Nephrol Dial Transplant, 2024, **0**, 1–17
https://doi.org/10.1093/ndt/gfae200
Advance access publication date: 14 September 2024

ORIGINAL ARTICLE

Effects of dietary interventions for metabolic acidosis in chronic kidney disease: a systematic review and meta-analysis

Sepideh Mahboobi[1,2], Rebecca Mollard[1,2], Navdeep Tangri[2,3], Nicole Askin[4], Thomas Ferguson[2], Tahmina Rahman[1], Rasheda Rabbani[5], Ahmed M. Abou-Setta[6] and Dylan MacKay[1,7]

[1]Department of Human Nutritional Sciences, Faculty of Agriculture and Food Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[2]Chronic Disease Innovation Center, Seven Oaks General Hospital, Winnipeg, Manitoba, Canada
[3]Department of Internal Medicine, Max Rady Faculty of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[4]Neil John Maclean Health Sciences Library, University of Manitoba, Winnipeg, Manitoba, Canada
[5]George and Fay Yee Centre for Healthcare Innovation, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[6]Department of Community Health Sciences, Max Rady Faculty of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[7]Department of Internal Medicine, Section of Endocrinology, Max Rady Faculty of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg Manitoba, Canada
Correspondence to: Dylan MacKay; E-mail: dylan.mackay@umanitoba.ca

Watch the video of this contribution at https://academic.oup.com/ndt/pages/author_videos

ABSTRACT

Background. Metabolic acidosis is a common complication of kidney disease and can result in further disease progression. Alkali therapy has been used to treat metabolic acidosis for decades. However, some concerns have been raised regarding its safety and long-term tolerability. Existing data suggest that dietary interventions can be beneficial in the management of chronic kidney disease (CKD). This systematic review and meta-analysis aims to summarize findings from studies comparing dietary interventions with placebo/usual care/no treatment in the management of metabolic acidosis in outpatient adults with CKD.

Methods. Medline, Embase, Cochrane Central, CINAHL and Web of Science Core Collection were searched from inception to June 2022. Our primary outcome measure was change in serum bicarbonate. Any dietary intervention looking to manipulate dietary acid load was considered as an intervention. Data screening and extraction were performed by two independent reviewers. Random effects meta-analysis was performed to pool data.

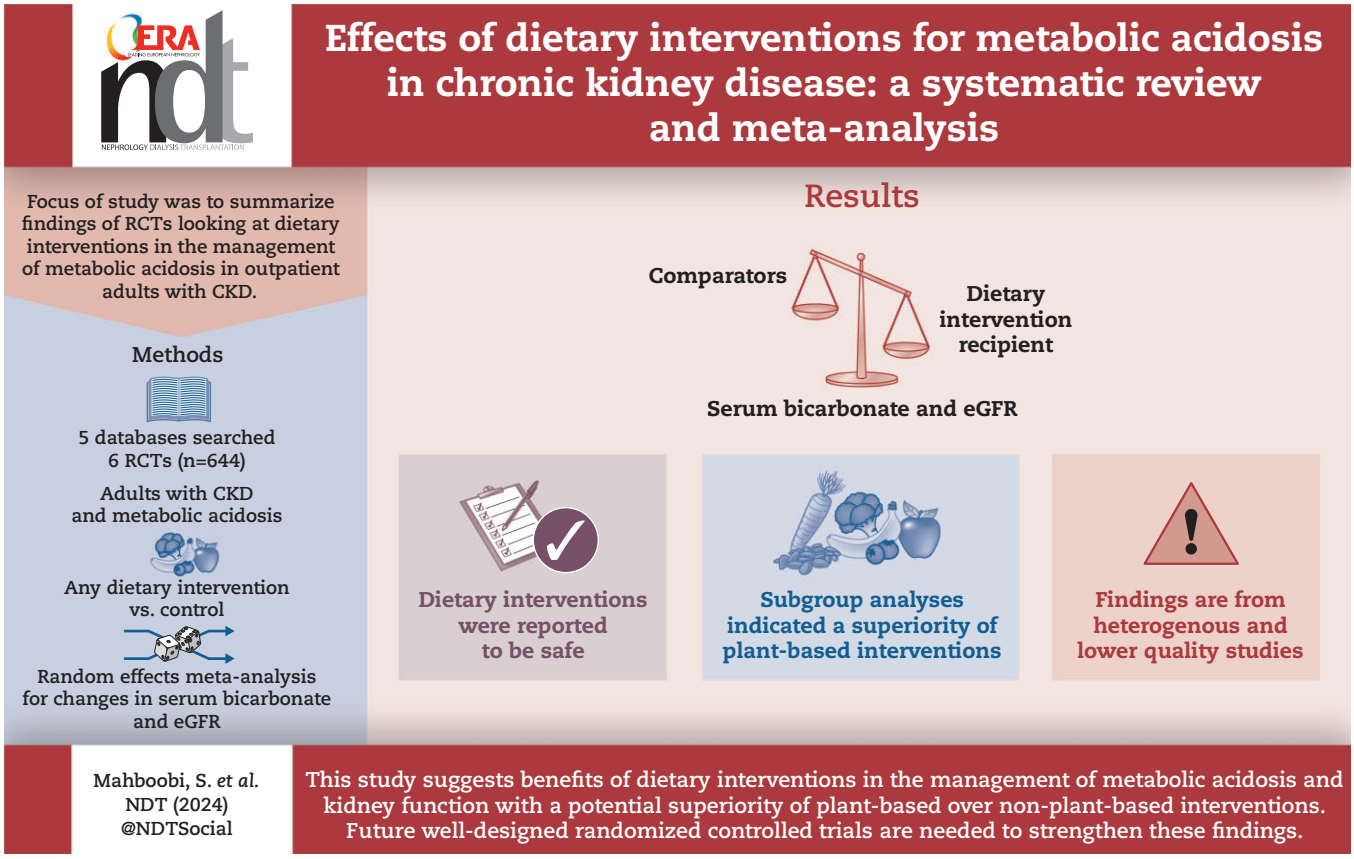
Results. Dietary interventions resulted in clinically significant improvement in serum bicarbonate [mean difference 2.98 (95% confidence interval 0.77, 5.19); I^2: 91%] and higher estimated glomerular filtration rate (eGFR) levels [mean difference 3.16 (95% confidence interval 0.24, 6.08); I^2: 67%] compared with controls. Serum potassium, albumin and body mass index remained unchanged. Dietary interventions were reported to be safe. Subgroup analyses indicated a superiority of plant-based over non-plant-based interventions in the improvement of acid–base balance and eGFR; however, these findings are from low-quality and heterogenous studies.

Conclusion. Our findings support the beneficial effects of dietary interventions aimed at reducing acid or adding base in the management of metabolic acidosis and kidney function in adults with CKD, with no adverse effects on serum potassium and nutritional status. Well-designed clinical trials looking at the treatment of metabolic acidosis with dietary interventions with a focus on adding base through fruit and vegetables are required.

Keywords: chronic kidney disease, dietary acid load, dietary interventions, fruit and vegetables, metabolic acidosis

Received: March 18, 2024; Editorial decision: August 13, 2024

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Metabolic acidosis is a known complication of advanced kidney disease.
- Alkali therapy is the most common treatment for metabolic acidosis and has substantial pill burden.
- Dietary interventions have been shown to be beneficial in the management of metabolic acidosis but are not widely prescribed.

This study adds:

- This study synthesized the best available evidence regarding the effects of dietary interventions on metabolic acidosis in chronic kidney disease.
- Dietary interventions could improve acid–base balance and kidney function with the superiority of plant-based over non-plant-based interventions.
- Higher quality studies are needed in this regard.

Potential impact:

- Dietary interventions focusing on plant-based diets can be considered as a potential alternative treatment for metabolic acidosis.
- These interventions are safe and effective, and do not adversely affect nutritional status.
- These interventions can be facilitated through food deliveries.

INTRODUCTION

Chronic kidney disease (CKD) is a common public health problem affecting nearly one in eight individuals worldwide [1]. The kidney's capacity to excrete the daily acid load is impaired in people with CKD [2], which leads to metabolic acidosis, one of the first recognized complications of advanced disease [3]. With a definition of plasma or venous bicarbonate concentration <22 mmol/L, the prevalence of metabolic acidosis is 20% in people with CKD Stages G3–G5 [4]. If left untreated, metabolic acidosis can lead to CKD progression, muscle wasting, bone disease, stimulating inflammation and increased mortality [5].

