CI)			**161**			**157**	**100.0%**	**0.10 [−0.12, 0.32]**

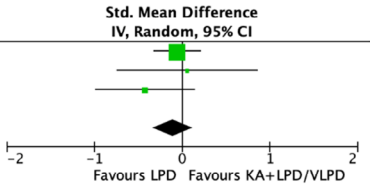
Heterogeneity: Tau² = 0.00; Chi² = 1.74, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)



(D) Lean body mass (kg)

Study or Subgroup	KA+LPD/VLPD Mean	SD	Total	LPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellizzi 2022	36.4	11.2	107	37	8.35	116	75.4%	−0.06 [−0.32, 0.20]
Feiten 2005	51.2	12.5	12	50.5	11.7	12	8.1%	0.06 [−0.74, 0.86]
Malvy 1999	22.3	5.1	25	25.3	8.4	25	16.5%	−0.42 [−0.99, 0.14]
Total (95% CI)			**144**			**153**	**100.0%**	**−0.11 [−0.34, 0.12]**

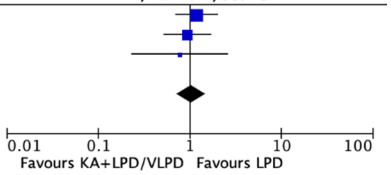
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)



(E) Undernourishment (subjective global assessment, category B or C)

Study or Subgroup	KA+LPD/VLPD Events	Total	LPD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bellizzi 2022	24	107	22	116	50.9%	1.18 [0.71, 1.98]
Garneata 2016	18	104	19	103	39.6%	0.94 [0.52, 1.68]
Mircescu 2007	4	27	5	26	9.4%	0.77 [0.23, 2.56]
Total (95% CI)		**238**		**245**	**100.0%**	**1.04 [0.72, 1.50]**
Total events	46		46			

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)



follow-up duration exceeding one year. Although the primary analyses suggest that ketoanalogue supplementation did not elevate the risk of developing ESKD or all-cause

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◂**Fig. 4** Pooled estimates comparing ketoanalogue supplementation combined with a low-protein diet or very low-protein diet versus a low-protein diet alone on outcomes of **A** serum albumin, **B** triceps skin fold, **C** mid-arm muscle circumference, **D** lean body mass, and **E** undernourishment. For study outcomes (**B**) and (**C**), "Feiten 2005" reported data in the unit of percent standard, based on the National Health and Nutrition Examination Survey (NHANES) percentile distribution tables derived by Frisancho (1981). *CI* confidence interval; *IV* inverse variance; *KA + LPD/VLPD* ketoanalogue supplementation combined with a low-protein diet or very low-protein diet; *LPD* low-protein diet; *M–H* Mantel−Haenszel; *SD* standard deviation

mortality, we observed a marginally lower risk of developing ESKD in the subgroup of non-diabetic CKD patients when their protein-restricted diet was supplemented with ketoanalogues.

In a systematic review incorporating RCTs and cohort studies of diabetic patients with CKD, Bellizi et al. reported that a protein-restricted diet supplemented with ketoanalogues significantly decreased BUN and increased serum albumin [12]. However, changes in GFR were not significant, and the risk of dialysis could not be synthesized due to the limited available data [12]. In our systematic review, seven RCTs enrolled CKD patients without diabetes, while two RCTs specifically enrolled those with diabetes. Owing to the limited number of trials including diabetic participants and the absence of data on many outcomes in those trials, the subgroup analyses did not reveal significant differences between participants with and without diabetes across all outcomes. Nevertheless, the subgroup of patients without diabetes showed similar findings to those of the main analyses across all outcomes. This not only strengthens the evidence supporting the efficacy of ketoanalogue supplementation in protein-restricted diets for the non-diabetic CKD population but also suggests that more RCTs are needed to evaluate its efficacy among CKD patients with diabetes.

