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NEPHROLOGY - ORIGINAL PAPER

Effect of restricted protein diet supplemented with keto analogues in chronic kidney disease: a systematic review and meta-analysis

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Abstract
Background To evaluate the efficacy and safety of the restricted protein diet (low or very low protein diet) supplemented with keto analogues in the treatment of chronic kidney disease (CKD).
Methods The Cochrane library, PubMed, Embase, CBM and CENTRAL databases were searched and reviewed up to April 2015. Clinical trials were analyzed using RevMan 5.3 software.
Results Seven random control trials, one cross-over trial and one non-randomized concurrent control trial were selected and included in this study according to our inclusion and exclusion criteria. The changes of eGFR, BUN, Scr, albumin, PTH, triglyceride, cholesterol, calcium, phosphorus and nutrition indexes (BMI, lean body mass and mid-arm muscular circumference) before and after treatment were analyzed. The meta-analysis results indicated that, comparing with normal protein diet, low protein diet (LPD) or very low protein diet (vLPD) supplemented with keto analogues (s(v)LPD) could significantly prevent the deterioration of eGFR ($P < 0.001$), hyperparathyroidism ($P = 0.04$), hypertension ($P < 0.01$) and hyperphosphatemia ($P < 0.001$). No differences in BUN, Scr, Albumin, triglyceride, cholesterol, hemoglobin, calcium and nutrition indexes were observed between different protein intake groups.
Conclusion Restricted protein diet supplemented with keto analogues (s(v)LPD) could delay the progression of CKD effectively without causing malnutrition.

Keywords Restricted protein diet · Keto analogues · Chronic kidney disease · Meta-analysis · Systematic review

Introduction

Chronic kidney disease (CKD) is a slow and progressive loss of kidney function over a period of several years. The goal of CKD treatment is to prevent or slow further damage to kidneys. In addition to treatment of underlying diseases, such as diabetes, lupus or vasculitis, therapeutic life style change has already been reported to be helpful. Considering that protein intake is the main source of uremic toxins, change of diet style, especially the restriction of diet protein intake, is thought to be an important therapeutic measure for CKD patients. Therefore, low protein diet (LPD, 0.6–0.8 g/kg/day) and even very low protein diet (vLPD, 0.3–0.4 g/kg/day) were recommended to CKD patients. However, the potential malnutrition risk in patients with decreased food protein intake jeopardizes the clinical application of restricted protein diet in CKD patients. Keto analogues are precursors of essential amino acid, which could be transferred into amino acids by transaminase. During this reaction, NH_3 (main part of uremic toxin) would be consumed. Therefore, theoretically, restricted protein diet (LPD or vLPD) supplemented with keto analogues could decrease uremic toxin, relieve renal burden, prevent malnutrition and delay CKD progression [1, 2]. Although several clinical trials of LPD/

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vLPD supplemented with keto analogues (s(v)LPD) have been reported in CKD patients, no systematic review or meta-analysis have been published recently. Therefore, this study sought to evaluate the efficacy and safety of s(v) LPD in CKD patients in order to give more evidence for clinical choice of CKD patients.

Method

Search strategy

A literature search was performed in PubMed, Cochrane Library, China Biology Medicine (CBM) and Embase databases. PubMed (1966 to April 2015), Embase (1974 to April 2015), Central Register of Controlled Trials (1999 to April 2015), Cochrane Renal Group (1999 to January 2015) and CBM were searched for identification of relevant trials. The following search terms were used: ketoacid, α-ketoacid, keto analogue, CRF (chronic renal failure), CKD, low protein diet, very low protein diet, LPD, vLPD, sLPD and svLPD. Eligible interventions were also searched. We also hand-searched the bibliographies of articles for additional references. The results were limited to human studies with no restrictions on language.

Inclusion criteria and risk of bias

Articles were selected and subsequently screened based on the patient problem intervention comparison outcome (PICO) principle. Seven random controlled trials (RCTs) and one cross-over trial (COT) and one non-randomized concurrent control trial (NRCCT) were finally selected. Inclusion criteria were: (1) study subjects were adults predialysis CKD (stage 3–5) patients; (2) study subjects were treated with LPD/vLPD supplemented with keto analogues or free diet; (3) laboratory test indexes such as blood urea nitrogen (BUN), serum creatinine (Scr), estimated GFR (eGFR, measured using Cockroft's [3] or MDRD formula [4], isotope [5, 6], inulin or creatinine clearance rate [7, 8]), serum albumin (Alb), serum triglyceride (TG), cholesterol (CHO), calcium (Ca) and phosphorus (P), body mass index (BMI), lean body mass and mid-arm muscular circumference (MAC) were clearly reported; and (4) study subjects were followed up for at least 3 months. The exclusion criteria applied were as follow: (1) study subjects were child or animal; (2) old low-quality studies (before 1980); (3) studies without detailed observe indexes and (4) studies whose full texts are unavailable. Full texts of all potential articles were retrieved and reviewed independently by at least 2 investigators. Risk of bias tables recommended by Cochrane network was used to assess the risk of bias.