Oral bicarbonate supplementation has been used to correct metabolic acidosis for decades [3], and has been hypothesized to delay the progression of kidney failure [6]. A recent meta-analysis, including 3695 participants comparing oral alkali therapy with placebo or standard of care, showed beneficial effects of alkali therapy in delaying kidney failure and preserving function, with

no effects on proteinuria, all-cause mortality and cardiovascular events [7]. Despite these favorable effects, clinical studies have reported a number of notable side effects in regard to alkali therapy, including gastric discomfort, belching and flatulence [8]. The latest Kidney Disease: Improving Global Outcomes (KDIGO) guideline (2024) for the evaluation and management of CKD adopts a more conservative approach regarding alkali therapy in metabolic acidosis. It recommends considering pharmacological treatment for adults with bicarbonate levels <18 mmol/L, with or without dietary interventions, while closely monitoring to ensure that serum bicarbonate levels do not exceed the upper limit of normal and that the treatment does not negatively impact blood pressure control, serum potassium levels or fluid status [9].

Diet has long been known as a key determinant of acid–base balance [10]. In general, foods like cheese, meat, eggs and grains contribute to increased dietary acid load while fruit and vegetables (F + V) are considered base producing [11]. Previous single-center trials have shown that adding base, by incorporating F + V into diet, is beneficial in improving metabolic acidosis and preserving kidney function, along with indices of cardiovascular disease compared with bicarbonate therapy and usual care [12–14]. Dietary protein restriction (daily intake <0.8 g/kg body weight), which is a method to reduce dietary acid load, has also been prescribed in people with moderate to advanced CKD to decrease proteinuria and improve kidney function [15]. A 2019 meta-analysis indicated that either oral alkali or reducing dietary acid can slow the rate of CKD progression (with low to moderate certainty) [16], while oral alkali was associated with worsening hypertension or requiring anti-hypertensive therapy. There remains a need for a comprehensive review of the literature specifically examining the effects of dietary interventions, with a plan to compare interventions that add dietary base versus reducing dietary acid, on kidney outcomes and acid–base balance, as well as the related compliance and safety.

Our purpose was to summarize findings from randomized clinical trials (RCTs) comparing dietary interventions focused on adding base, via F + V consumption, with dietary interventions focusing on lowering acid load, versus placebo/usual care/no treatment in the management of metabolic acidosis in outpatient adults with CKD.

MATERIALS AND METHODS

Study population and eligibility criteria

The inclusion criteria for studies were as follows: RCTs and crossover randomized trials on adult participants (18 years of age or older), with CKD (as diagnosed using any recognized diagnostic criteria or author-defined) with estimated glomerular filtration rate (eGFR) between 15 and 40 mL/min/1.73 m^2 and serum bicarbonate levels of 14–24 mEq/L. Studies were excluded if participants were undergoing dialysis or had chronic obstructive pulmonary disease requiring oxygen therapy.

Interventions and comparators

Any dietary intervention looking to manipulate dietary acid load was considered as an intervention, while usual care/diet, no treatment or placebo were considered as comparators.

Outcome measures

Our primary outcome was change in serum bicarbonate concentrations (mEq/L). Secondary outcomes were systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate, anthropometric measurements, blood urea nitrogen (BUN), creatinine, eGFR, glucose, albumin, calcium, chloride, phosphorus, potassium, sodium and HbA1c, albumin/creatinine ratio in urine samples, quality of life, reported adverse effects, mortality and KDIGO criteria for acute kidney injury. This systematic review also investigated the safety and tolerability of dietary interventions, compared with bicarbonate therapy or placebo, in the management of metabolic acidosis in people with CKD.

Design and search strategy

This study was performed in accordance with a prespecified protocol registered at PROSPERO (https://www.crd.york.ac.uk/, registration ID: CRD42022342612) and is reported in line with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [17].

A knowledge synthesis librarian (N.A.) developed the literature search strategy for MEDLINE (Ovid) using a modified version of the SIGN RCT filter (www.sign.ac.uk). This strategy was then peer-reviewed by a second independent librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist [18]. The final search strategy was then adjusted for use in Cochrane Central (Ovid), Embase (Ovid), Web of Science Core Collection (Clarivate) and CINAHL (EBSCO) and applied from inception to June 2022. The search strategy for this systematic review is presented in Supplementary data, Table S1. Records retrieved were then imported to Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org).

Data extraction and quality assessment

Data screening was performed by a team of two reviewers (S.M., R.M.), independently, through Covidence. Any conflicts were resolved by a third reviewer (D.M.). Ineligible citations were recorded and the number and reason for exclusion were documented at the full text article screening phase. Data were extracted in duplicate by two independent reviewers (S.M., T.R.) into a form designed using the Extraction 2 feature of Covidence. The parameters extracted from selected studies included: (i) general information (first author, year of publication, geographical region); (ii) study characteristics (clinical trial type, number of centers, inclusion/exclusion criteria, study aim, number of participants, intervention duration, funding source and conflict of interest); (iii) participants' characteristics (age, sex distribution, CKD stage, comorbidities); (iv) details regarding intervention and comparators (type, dosage, method of delivery, number of participants in each group); (v) data regarding compliance, safety and tolerability; and (vi) outcome measures described in previous section (pre- and post-intervention or change from baseline values for continuous outcomes and number of participants with or without event for dichotomous outcomes).

For incomplete data, we consulted study protocols using the reported clinical trial registry identifiers, and/or contacted study authors. Two independent reviewers (S.M., N.T.) evaluated the methodological quality of included studies using the Cochrane Risk of Bias (ROB) Tool [19] via Covidence. The reviewers assessed each individual study across seven domains namely: "random sequence generation," "allocation concealment," "blinding of participants and personnel," "blinding of outcome assessment," "incomplete outcome data," "selective reporting" and "other bias." Based on these domains, the studies were categorized as having a "low risk of bias," being "unsure" and having a "high risk of bias." In