There have been concerns regarding the long-term safety of a very low-protein diet in CKD patients, particularly in relation to potential malnutrition or muscle mass loss. Menon et al. reported the long-term follow-up of study B from the Modification of Diet in Renal Disease (MDRD) study [24]. This study compared a low protein diet (0.58 g/kg/day) to a very low-protein diet (0.28 g/kg/day) supplemented with ketoanalogues, focusing on individuals with a GFR between 13 and 24 mL/min/1.73 m^2, and examined the outcomes of ESKD or death [24, 25]. While no significant differences were observed between the two intervention groups during the in-trial period, the post-trial follow-up revealed that those assigned to a very low-protein diet combined with ketoanalogue supplementation had a higher risk of death than those in the low-protein diet group (hazard ratio [HR]: 1.92; 95% CI 1.15–3.20), but the increased risk was not observed for the composite outcome of ESKD and death (HR: 0.89; 95% CI 0.67, 1.18) [24]. The major limitation in Menon's report was the absence of information regarding dietary protein intake, nutritional measurements, and medical conditions during post-trial follow-up [24]. In a recent systematic review that compared a very low-protein diet with a low-protein diet or a normal-protein diet among non-diabetic patients with CKD, Hahn et al. reported that a very low-protein diet reduced the risk of developing ESKD (RR: 0.64; 95% CI 0.49–0.85) [11]. However, no significant differences were found in all-cause death (RR: 1.26; 95% CI 0.62–2.54) or changes in the GFR (SMD, 0.12; 95% CI − 0.27, 0.52) between the groups [11]. While the effects of a very low-protein diet were examined with supplemented ketoanalogues in most of the included studies, Hahn et al.'s systematic review also included information from studies assessing a very low-protein diet alone in the very low-protein diet treatment arm [11]. In our present study, outcomes remained mostly consistent across subgroups, regardless of the degree of protein restriction by very low-protein diet or low-protein diet. The subgroup that assessed ketoanalogue supplementation combined with a very low-protein diet observed no increase in mortality or prevalence of undernourishment, and no decrease in lean body mass and serum albumin, but showed a rise in triceps skin fold compared to a low-protein diet alone. Based on our analyses and other pertinent systematic reviews, current evidence supports the safety of ketoanalogue supplementation combined with a very low-protein diet in terms of nutritional status and survival.

Our study is by far the largest and the most up-to-date systematic review of the effects of ketoanalogue supplementation in non-dialysis patients with stages 3–5 CKD, incorporating data from 1344 patients across 16 RCTs. We followed a pre-specified protocol and utilized a comprehensive search strategy for this systematic review. All the included studies were parallel RCTs with a minimum follow-up duration of three months, ensuring the quality and homogeneity of the evidence incorporated in the systematic review. We evaluated a broad range of short-term and long-term outcomes from the in-trial period, including renal function, mineral and bone disorders, nutritional status, and kidney and overall survival, some of which were seldom addressed in previous systematic reviews. The robustness of our results is supported by consistent findings across a series of subgroup and sensitivity analyses.

There were several limitations in our study. First, the majority of the included RCTs were open-label, as the interventions involved changes in dietary content. While most trials confirmed dietary compliance through food diaries and urine collection for urea, potential biases arising from deviations from the intended intervention might still be present. Second, the etiology of CKD and the GFR range of participants varied across the included RCTs. Although we conducted subgroup analyses to explore potential differences

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between participants with and without diabetes or those with varying GFRs, the limited number of trials might have constrained the power of these subgroup analyses, leading to no significant differences between the subgroups. Third, dietary protein intake and ketoanalogue prescriptions varied among the studies, which might have contributed to heterogeneity in some of the outcomes, even after subgroup analyses. Further subgroup analyses or meta-regressions would be difficult due to the small study numbers. Fourth, the median follow-up duration of the RCTs included was 13 months, and only one-third had a follow-up period of three years or more. This could limit the power to detect differences in long-term outcomes such as ESKD or death. Although our analyses did show a significant effect in slowing the decline in the GFR with ketoanalogue supplementation, future trials with extended follow-up durations are needed to confirm the long-term effects of ketoanalogue supplementation on ESKD and mortality.

Conclusion

In patients with stages 3–5 CKD, the addition of ketoanalogues to a protein-restricted diet may help postpone the initiation of dialysis, improve the balance of calcium and phosphate, and slow the decline in the GFR, while maintaining a similar nutritional status and all-cause survival compared to a low-protein diet alone. Current evidence is still limited, and larger, long-term studies are needed to confirm these potential benefits, especially in CKD patients with diabetes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-024-02065-9.

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Author contributions Drs. Chen and Wu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: Chen, Tsai W–C, Wu. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Chen, Tsai P–H, Hsu, Wu. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Chen, Tsai P–H, Hsu, Wu. Acquisition of funding: Ko, Chien, Hung, Wu. Administrative, technical, or material support: Hsu, Chien, Hung, Wu. Supervision: Chien, Hung, Wu.

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Data availability All data generated or analyzed during this study are included in this article and its supplementary materials.

Declarations

Conflict of interest The authors declare that there are no competing interests.

Ethical approval Not applicable. This study was a systematic review and meta-analysis based exclusively on published data.

Research involving human participants and/or animals This study was a systematic review and meta-analysis based solely on published data and did not involve any new studies with human or animal subjects conducted by the authors.

Informed consent Not applicable. This study was a systematic review and meta-analysis based exclusively on published data.

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