Data extraction and management

Two authors (Zheng Jiang and Xiaoyan Zhang) performed data extraction independently using standard data extraction forms, Dr Wei Qin was consulted whenever there was a discrepancy. For studies from which detailed data could not be extracted, the authors were contacted by emails. Basic information such as first author, year of publication, study design, inclusion criteria, study sample size, basic characteristics of study subject, intervention regimen, drug dosage, follow-up time, outcome data and adverse effects were recorded for each study included.

Statistical analysis

Review Manager 5.3 software was used to perform analysis. Risk ratios (RR) and 95 % CIs were used to express the results of dichotomous outcomes. Mean difference (MD) was used for results with continuous scales, and standardized mean difference (SMD) was used when different scales were used. Heterogeneity was analyzed using Cochran Q test (n − 1 *df*), with $P < 0.05$ denoting statistical significance and I^2 measuring the proportion of variation in efficacy estimates due to heterogeneity beyond chance. Random-effects analysis ($I^2 > 50$ %) and fixed-effects analysis ($I^2 < 50$ %) were used in meta-analysis according to the protocol. *Z* test was used to analyze the overall effect, with $P < 0.05$ denoting statistical significance. When *P* values are smaller than 0.001, we replace them with $P < 0.001$.

Study selection and Trial characteristics

We identified 2996 articles in the first search. Among them, after careful examination of the title and abstract, 2966 articles were excluded because of duplicate references, reviews, case reports, basic researches, non-controlled studies, systematic reviews and meta-analyses. Full texts of the remaining 30 articles were retrieved for further selection. An additional 21 articles were excluded: four studies included patients who were not CKD stage 3–5, nine low-quality studies, eight studies included patients on dialysis. Eventually, nine studies were included in this systematic review and meta-analysis [3–11]. The article search strategy used in our review is described in Fig. 1.

Characteristics of included studies are listed in Table 1. In the study reported by Vladimir [7], BMI > 30 kg/m^2 was also acquired as inclusion criterion. In Bellizzi's study [8] patients could decide their treatment group; therefore, it was not a strictly RCT. Though only 12 patients in Jacques's study meet all criteria of our study, we did not exclude it because it was a good designed RCT [11]. However, protein and keto analogues intake level differed from each study, which may affect heterogeneity of studies. Risk

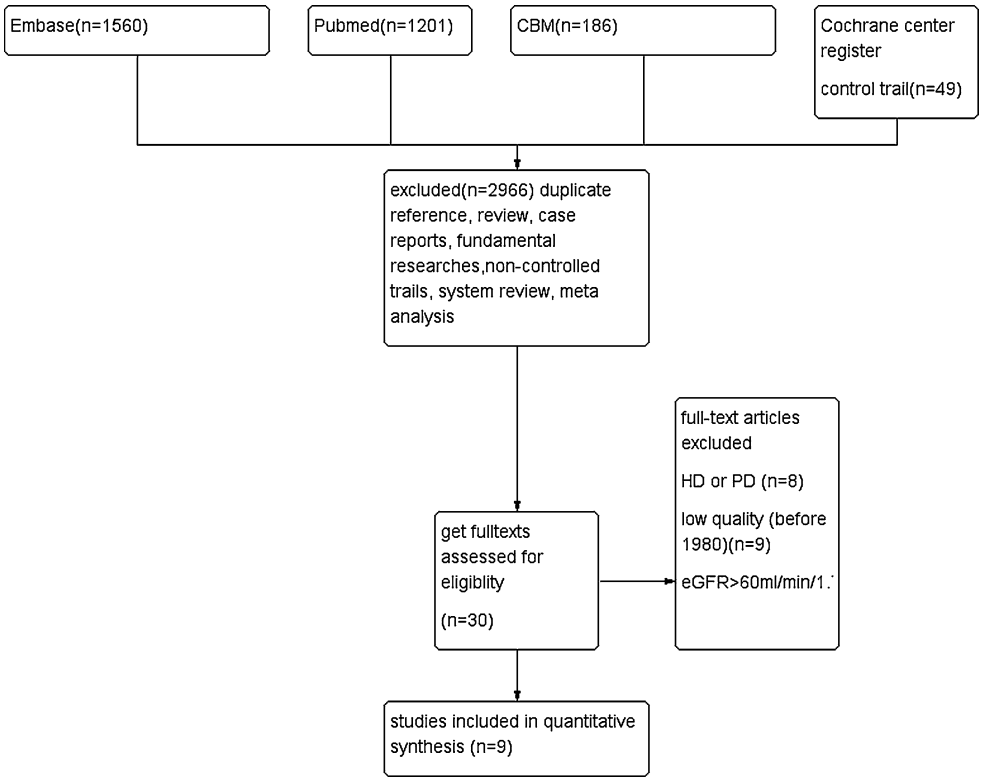

Fig. 1 Flow diagram of articles considered for inclusion

of bias assessment included was performed using a risk of bias table recommended by Cochrane (Table 2).