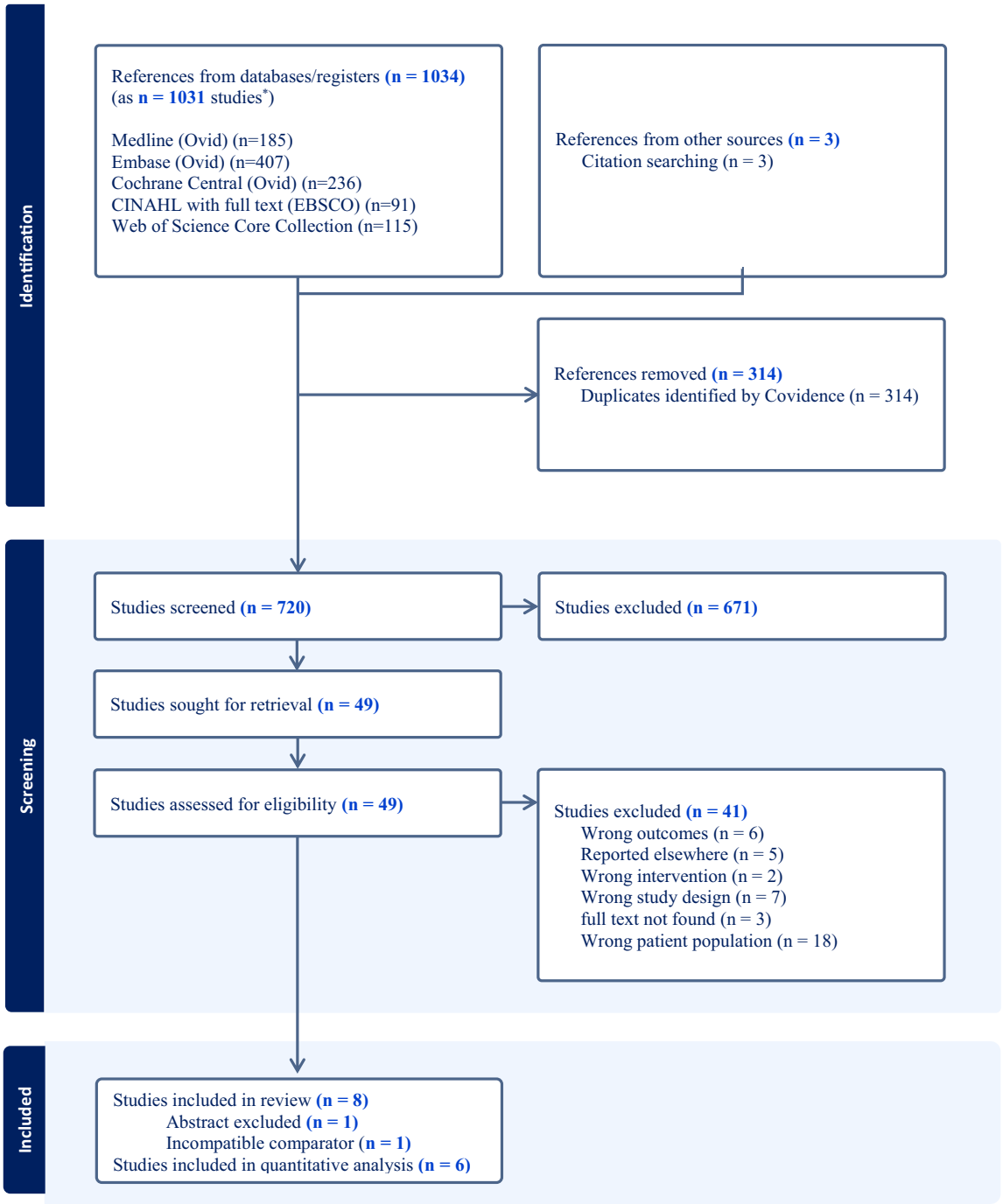


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of articles for inclusion in the systematic review of dietary interventions in the management of metabolic acidosis in adults with chronic kidney disease.
*Four publications were considered as 1 study, since they were inherently from the same original study. We selected the one with the most comprehensive dataset or data collected over the longest duration of follow-up.

the case of any discrepancies in the judgements, a third reviewer (D.M.) was consulted to resolve them.

The comma-separated values (CSV) of extracted data was then exported for further data synthesis.

Statistical analysis

For continuous outcomes, means and their standard deviations (SDs) were recorded. Whenever SD was not reported directly, we calculated them from either standard error (SE) or 95% confidence interval (CI) using formulas provided in the Cochrane Handbook for Systematic Reviews of Interventions [20]. To enter the meta-analysis, change from baseline (mean difference) was calculated for all outcome variables in each arm; the corresponding SDs were then imputed using the formula provided in Cochrane Handbook for Systematic Reviews of Interventions [21]. The correlation in this formula was assumed to be zero as applied for parallel studies. For dichotomous outcomes, the number of events in

each group were recorded to enable us to calculate risk ratios (RR), wherever possible.

One study [22] had reported median and its 95% CI for all values, so we decided to alternatively include medians in the analysis, and calculate the corresponding SD using Cochrane formulas [20] to avoid losing valuable data.

We applied random effects models to estimate pooled mean differences (MDs) and 95% CIs. Statistical heterogeneity was assessed between the included studies using the I-squared (I^2) statistic [23]. Subgroup analysis was performed based on the type of intervention (plant-based food interventions vs non-plant-based food interventions) to evaluate the effects of dietary interventions on serum bicarbonate and eGFR levels, for which enough numbers of included studies were available ($n = 3$). All analyses were performed with R statistical software (version 4.3.1).

RESULTS

Characteristics of included studies

We identified 1037 publications (as 1034 distinct studies) through our initial retrieval; after two phases of screening, eight RCTs were identified eligible for being included in the review [12–14, 22, 24–30]. Figure 1 shows a flowchart of study selection. Tables 1 and 2, respectively, present the study characteristics and summarize the findings among the included studies. A range of dietary interventions was applied among these studies. Table 3 provides detailed information on the dietary interventions and their comparators in the included studies.

Two studies were excluded from quantitative synthesis due to quality reasons [26] and having inherently different comparators from other studies included [12]. Ultimately, a maximum number of six studies ($n = 644$) entered the meta-analysis. From retrievals by Goraya *et al.* [13, 14, 24, 25], we incorporated the most comprehensive dataset or data collected over the longest duration of follow-up.

From two intervention arms in studies by Goraya (2021) [25] and Williams (1991) [29], one arm was eligible to enter the meta-analysis (F + V delivery, dietary protein and phosphate restriction, respectively).

The quality of included studies

Supplementary data, Fig. S1 demonstrates the quality of included studies using the Cochrane ROB tool. Only two studies had reported sequence generation [29, 30], while the other five had not mentioned sequence generation [22, 12, 25, 27, 28]. One study [22] was categorized as high risk for incomplete outcome data, and one [29] for selective reporting and other sources of bias. All studies [12, 22, 25, 27–30] were rated high risk for blinding of participants and personnel and blinding of outcome assessment. In general, five out of seven studies were rated high risk of bias in three or more domains [22, 12, 25, 28, 29], which indicates the overall low quality of studies in this systematic review and meta-analysis.

Outcome variables

Of our predefined outcome variables in the initial study protocol, data were insufficient to examine effects on glucose, HbA1C, albumin:creatinine ratio, DBP, chloride, sodium, weight, heart rate, quality of life and KDIGO criteria for acute kidney injury, to be entered in the meta-analysis. Therefore, we pooled available data for serum bicarbonate, eGFR, serum urea nitrogen (SUN), creatinine, albumin, potassium, phosphorus, calcium, body mass index (BMI) and SBP. We also performed a narrative synthesis of findings, including safety and compliance (Table 2).

Acid–base balance

Data from six studies [22, 25, 27–30] ($n = 644$) were pooled for evaluating effects of dietary interventions on serum bicarbonate. These dietary interventions included a vegetarian supplemented very low protein diet (sVLPD) in two studies [22, 28], very low protein diet (VLPD) in one study [27], low protein and phosphate diet in one study [29], 6-tip diet (6-TD) in one study [30], and F + V delivery in one study [25]. Based on our meta-analysis, dietary interventions led to an increase in serum bicarbonate [mean difference (MD) 2.98 (95% CI 0.77, 5.19); I^2: 91%] compared with control group (Fig. 2).

Kidney function and blood pressure

We pooled data from up to six studies [22, 25, 27–30] that evaluated effects of dietary interventions on markers of kidney function including eGFR/creatinine clearance ($n = 635$), SUN ($n = 306$) and creatinine ($n = 105$). Dietary interventions in these studies included vegetarian sVLPD, VLPD, 6-TD, protein and phosphate restriction, and F + V. Pooled data revealed that experimental group had an eGFR higher than the control group, post-intervention [MD 3.16 (95% CI 0.24, 6.08); I^2: 67%] (Fig. 3). Pooled data from studies targeting SUN levels was indicative of a decrease in SUN in intervention group compared with control [MD –40.21 (95% CI –68.81, –11.61); I^2: 60%] (Supplementary data, Fig. S2a). Serum creatinine levels remained unchanged in intervention group compared with control group [MD –0.26 (95% CI –1.28, 0.76); I^2: 0%] (Supplementary data, Fig. S2b).

Two studies with vegetarian sVLPD and F + V as intervention ($n = 117$) [25, 28] reported SBP. The meta-analysis showed that dietary intervention could decrease SBP compared with control group [MD –13.10 (95% CI –18.27, –7.94); I^2: 0%] (Supplementary data, Fig. S2c). Our pooled analysis showed that dietary interventions aimed at reducing acid/adding base did not reduce the risk of progression to kidney failure [defined by renal replacement therapy (RRT) initiation] [RR 0.59 (95% CI 0.24, 1.45); I^2: 69%] (Supplementary data, Fig. S2d).

Serum phosphorus and calcium

Three studies [22, 28, 30] with vegetarian sVLPD and 6-TD as interventions were available for serum phosphorus ($n = 306$) and two [22, 28] studies with vegetarian sVLPD targeted serum calcium ($n = 252$). Dietary interventions resulted in a decrease in phosphate levels and an increase in calcium levels compared with the control group [MD –1.22 (95% CI –2.34, –0.10); I^2: 82%] (Supplementary data, Fig. S3a) and [MD 0.51 (95% CI 0.30, 0.73); I^2: 0%] (Supplementary data, Fig. S3b), respectively).

Safety parameters and adherence

We pooled data for serum potassium [two studies [22, 25], one with vegetarian sVLPD and one with F + V as intervention ($n = 279$)], serum albumin [three studies [22, 28, 30], two with vegetarian sVLPD and one with 6-TD as intervention ($n = 306$)] and BMI [three studies [22, 25, 28], two with vegetarian sVLPD and one with F + V as intervention ($n = 324$)]. Serum potassium, albumin and BMI remained unchanged in intervention group compared with control [MD –0.01 (95% CI –0.19, 0.18); I^2: 31%; MD 0.04 (95% CI –0.17, 0.25); I^2: 61%; MD –0.84 (95% CI –2.09, 0.41); I^2: 49%, respectively] (Supplementary data, Fig. S4a–c). Table 2 summa-

Table 1: Characteristics of identified clinical trials investigating the effects of dietary interventions on metabolic acidosis in CKD and their population.

Source	Publication type	Country	Study population	Age (years)[a]	Sex (% males)	CKD stage	Comorbidities	Baseline serum bicarbonate (mEq/L)[a, b]	Baseline e GFR (mL/min/1.73 m^2)[a]
Williams 1991 [29][c]	Peer reviewed	UK	95 adults (<70 years) with chronic renal failure	I-1: 43 (2.3); I-2: 47.7 (2.2); C: 44.5 (2.2)[d]	Both sexes (I-1: 60.6; I-2: 73.3; C: 65.6)	n/r	Diabetes, hypertension	I-1: 23.1 (0.8); I-2: 21.4 (0.9); C: 22 (0.7)[d]	I-1: 23.4 (2.8); I-2: 28.8 (4.7); C: 28.3 (3.1)[d]
Gennari 2006 [27] (Study B)	Peer reviewed	USA	255 adults (18–75 years) with CKD (eGFR 13–24[e])	I: 50.5 (12.9); C: 51.1 (12.8)	Both sexes (I: 58; C: 60.5)	4+	Diabetes, hypertension	I: 21.6 (3.6); C: 22.3 (3.7)	I: 20.4 (4.8); C: 20.2 (3.9)
Mircescu 2007 [28]	Peer reviewed	Romania	53 adult non-diabetic patients with eGFR <30	I: 55 (12.7); C: 53.6 (11)	Both sexes (I: 63; C: 58)	4	Hypertension	I: 18.1 (1.5); C: 18.3 (1.3)	I: 18.3 (4.6); C: 17.9 (4.3)
Goraya 2013 [12]	Peer reviewed	USA	71 non-diabetic adults (≥18 years) with CKD (eGFR 15–29) and TCO_2[b] <22 mM and controlled hypertension (non-malignant)	I: 53.9 (6.9); C: 54.2 (5.3)	Both sexes (I: 56; C: 51)	4	Hypertension	I: 19.3 (1.9); C: 19.5 (1.5)	I: 21.6 (4.6); C: 21.7 (3.4)
Goraya 2021 [25][c]	Peer reviewed	USA	108 non-diabetic adult patients (≥18 years) with CKD (GFR 35–59) and metabolic acidosis (serum bicarbonate 22–24)	I-1: 53.6 (5.3); I-2: 53.5 (5.2); C: 53.9 (4.8)	Both sexes (I-1: 44.4; I-2: 44.4; C: 44.4)	3	Hypertension	I-1: 23.1 (0.6); I-2: 22.9 (0.6); C: 22.9 (0.6)	I-1: 39.6 (6.6); I-2: 39.4 (6.4); C: 39.5 (6.9)
Pisani 2016 [30]	Peer reviewed	Italy	57 adult patients (>18 years) with CKD (eGFR ≤45)	I: 58.8 (12.06); C: 56.1 (12.06)	Both sexes (I: 52; C: 52)	3B-5	Diabetes; hypertension; other: ADPKD, GN	I: 23.5 (2.4); C: 24.1 (3.3)	I: 21.2 (7.4); C: 21 (8.3)
Garneata 2016 [22]	Peer reviewed	Romania	207 non-diabetic individuals with CKD (eGFR <30) and good nutritional status, controlled BP and proved dietary compliance	I: 55.2; C: 53.6 (median)	Both sexes (I: 63, C: 59)	4+	Hypertension	I: 16.7 (15.8, 17.6); C: 16.8 (15.9, 17.8)[f]	I: 18 (15.5, 20.1); C: 17.9 (14.3, 19.3)[f]
Garneata 2019 [26]	Abstract	Romania	a 5-year follow up of all the subjects who were still alive, monitored and not on RRT from Garneata 2016 (n = 200)	n/r[g]	n/r[g]	n/r[g]	n/r[g]	n/r[g]	n/r[g]

[a] Values are reported as mean (SD) unless otherwise specified.
[b] Serum bicarbonate and serum total CO_2 (TCO_2) are used interchangeably in this table and their units are either mEq/L or mM where not specified.
[c] Studies with two intervention arms.
[d] Values are reported as mean (SEM).
[e] Unit for eGFR or creatinine clearance is mL/min/1.73 m^2 where not specified.
[f] Values are reported as median (LCI, UCI).
[g] Baseline data was not directly reported in the abstract (it was a follow-up of another study whose data is included in the table).
C, comparator; I, intervention; LCI, lower confidence interval; UCI, upper confidence interval; ADPKD, autosomal dominant polycystic kidney disease; GN, glomerulonephritis.

Table 2: A summary description of outcome variables, interventions and comparators, main findings and safety/compliance across identified clinical trials investigating the effects of dietary interventions on metabolic acidosis in chronic kidney disease.

Source	Outcomes	N (analyzed)[a]		Intervention (type and method of delivery)[b]	Comparator[b]	Intervention Duration	Main findings	Safety and compliance
		N (intervention)	N (control)					
Williams 1991 [29][c]	Progression of renal failure, urine urea excretion, protein catabolic rate, phosphate excretion, BP, BW, body mass, transferrin, albumin, immunoglobulins, the requirement for maintenance dialysis facilities	31	29	I-1: LPD (protein and phosphate restriction); I-2: dietary phosphate restriction only; education	No protein/ phosphate restriction	19 ± 3 months	The rate of fall in creatinine clearance decreased in both LPD and low phosphate diet groups and increased in control group, with no significant differences No difference in the requirement for maintenance dialysis facilities were observed between groups and therefore, no significant benefit of protein and phosphate restriction was demonstrated A fall in urinary urea excretion was observed only in LPD group. The mean protein catabolic rate was significantly lower in LPD group compared with other groups. There was a modest but significant fall in phosphate excretion in both dietary restricted groups. No significant differences were observed in anthropometric measures (BW, MAMC) between groups at no time	Intervention group: protein intake fell significantly to 0.69 g/kg BW/day, phosphate intake fell from 1406 to 815 mg/day, 24-h urinary phosphate had a modest but significant fall; all indicative of good compliance to LPD diet Control group: patients in the control group had a fairly steady protein intake at 1.25 g/kg BW/day before the trial and 1.14 g/kg BW/day afterwards Phosphate excretion remained unchanged in this group Transferrin and immunoglobulin levels remained within normal range in each arm during study period
Gennari 2006 [27] (Study B)	Primary: interrelationships among serum (total CO_2)[d], eGFR[e] and EPI at the initial baseline visit; secondary: longitudinal examination of the effect of dietary protein restriction on serum (total CO_2)	94	103	VLPD; education	LPD	1 year	In a cross-sectional analysis of baseline variables, after controlling for clinical center, serum HCO_3 had a significant and direct association with eGFR and male sex, while a significant and inverse association was observed between serum bicarbonate and EPI, age and ACEI therapy In Study B, serum bicarbonate did not change in LPD but increased in VLPD, this change, however, was not significantly different from LPD. Authors stated that "Regardless of the outcome, however, according to the authors' interpretation, one cannot draw any conclusions about the effect of diet in Study B because of the potential alkali contained in the supplements that were given to the VLPD"	No significant differences in the number or causes of deaths or stopping points between diet groups, most patients did not achieve the prescribed protein intake and marked changes in intake were observed among patients assigned to the LPD than usual diet in study A. EPI was decreased by 0.46 g/kg BW/day in VLPD compared with the 0.22 g/kg BW/day in LPD in Study B Long-term average percent adherence to ketoacid and AA supplements estimated by pill counts was 83.2% and 76.7%, respectively; no patient reached a weight loss stop point