sLPD/sVLPD could slow the progression of CKD

In order to clarify the efficacy of restrict protein diet (sLPD/sVLPD) in preventing CKD progression, renal function indexes were analyzed. Comparison of eGFR between sLPD/sVLPD and regular food treatment group included 4RCTs + 1NRCCT. Meta-analysis was performed using fixed-effects models because tests for heterogeneity indicated $I^2 = 45$ %. The results suggested a significant effect of sLPD/sVLPD in protecting eGFR (MD −3.53, 95 % CI −5.24, −1.82, $P < 0.001$). Comparison of BUN included 3RCTs + 1NRCCT + 1COT. Random-effects models was used to compare BUN level in 3RCTs + 1NRCCT + 1COT because $I^2 = 97$ %. The results suggested no significance (MD −14.25, 95 % CI −28.79, −0.30, $P = 0.05$). Comparison of Scr included 3 RCTs + 1COT, and fixed-effects model was used because $I^2 = 0$ %. No significant difference was observed (MD −13.74, 95 % CI −70.02, 42.54, $P = 0.63$) (Fig. 2).

sLPD/sVLPD would not cause malnutrition in CKD patients

Although restricted protein diet could benefit the patients in delaying CKD progression, concerns about potential malnutrition risk hindered its clinical application. Therefore, nutritious factors were also analyzed in this study. Comparison of serum albumin level (Alb) between sLPD/sVLPD and regular food treatment group included 7RCTs + 1COT + 1NRCCT. Meta-analysis was performed using random-effects models because tests for heterogeneity indicated $I^2 = 80$ %. No significant difference between sLPD/sVLPD and control was observed (MD −0.95, 95 % CI −2.62, 0.73, $P = 0.27$). Comparison of cholesterol (CHOL), triglyceride (TG) and BMI included 5RCTs + 1COT + 1NRCCT, 3RCTs + 1NRCCT and 4RCTs, respectively. No difference was observed in meta-analysis. Analyses of lean body mass and mid-arm muscular circumference (MAC) were performed in 2 RCTs, which did not show significant difference (Fig. 3). Additionally, 1RCT reported no significant change in triceps skinfold and subjective global assessment (SGA) [4].

sLPD/sVLPD could ameliorate MBD in CKD patients

Comparison of serum phosphorus (P) level between sLPD/sVLPD and regular food treatment group included 5RCTs + 1COT. Meta-analysis indicated significant lower serum phosphorus level in sLPD/sVLPD group (MD −0.20, 95 % CI −0.29, −0.11, $P < 0.001$). Comparison of serum calcium (Ca) level included 3RCTs + 1COT. No significant difference was observed (MD 0.07, 95 % CI −0.06, 0.20, $P = 0.28$). Comparison of serum PTH level

Table 1 Characteristics of the studies included

References	Country	Number		Age		Treatment regime		Follow-up (m)	CKD stage	eGFR	Result
		T(F/M)	C(F/M)	T	C	T	C				
Bellizzi et al. [8]	Italy	30	23	58.0 ± 16.1	56.3 ± 15.6	VLPD (0.55 ± 0.11 g/kg/d) + KA (1pill/5 kg/d)	FD	6 M	4–5	<25	P
Malvy et al. [3]	France	25 (14/11)	25 (15/10)	53.6 ± 11.0	56.0 ± 14.0	VLPD (0.3 g/kd/d) + KA (0.17 g/kg/d)	Reg	3 M	4–5	<20	P
Feiten et al. [10]	Brazil	12 (5/7)	12 (4/8)	49.7 ± 11.3	43.9 ± 16.3	VLPD (0.3 g/kd/d) + KA (1pill/5 kg/d)	Reg	3 M	3–5	<25	P
Mircescu et al. [4]	Romania	27 (10/17)	26 (11/15)	55.0 ± 12.7	53.6 ± 11.0	VLPD (0.3 g/kd/d) + KA (1pill/5 kg.d)	Reg	15 M	4–5	<30	P
Hecking et al. [9]	Germany	15 (8/7)	15 (8/7)	43.7 ± 12.6	43.7 ± 12.6	LPD (0.55 g/kg/d) + KA (1.05 g/10 kg/d)	Reg	4 M	5	<15	P
Bernhard et al. [11]	France	6 (2/4)	6 (0/6)	49.5 ± 7.0	39.0 ± 5.8	LPD (0.71 g/kg/d) + A (1pill/5 kg/d)	Reg	6 M	3–4	±30	P
Prakash et al. [5]	India	18 (8/10)	16 (9/7)	52.8 ± 14.1	55.9 ± 17.6	VLPD (0.3 g/kg/d) + KA (1pill/5 kg/d)	Reg	9 M	4–5	<30	P
Teplan et al. [7]	Czech	66	65	52 ± 7	52 ± 7	LPD (0.6 g/kg/d) + KA (100 mg/kg/d)	Reg	36 M	3–4	22–40	P
Qiu et al. [6]	China	12	11	63 ± 8.90	61.60 ± 9.67	LPD (0.6 g/kg/d) + KA (1pill/5 kg/d)	Reg	52 M	3–4	15–60	P