Table 2: Continued

Source	Outcomes	N (analyzed)[a]		Intervention (type and method of delivery)[b]	Comparator[b]	Intervention Duration	Main findings	Safety and compliance
		N (intervention)	N (control)					
Mircescu 2007 [28]	Primary: serum BUN, creatinine, calcium, phosphate, calcium-phosphorus products, ALP activity, serum bicarbonate; secondary: death of the patients or death of the kidney and eGFR Safety parameters: SGA, anthropometrics (BMI, tricipidal skinfold, MAMC), serum albumin, serum total cholesterol, compliance, occurrence of adverse events, and number of withdrawals	26	19	sVLPD; education	LPD	48 weeks	After 48 weeks, sVLPD group showed significant decrease in serum urea. A significant improvement in serum bicarbonate, calcium, phosphate and calcium-phosphate product were also noted (baseline vs post-intervention serum bicarbonate was 18.1 ± 1.5 mmol/L vs 23.4 ± 2.1). Significantly lower percentage of patients in sVLPD group required RRT initiation (4% vs 27%). eGFR did not significantly change in SVLPD group but had a significant reduction in control group. No death was registered in either group	In general, good compliance (due to strict eligibility criteria) (the compliance with the prescribed diets, assessed by protein and energy intake, was good throughout the study in both arms) Intervention group: no deleterious effect on nutritional status; good compliance (strict eligibility); ketoanalog supplementation was well tolerated. No adverse reactions to Ketosteril (Fresenius Kabi) administration were noted. SGA score remained constant (87%) Control group: no significant changes in parameters of the nutritional status; SGA score remained constant (90%)
Goraya 2013 [12]	Primary: cystatin C eGFR and creatinine eGFR; secondary: plasma and urine acid– base measures: urine excretion of cystatin C and creatinine; SBP; BW; urine measures of kidney injury (urine albumin, UNAG and UTGF); plasma K^+; urine K^+ excretion; plasma and urine aldosterone and 11b hydroxysteroid de-hydrogenase type 2 activity, assessed as urine THF/THE ratio	36	35	F + V; Provision	Oral $NaHCO_3$	12 months	One year compared with baseline values of serum bicarbonate were higher in both NaHCO3 and F + V groups ($P < .01$). One year compared with baseline 8-h urinary NAE values were lower in both $NaHCO_3$ and F + V groups ($P < .01$) and 1-year urinary NAE values were lower in $NaHCO_3$ group than F + V group ($P < .01$) Baseline PRAL was not different between groups, although, 1-year PRAL was lower in F + V than $NaHCO_3$ group Baseline SBP values did not differ between groups at baseline, but it was lower than its respective baseline in F + V group ($P < .01$) but not in $NaHCO_3$ group ($P = .88$). One-year SBP was lower in F + V group compared with $NaHCO_3$ arm. Baseline BW was not different between groups but 1-year BW was lower than baseline in F + V group ($P < .01$) but not $NaHCO_3$ group ($P = .87$)	Baseline 8-h urine NAE did not differ between groups ($P = .89$) and 1-year compared with baseline values were lower in the $NaHCO_3$ ($P = .01$) group. 8-h urinary K^+ execration was increased in F + V arm significantly at 1 year compared with its baseline and control group 8-h urinary Na^+ excretion was significantly increased in $NaHCO_3$ group at 1 year which was also significantly higher than F + V group Baseline PRAL was not different between groups but 1-year PRAL was lower in F + V than $NaHCO_3$ group Plasma K^+ levels remained in normal range in F + V group (4.1 ± 0.2mEq/l at baseline to 4.1 ± 0.1 mEq/L at 1 year)

Table 2: Continued

Source	Outcomes	N (analyzed)[a]		Intervention (type and method of delivery)[b]	Comparator[b]	Intervention Duration	Main findings	Safety and compliance
		N (intervention)	N (control)					
Pisani 2016 [30]	Primary efficacy endpoint: protein intake, UUN excretion, serum urea nitrogen, urinary phosphate excretion, and serum phosphate concentration; secondary endpoints: patients' adherence to the prescribed diet, and the effects of both diets on several additional metabolic (sodium, K^+, bicarbonate, hormone) and nutritional (BMI, serum albumin) parameters	27	27	6-TD; education	Standard LPD	6 months	Both groups showed progressive reduction in protein intake and UUN compared with baseline but the decrease was more pronounced in 6-TD group than LPD group. 6-TD had greater effect on serum levels of urea nitrogen and urinary phosphate excretion Plasma levels of phosphate, HCO_3, PTH and urinary NaCl excretion remained unchanged In general, this study concluded that "A simplified diet, consisting of 6 clear points easily managed by CKD patients, produced beneficial effects either on the metabolic profile of renal disease and on patients' adherence to the dietary plan, when compared with a standard LPD"	Intervention group showed 70% adherence while control group showed 44% adherence In both groups, the main laboratory data were in the desired range, mostly considering the severely reduced eGFR The decreased UUN and phosphate mirrored the significant reduction in protein intake in both groups during the follow-up period, observed since the third month of study Furthermore, the protein intake had a significant reduction in both groups, throughout the study No patient had a protein intake below 0.7 g/kg BW/day throughout the follow-up period As BW remained stable in both groups during the entire study period, the caloric intake was considered acceptable in both in LPD and 6-TD patients

Table 2: Continued

Source	Outcomes	N (analyzed)[a]		Intervention (type and method of delivery)[b]	Comparator[b]	Intervention Duration	Main findings	Safety and compliance
		N (intervention)	N (control)					
Garneata 2016 [22]	Primary composite end point: need for RRT initiation/>50% reduction in initial GFR any time during the assessment phase; secondary efficacy parameters: need of RRT initiation, decline in GFR, correction of metabolic complications of CKD (serum urea, calcium and phosphate disorders, acidosis) Safety variables: parameters of nutritional status (SGA, anthropometrics, serum albumin, CRP, total cholesterol); compliance to prescribed diet, occurrence of adverse events, number of patients withdrawing from the study	104	103	sVLPD; education	LPD	15 months	A lower percentage of patients in sVLPD arm reached primary composite end point (progression of CKD) compared with LPD (13% vs 42%, $P < .001$). Cumulative probability to reach this endpoint during 1 year was also lower in sVLPD arm RRT initiation was required in a lower percentage in sVLPD arm (11% vs 30%, $P < .001$) Only sVLPD group showed a trend towards higher levels of eGFR at the study end ($P = .08$) and the decrease in eGFR was lower in sVLPD than LPD (3.2 mL/min/year lower decline in KD) No differences between groups in achieving and maintaining BP control, nor in the percentage of patients receiving antihypertensive medications throughout the study The need for vitamin D supplementation was higher in LPD than sVLPD (54% vs 22%, $P = .004$) Significant improvement in most of metabolic parameters and calcium-phosphorus metabolism in sVLPD compared with LPD The need for bicarbonate therapy was higher in LPD group than sVLPD (51% vs 29%, $P < .01$), LPD also needed higher doses of sodium bicarbonate Authors have attributed these finding to not only the quantity of protein (VLPD vs LPD) but also the difference in quality of protein between groups (vegetables only in sVLPD versus conventional mixed LPD in controls) and the fact that vegetable proteins are base producing	In general: good compliance to protein restriction and energy intake in randomized participants (median protein intake in sVLPD and LPD were 0.29 and 0.59 g/kg BW/day, respectively and median energy intake 31 kcal/kg BW/day) which might be due to carefully selection of study participants (only 14% of screened patients were randomized); no patient death was registered for any arm during the study; only seven participants abandoned the diet, with no difference between study arms Intervention group: despite the low protein intake and even vegetarian diet, serum K^+ did not change significantly during the study and remained in normal range; ketoanalogs supplements were well tolerated; 3 people discontinued Control group: nutritional status was preserved; 4 participants discontinued

Table 2: Continued

Source	Outcomes	N (analyzed)[a]		Intervention (type and method of delivery)[b]	Comparator[b]	Intervention Duration	Main findings	Safety and compliance
		N (intervention)	N (control)					
Garneata 2019 [26]	Long term effects of prescribed diets on patients' and kidney survival, nutritional status as well as compliance to these diets	101	99	sVLPD; education	LPD	5 years	The median follow-up time was significantly higher in sVLPD than LPD group (129 vs 114 months) The probability of patients' survival at 5 years was significantly higher in sVLPD group (96% vs 82%) and based on regression model, only type of nutritional intervention was related to the survival advantage RRT was required by a significantly lower proportion in sVLPD (51% vs 93%) In overall, the vegetarian severe hypoproteic diet supplemented with ketoanalogs seems to result in better patient and kidney survival	In patients still not on RRT, the adherence to dietary interventions remained very good throughout the follow up in both groups No change in nutritional status was observed in any arms In summary this report shows that the sVLPD seems to be feasible and safe in this CKD population on a long term
Goraya2021 [25][c]	Primary: change in eGFR; secondary (Goraya 2014): plasma creatinine, eGFR; urine albumin; UNAG; urine angiotensinogen; secondary (Goraya 2021): urine excretion of parameters of kidney injury, BMI, SBP, plasma LDL, HDL, HCO3, number of participants with MIs and CVAs; changes in dose of top 7 medications taken by the groups (*post hoc*), intervention costs (*post hoc*), diagnosis-related group charge for hospitalization, estimated retail for F + V costs (per household) - Mean overall health score - Proportion of CKD3 subjects who transition to CKD 4	36	36	I-1: oral NaHCO3; I-2: F + V; provision	Usual care (according to extant guidelines)	3 years (Goraya 2014) and then up to 5 years (Goraya 2021)	Three-year SBPs were lower than respective baselines for all three groups and the 3-year value was lower in F + V than in $NaHCO_3$ and usual care groups Plasma K^+ was lower than its respective baseline in $NaHCO_3$ arm but not different from baseline in either F + V and usual care groups 3-year compared with baseline plasma HCO_3 was lower in usual care (22.4 ± 0.6 vs 23 ± 0.5 $P < .01$) but was significantly higher in both NaHCO3 and F + V groups (24.0 ± 0.6 vs23.1 ± 0.6 and 23.9 ± 0.6 vs 23.0 ± 0.6, respectively, $P < .01$ for both) Urine excretion of angiotensinogen, an index of kidney angiotensin II, increased in usual care and decreased in both NaHCO3 and F + V arms After 5 years, average health scores were significantly different among groups and descriptively larger in F + V group than NaHCO3 or usual care groups	At 3 years, NAE remained unchanged in usual care group but significantly dropped in both $NaHCO_3$ and F + V groups compared with baseline, which is consistent with intake of prescribed $NaHCO_3$ and F + V in the two intervention arms. The intake of F + V was increased from 0.98 cups/day in baseline to 3.1 cup/day at 5 years (2.1 units increase in mean and CI: 2–2.2) in F + V group. Furthermore, Urinary excretion of K^+ at 5 years was increased significantly in F + V group which could also be as indicator of good compliance

Table 2: Continued

Source	Outcomes	*N* (analyzed)[a]		Intervention (type and method of delivery)[b]	Comparator[b]	Intervention Duration	Main findings	Safety and compliance
		N (intervention)	*N* (control)					
							In general, the study concluded that 'F + V compared with NaHCO3 treatment of metabolic acidosis yields more and better health outcomes, does so cost-effectively, and supports further exploration of this treatment for metabolic acidosis because of its apparent more comprehensive individual health and population benefits'	8-h urinary excretion of Na^+ at 5 years was increased in $NaHCO_3$ group compared with other groups

[a] This column exclusively demonstrates the number of participants in arms that were included in the meta-analysis.
[b] Details on intervention and comparators have been elaborated in Table 3.
[c] Studies with more than one intervention arm.
[d] Serum bicarbonate and serum total (CO_2) are used interchangeably in this table and their units are either mEq/L or mM where not specified.
[e] Unit for eGFR or creatinine clearance is mL/min/1.73 m^2 where not specified.
AA, amino acids; ACEI, angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; BW, body weight; CRP, C-reactive protein; CVA, cerebrovascular accident; EPI, estimated protein intake; HDL, high-density lipoprotein; K^+, potassium; Kcal, calories; LDL, low-density lipoprotein; MAMC, mid-arm muscle circumference; MI, myocardial infarction; Na^+, sodium; NAE, net acid excretion; PRAL, potential renal acid load; PTH, parathyroid hormone; SGA, Subjective Global Assessment; sVLPD, severe hypoproteic diet supplemented with ketoanalogs; THE, tetrahydrocortisone; THF, tetrahydrocortisol; UNAG, urine N-acetyl-β-D-glucosaminidase; UTGF, urine TGF-β; UUN, urinary urea nitrogen.

rizes a narrative report of safety and adherence to the interventions in included studies.

Subgroup analysis

We originally planned to compare interventions focused on adding base via F + V, versus interventions that reduced acid, mostly by reducing dietary protein. However, the number of trials and the heterogeneity in the interventions did not make this possible. We were able to compare interventions focused on increasing plant-based foods, where the diet was entirely vegetarian or where F + V were provided to participants as the intervention, to dietary interventions that were not focused on plant-based foods. Our subgroup analysis revealed that plant-based food interventions increased serum bicarbonate levels by 4.79 units [(95% CI 1.74, 7.85); I^2: 96%] (Fig. 4a) while non-plant based dietary interventions did not increase serum bicarbonate [MD 0.95 (95% CI –0.18, 2.08); I^2: 0%] (Fig. 4b). Furthermore, plant-based food interventions led to a smaller reduction in eGFR [MD 4.83 (95% CI 0.65, 9.02); I^2: 68%] (Fig. 5a) while non-plant-based interventions showed no effects on eGFR [MD 0.47 (95% CI –1.17, 2.12); I^2: 0%] (Fig. 5b). A summary of the subgroup analysis results can be found in Supplementary data, Table S2.

DISCUSSION

This systematic review and meta-analysis of RCTs aimed to identify, appraise and synthesize the best available evidence regarding the effects of dietary interventions, which reduced dietary acid or added dietary base, in the management of metabolic acidosis, as well as their safety and compliance, in people with CKD and metabolic acidosis. Taken together, these findings suggest beneficial effects of dietary interventions on serum bicarbonate, parameters of kidney function, calcium, phosphorus and SBP, with no significant effects on albumin, BMI and serum potassium.

To date, there are no well-established treatments for metabolic acidosis, and current clinical practice guidelines do not recommend a specific therapy, or strongly endorse a threshold for treatment and maintenance [31]. Concerns regarding pill burden are important in patients with CKD, and dietary interventions, with their other pleotropic effects are an appealing alternative management strategy. Our findings suggest that dietary interventions may be effective at treating metabolic acidosis, with minimal adverse effects and high tolerability.

For serum bicarbonate, the pooled dietary treatment effect of 2.98 (0.77, 5.19) mEq/L was similar to the effects seen in studies of oral alkali [2.59 (1.51, 3.66)] [32] or hydrochloric acid binders [3.08 (2.40, 3.77)] [33]. It is possible that these dietary interventions may lead to lower levels of uremic toxins and could therefore delay the initiation of dialysis, beyond effects on eGFR alone [34].

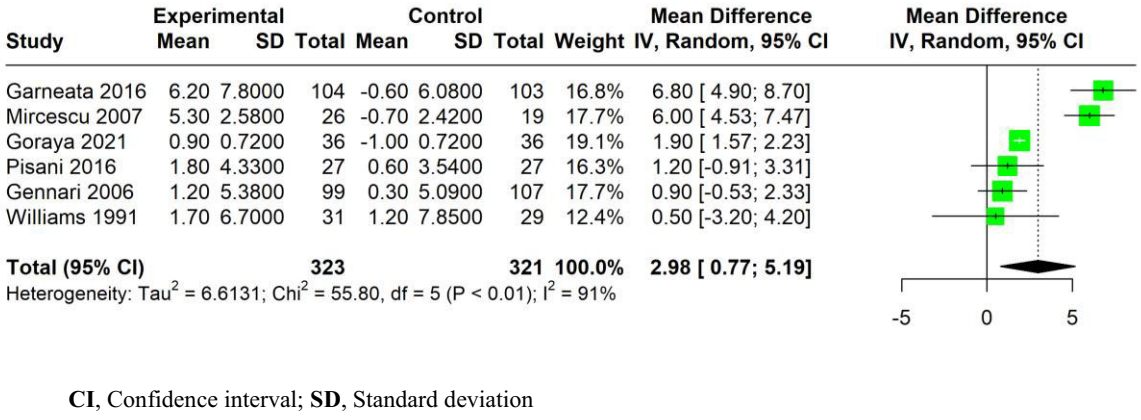
Our subgroup analysis indicated a superiority of plant-based dietary interventions over non-plant-based diets in improving serum bicarbonate. The common element of plant-based interventions in the current meta-analysis is F + V, which has the most base-producing potential [35].