T treatment group, *C* control group, *M* male, *F* female, *LPD* low protein diet, *VLPD* very low protein diet, *KA* keto analogues, *Reg* regular food, *FD* free diet, *P* positive, *1pill* Ketosteril, Fresenius Kabi, Bad Homburg, Germany, The unit of eGFR is ml/min/1.73 m^2

Table 2 Risk of bias summary

References	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Selective reporting	Incomplete outcome data	Other
Bellizzi et al. [8]	−	?	−	+	+	+	?
Malvy et al. [3]	+	?	+	+	+	+	?
Feiten et al. [10]	+	?	+	+	+	+	?
Mircescu et al. [4]	+	?	+	+	+	+	?
Hecking et al. [9]	−	?	+	+	−	+	?
Bernhard et al. [11]	+	?	+	+	+	_	?
Prakash et al. [5]	+	?	+	+	+	+	?
Teplan et al. [7]	+	?	+	+	+	+	?
Qiu et al. [6]	+	+	+	+	+	+	?

Review of the authors' judgments about each risk of bias item for each included study. Abbreviations: +, good quality (low risk of bias); ? unclear quality (unclear risk of bias); − lower quality (high risk of bias)

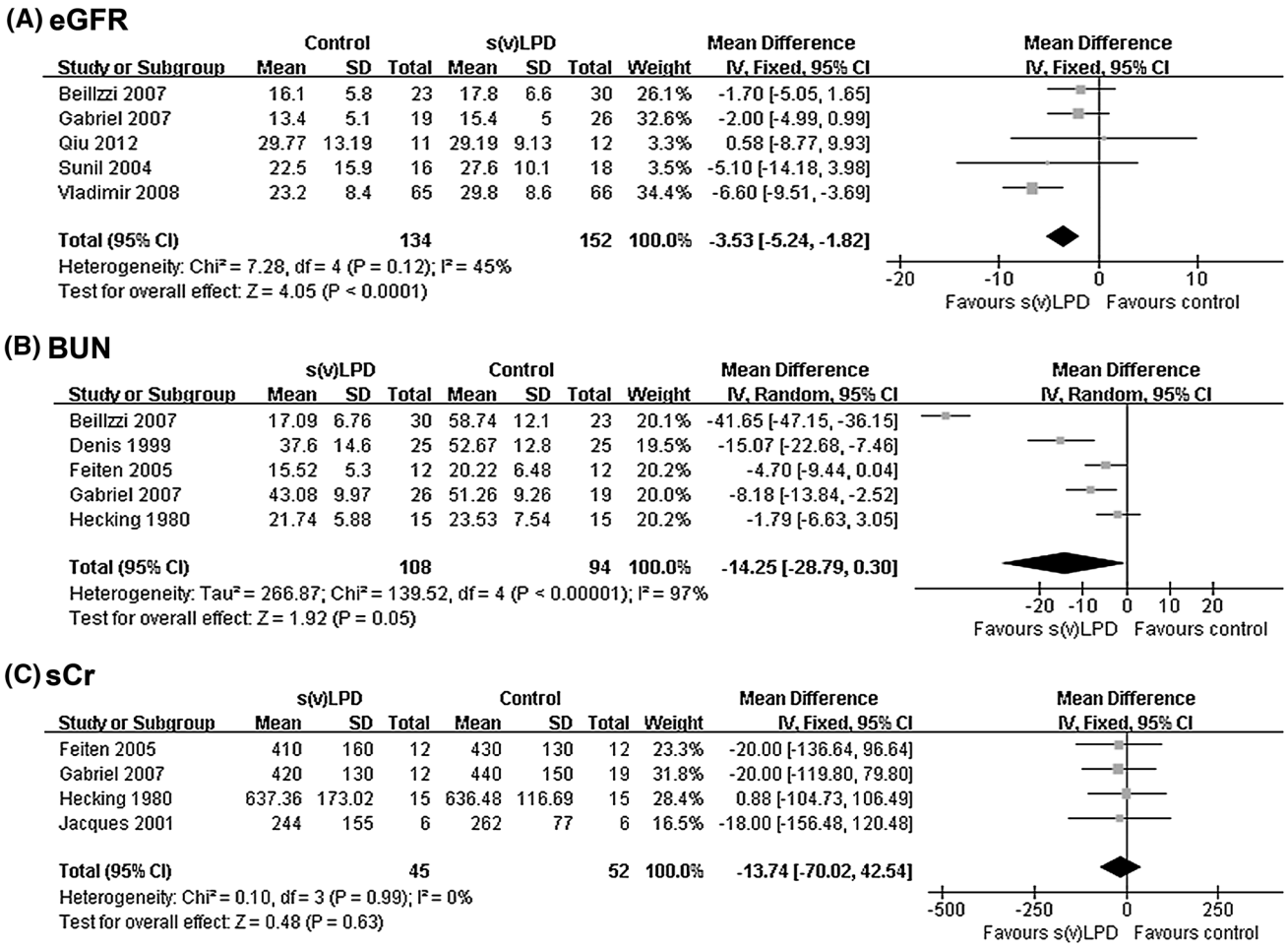

Fig. 2 Comparison of **a** eGFR, **b** BUN, **c** Scr

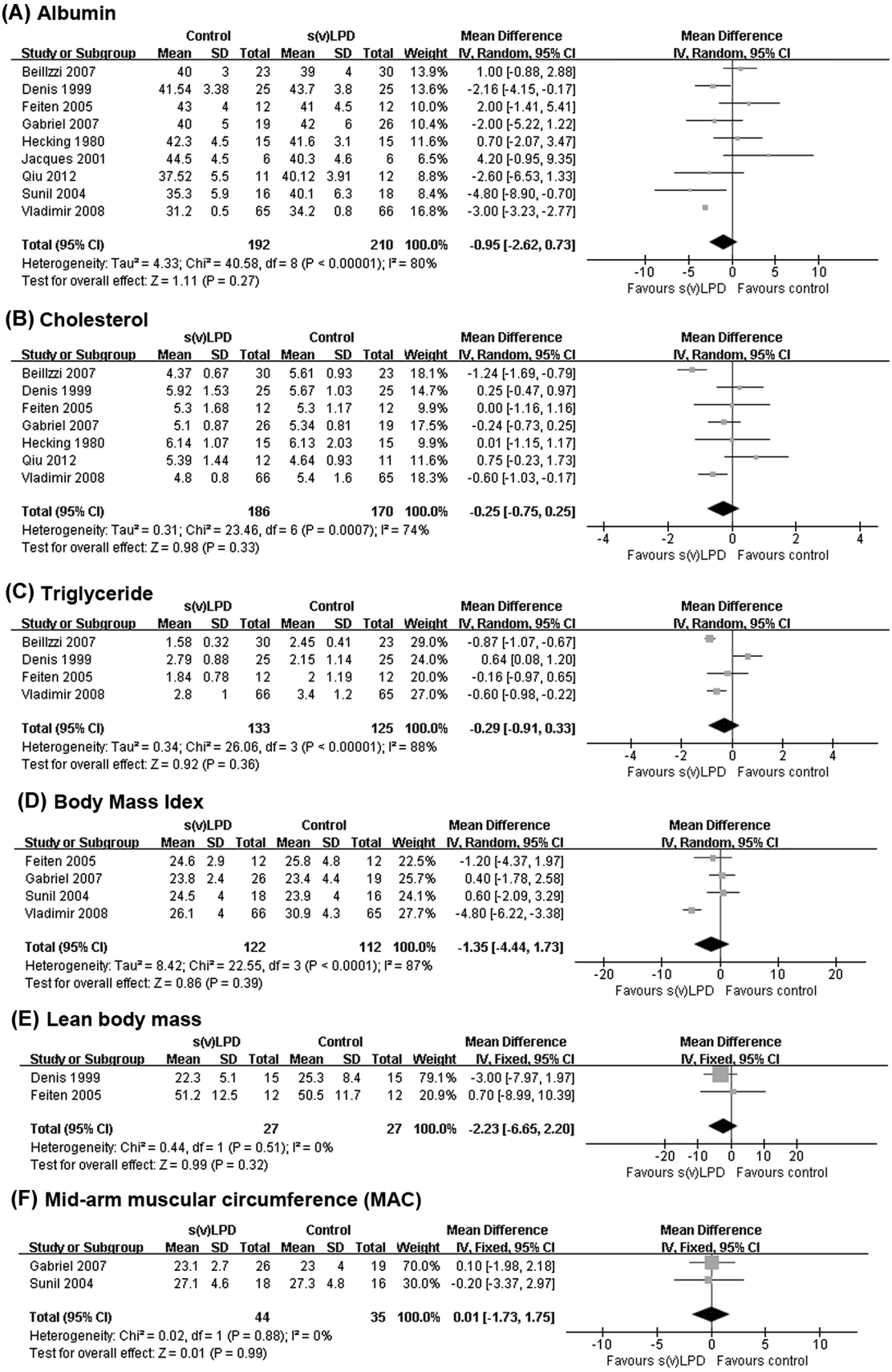

Fig. 3 Comparison of **a** albumin, **b** cholesterol, **c** triglyceride, **d** body mass index, **e** lean body mass, **f** mid-arm muscular circumference