As per suggestions from the current KDIGO guideline, pharmacological therapy (with or without dietary interventions) is warranted for adults with clinical implication (serum bicarbonate levels <18 mEq/L) [9]. From all studies included in this review, one study (Garneata 2016) had participants who met this KDIGO criteria in which sVLPD was shown to improve serum bicarbonate levels, compared with LPD [22]. Nevertheless, in studies included, all levels of serum bicarbonate have been randomized and our

Table 3: Detailed summary of the dietary interventions and their comparators in the included studies.

Study	Intervention	Comparator
Williams 1991 [29]	I-1: LPD (dietary protein and phosphate restriction with 0.6 g/kg BW/day protein and 800 mg/day phosphate); I-2: dietary phosphate restriction only (1000 mg/day phosphate)	Neither protein nor phosphate restriction
Gennari 2006 [27] (Study B)	VLPD (0.28 g/kg BW/day protein, supplemented with a mixed salt preparation of basic AAs, totaling 0.28 g/kg BW/day)	LPD (0.575 g/kg BW/day protein with 65% of protein from high biologic value sources)
Mircescu 2007 [28]	sVLPD (0.3 g/kg BW/day of vegetable proteins and ketoanalogs of EAAs)	Conventional LPD (0.6 g/kg BW/day protein, including high biological value proteins)
Goraya 2013 [12]	F + V (fruit and vegetables, free of charge, to reduce dietary PRAL by half)	Alkali therapy [oral $NaHCO_3$ (1.0 mEq/kg BW/day)]
Pisani 2016 [30]	6-TD (this 6-TD intervention, was a list of 6 simple points that guided participants to modify their dietary habits (like avoiding salt, dairy, sausages, salami, limiting fish, meat and egg, replacing regular noodle/bread with hypoproteic foods); all participants were also encouraged to eat F + V during their 3 daily meals, no further nutritional counseling thereafter + pharmacological therapies)	Standard LPD (a standard diet with 0.8 g of protein/kg BW/day, minimum 30 kcal/kg BW/day (25 in overweight patients), 3–6 g NaCl/day, and hypoproteic noodle and bread); written standard diet not customized to patients' dietary habits—no further nutritional counseling thereafter + pharmacological therapies
Garneata 2016 [22]	sVLPD [0.3 g/kg BW/day protein + ketoanalogs of EAAs 0.125 g/dry BW/day (Ketosteril)]	Conventional LPD (0.6 g/kg BW/day protein, including high biological value proteins)
Goraya 2021 [25]	I-1: F + V (fruit and vegetables, free of charge, to reduce dietary PRAL by half); I-2: alkali therapy [oral $NaHCO_3$ (0.3 mEq/kg BW/day)]	Usual care (treated according to extant guidelines but without dietary acid reduction therapy)

BW, body weight; EAA, essential amino acid; I, intervention; PRAL, potential renal acid load; sVLPD, severe hypoproteic diet supplemented with ketoanalogs.



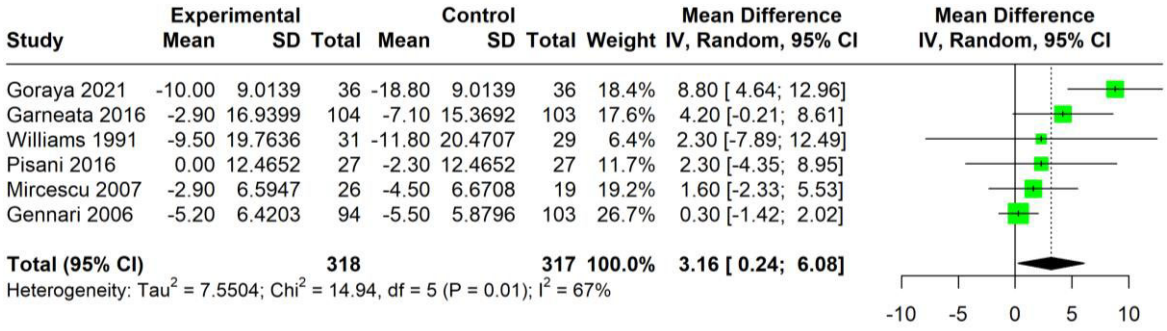
CI, Confidence interval; **SD**, Standard deviation

Figure 2: Effect of dietary interventions aimed at reducing acid and/or adding base on acid-base balance (serum bicarbonate).

findings from this review indicates that dietary interventions can be advised in people with all levels of serum bicarbonate (regardless of their need for pharmacological treatment), provided they are considered safe in terms of other aspects. To be able to draw more solid findings with this regard, RCTs with adequate sample size and proper design are needed.

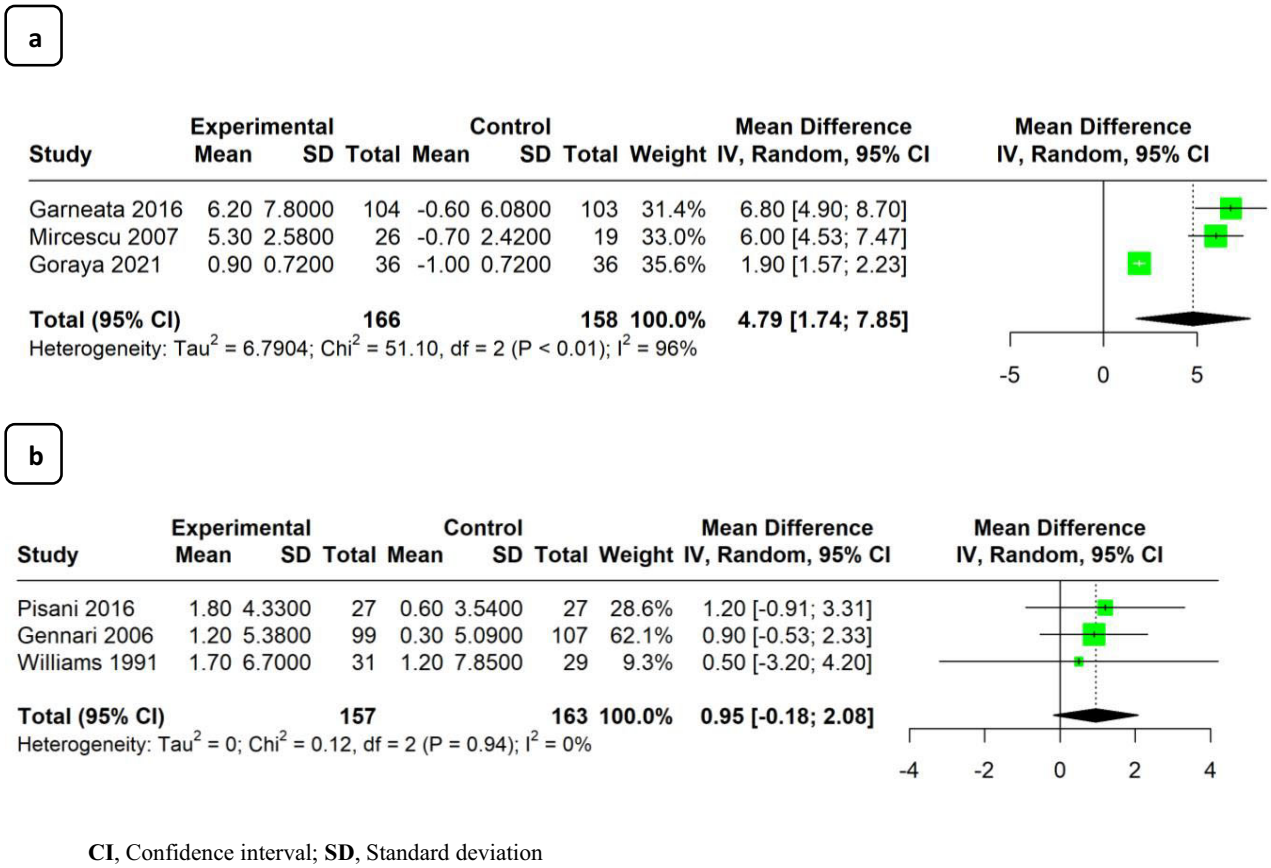
Our overall analysis did not show change in requirement of RRT from the dietary interventions, however we did not have data on the timing of dialysis initiation (eGFR) in any of the studies. Findings from our analysis are suggestive of a beneficial effect of dietary interventions on parameters of kidney function. Our overall analysis suggests that dietary interventions may help preserve eGFR and prevent its decline. In subgroup analysis, increasing plant-based food interventions [22, 25, 28] were more effective in preserving eGFR than non-plant based food interventions [27, 29, 30]. It is difficult to provide a safe eGFR above which most individuals can safely consume plant-based diets in this study. However, this is important to note that the largest study in our review [Garneata (2016), N = 207] had the baseline eGFR range 18 [intervention: 18 (15.5, 20.1); control: 17.9 (14.3, 19.3)]—which was also the lowest eGFR among included studies. This finding is supported by recent studies that showed beneficial effects of vegetarian diets on kidney function [36–38].