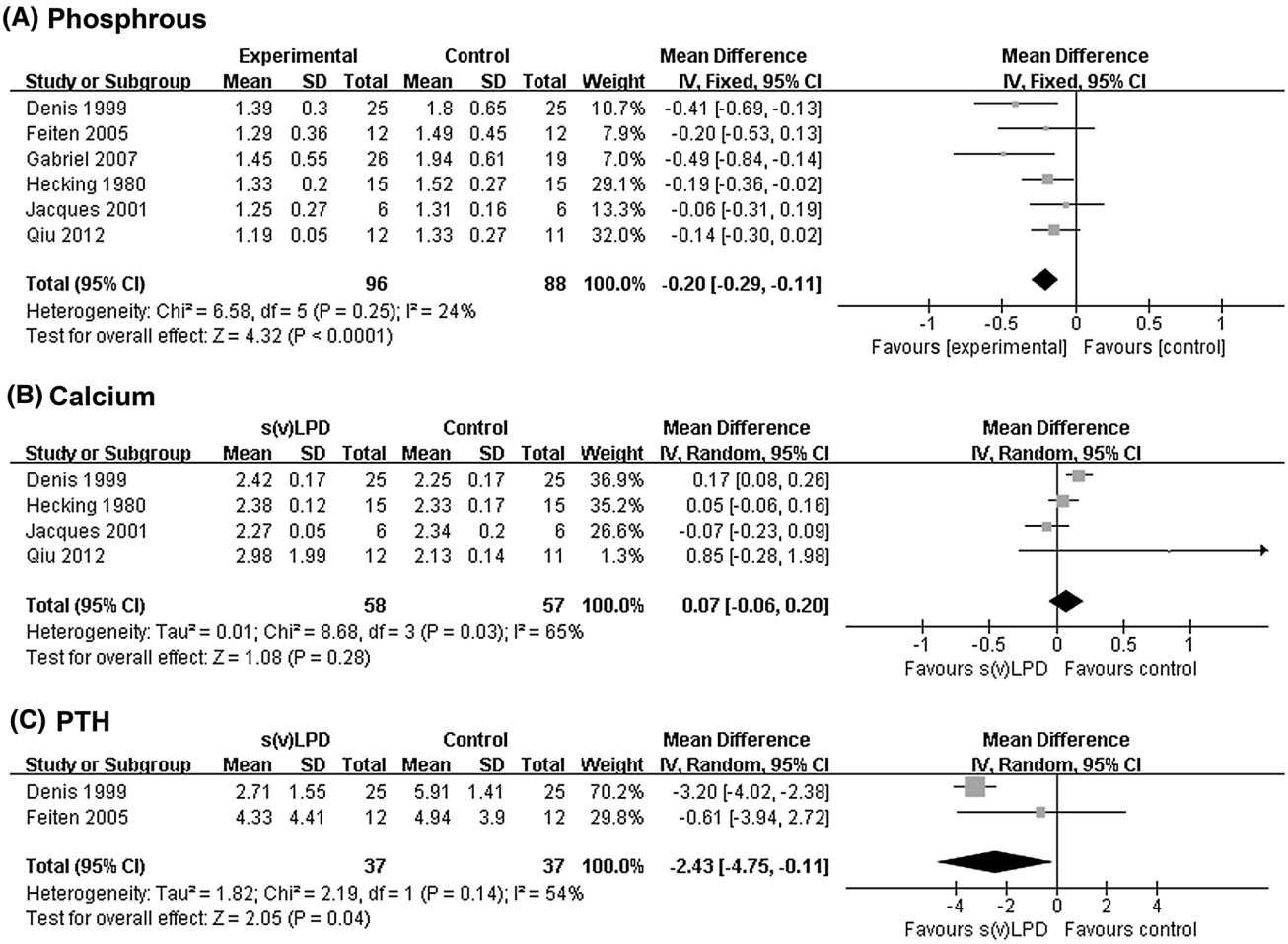

Fig. 4 Comparison of CKD-MBD indexes. **a** P, **b** Ca, **c** PTH

only included 2 RCTs, which showed a significantly lower PTH level in sLPD/sVLPD group (MD −2.43, 95 % CI −4.75, −0.11, $P = 0.04$) (Fig. 4).

Effect of sLPD/sVLPD on proteinuria, anemia and BP of CKD patient

Regarding that proteinuria, BP and anemia are prognostic factors of CKD; effect of restricted protein intake on them is also examined. Comparison of proteinuria level between sLPD/sVLPD and regular food treatment group included 4 RCTs. No apparent difference was observed in meta-analysis (MD −0.51, 95 % CI −1.20, 0.19, $P = 0.15$). 2RCT + 1NRCCT were included in the comparison of hemoglobin level, which suggested no significant difference between groups (MD −2.97, 95 % CI −7.41, 1.48, $P = 0.19$). Comparison of blood pressure included 2RCT + 1NRCCT. Meta-analysis indicated remarkable decrease in both diastolic (DBP) and systolic blood pressure (SBP) (DBP: MD −2.39, 95 % CI −4.18, −0.60, $P = 0.009$; SBP: MD −5.65, 95 % CI −7.98, −3.32, $P < 0.001$) (Fig. 5).

Discussion

Variable diseases can cause CKD, which may progress to end-stage renal disease (ESRD) eventually. It was reported that CKD is a major health burden in China, which affected almost 119.5 million people (10.8 %) [12]. Although new therapy has been introduced, we still lack of regimen to treat patients with advanced stage CKD. Therefore, slow down progression of CKD, preserve residual renal function, postpone renal replacement treatment and prevent complications are major strategies currently. For many years, in vivo and in vitro studies showed that high protein intake will increase albuminuria in short term and aggravate renal fibrosis in long term. Nevertheless, low protein

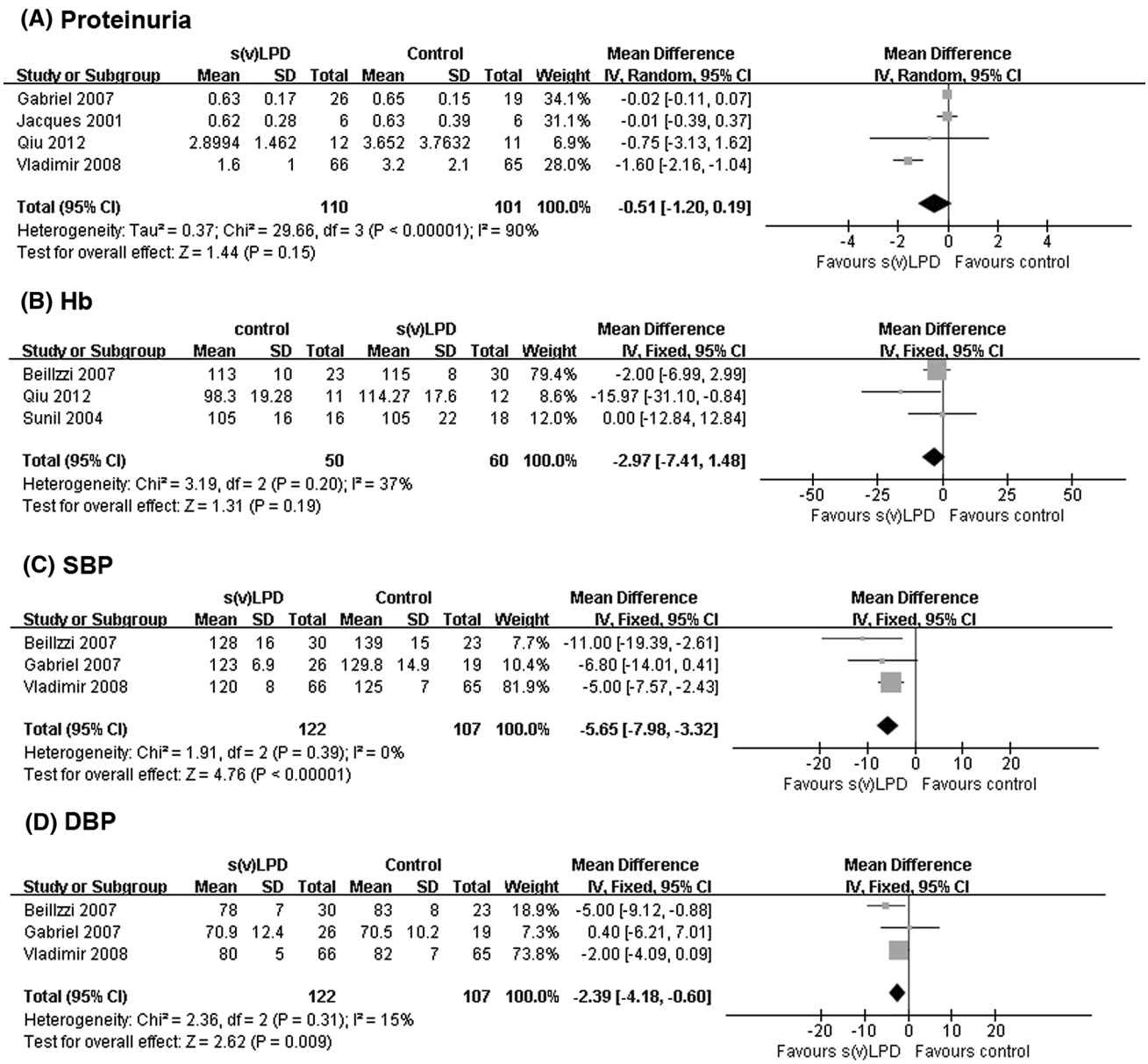

Fig. 5 Comparison of **a** proteinuria, **b** Hb, **c** SBP and **d** DBP

diet will decrease proteinuria, inhibit fibrosis, reduce oxidation and preserve renal function [13]. Aparicio reported that restricted protein diet supplemented with keto analogues could benefit CKD patients in more than 10 aspects [1]. In order to establish a general view of efficacy and safety of restricted protein diet supplemented with keto analogues, we performed this meta-analysis and systematic review.

In this study, 7RCTs + 1COT + 1NRCCT were included. We found that restricted protein diet (low protein diet or very low protein diet) supplemented with keto analogues could significantly slow down the progression of renal dysfunction. Our results suggested a significant effect of sLPD/sVLPD in protecting eGFR (MD −3.53, 95 % CI −5.24, −1.82, $P < 0.001$). Similar to our findings, several cohort studies also indicated that restricted protein diet (VLPD/LPD) supplemented with keto analogues could delay the progression of CKD [10, 14, 15]. Although the big cohort MDRD study suggested that intervention of dietary protein restriction on progression of CKD remains inconclusive and even increased risk of death, it should be noticed that lack of dietary protein measurements during follow-up, no supplementation of keto analogues and poor compliance of restricted protein diet might compromise the results [16, 17]. Therefore, based on the results of meta-analysis, we think that restricted protein diet supplemented with keto analogues should be recommended to CKD

patients in order to delay disease progression. However, tight monitoring of compliance and dietary protein intake measurement should also be applied during follow-up.

Malnutrition is a major complication in CKD patients. Anorexia caused by uremia and increased nutrition demand caused by underlying disease progressively deteriorate hypoalbuminemia and even cause protein energy wasting (PEW) [18, 19]. Several large numbers of investigations and studies have reported that restricted diet could result in worse survival and poor nutritional status, suboptimal adherence and low patient compliance [20]. Therefore, safety issues related with restricted protein diet have always been a concern in nephrologist and patients. In the current study, comparison of serum albumin level (Alb), cholesterol (CHOL), triglyceride (TG), BMI, Lean body mass, mid-arm muscular circumference (MAC), triceps skinfold and SGA between sLPD/sVLPD and regular food treatment group indicated no significant difference (Fig. 3) suggesting that sLPD/sVLPD would not compromise the nutrition status of CKD patients. Several long-term cohort studies also confirmed our findings [21, 22]. On the contrary, long-term follow-up in MDRD study suggested dietary protein restriction increased the risk of death. Considering that supplementation of keto analogues was not applied in that study, it is speculated that keto analogues should be prescribed when applying dietary control to avoid deterioration of PEW in CKD patients [23]. Keto analogues may be expensive; however, they are definitely more economical than dialysis therapy [24].

Mineral bone disease characterized as hyperphosphatemia, hypocalcemia and hyperparathyroidism is a major complication of CKD, which may lead to increased risk of cardiovascular events [25]. Previous studies demonstrated that sVLPD was associated with lower phosphate, FGF23 level and better control of osteodystrophy [26–28]. In the current study, meta-analysis also confirmed that restricted protein diet supplemented with keto analogues could decrease serum phosphate and PTH level and maintain serum calcium level.

Theoretically, restricted protein diet could reduce sodium intake and benefit BP control [13]. Meta-analysis indicated remarkable decrease in both diastolic and systolic blood pressure. Although several cohort studies indicated that sVLPD/sLPD may decrease proteinuria level [29, 30], our meta-analysis did not show apparent differences. The effect of restricted protein diet on proteinuria needs further studies. It was reported that in CKD patients, decrease in protein intake of 0.3 g/kg body weight/day induces a reduction of about 35 % of the EPO dose [31]. In the current study, we found that Hb level in restricted protein diet group is similar to control group, which indicated its safety in CKD patients.

Conclusion

Our meta-analysis indicated that restricted protein diet supplemented with keto analogues could delay progression of CKD, decrease hyperphosphatemia, prevent hyperparathyroidism and benefit blood pressure control without causing malnutrition. This regimen should be recommended to stage 3–5 CKD patients.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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