Our pooled analysis also showed that dietary interventions improved SBP compared with control group with very low heterogeneity. This is in line with research into the Dietary Approaches to



CI, Confidence interval; **eGFR,** estimated Glomerular Filtration Rate; **SD**, Standard deviation

Figure 3: Effect of dietary interventions aimed at reducing acid and/or adding base on eGFR.

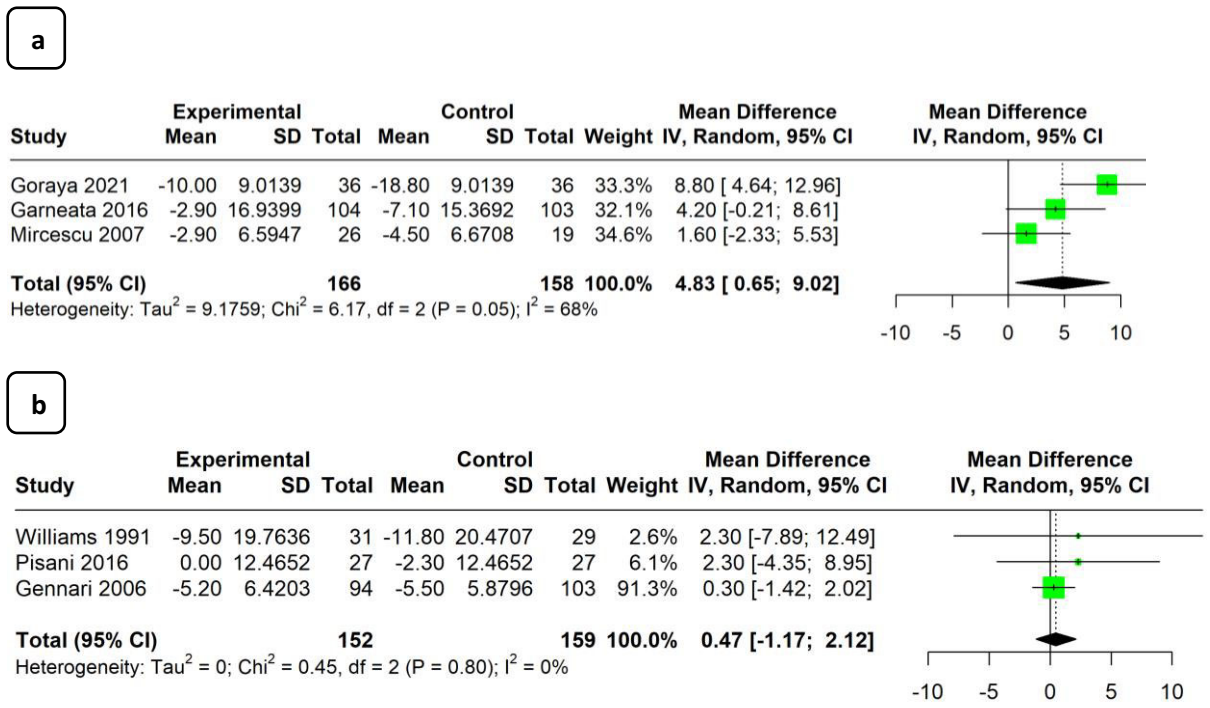


CI, Confidence interval; **SD**, Standard deviation

Figure 4: Subgroup analysis: effects of plant-based food interventions (a) vs. non-plant based food interventions (b) on serum bicarbonate.

Stop Hypertension (DASH) diet which is strongly associated with lowered blood pressure (BP) [39] and is the most typical dietary intervention strategy for BP control [40]. Part of the attributed antihypertensive effect of DASH diet can be related to high potassium content and reduced dietary acid load [41].

It is important to note that serum potassium was not affected by the dietary interventions in the pooled analysis, despite the increases in F + V consumption in many of the interventions such as the vegetarian sVLPD [22] and F + V delivery [25]. One potential explanation of this finding is that although potassium content of different foods is chemically equivalent, the distribution within the body and excretion of potassium is influenced by the other nutrients. Furthermore, the largest study in this meta-analysis [Garneata (2016), $N = 207$], had no serum potassium restriction in the eligibility criteria with no adverse events related to hyperkalemia [22]. Hence, potassium-rich plant-based foods might contribute to a higher intracellular distribution of dietary potassium, due to their ability to contribute dietary base and the stimulation of insulin from the accompanying carbohydrate, and a higher fecal excretion of potassium due to their fiber content [42]. We also found that dietary interventions reduced serum phosphate and increased serum calcium, thereby potentially adding another mechanism of improving kidney and cardiac function and outcomes.



CI, Confidence interval; **eGFR,** estimated Glomerular Filtration Rate; **SD**, Standard deviation

Figure 5: Subgroup analysis: effects of plant-based food interventions (a) vs. non-plant-based food interventions (b) on eGFR.

Previous meta-analyses have evaluated the effects of dietary interventions on CKD progression [43–45]. Our meta-analysis focused on studies looking into the effects of dietary acid–base modification on different parameters in CKD including bicarbonate, eGFR, potassium and markers of mineral metabolism. To our knowledge, one similar meta-analysis was conducted by Navaneethan *et al.* in 2019 evaluating effects of treatments of metabolic acidosis, including oral alkali supplementation or dietary intervention in CKD and found that these interventions significantly increased serum bicarbonate, reduced the rate of decline in eGFR, and reduced the risk of progression to end-stage renal disease [16]. Our findings can be applied as a complementary to the study by Navaneethan *et al.* We focused on dietary interventions and incorporated all possible data from Goraya (2013) [12] and Garneata (2019) [26] in the narrative synthesis in addition to the updated findings from Goraya (2021) [25]. Since compliance to diet is always a challenge [46], in our review we summarized available findings about compliance to dietary acid reduction which can be helpful in designing future studies in this area.

Our study has several limitations. Like all meta-analyses, the quality of our findings is dependent on the methodology of individual studies. The overall quality of the studies was low, however, the high-risk rating due to lack of blinding of participants and personnel should be interpreted cautiously and balanced against the nature of certain dietary interventions which make that inherently difficult, if not impossible, to blind in many circumstances. Furthermore, significant heterogeneity was observed for our main outcome (serum bicarbonate), as well as eGFR, RRT initiation, serum phosphorus and serum potassium. This heterogeneity could be related to the variety in dietary interventions, comparators, trial populations and geographical regions. We were able to perform subgroup analyses for two variables (serum bicarbonate and eGFR) based on dietary intervention type. Although the heterogeneity remained high in the increasing plant-based food subgroup, we believe the findings are still valuable and informative. We also have to acknowledge that although practical and widely used, serum bicarbonate may not be enough for evaluating acid–base balance in people with CKD; and studies suggest a complete measurement of acid–base indices for accurate assessment of acid–base status in people with CKD [47]. Future high quality studies with proper design and selection of accurate parameter will help in providing further understanding of the effects of dietary intake on parameters related to CKD. In order to overcome the limitations we faced in this meta-analysis, we complemented our quantitative results with a narrative synthesis of the findings (Table 2) to be able to draw more inclusive interpretation and we believe that reviewing the current limitations in the evidence can inform future high-quality research in this area.

Overall, our systematic review and meta-analysis is suggestive of the beneficial effects of dietary interventions aimed at reducing acid and/or adding base in the management of metabolic acidosis, kidney function, blood pressure, calcium and phosphate with no adverse effects on serum potassium and nutritional status. Furthermore, our subgroup analysis indicated a superiority of increasing plant-based foods in improving serum bicarbonate and preserving eGFR, over non-plant-based food interventions. Future large well-designed studies focusing on adding dietary base via F + V are needed to strengthen these findings.

SUPPLEMENTARY DATA

Supplementary data are available at *Nephrology Dialysis Transplantation* online.

ACKNOWLEDGEMENTS

We would like to thank Tyler Ostapyk for conducting the PRESS review of our search strategy.

FUNDING

This study is funded by University of Manitoba, Seven Oaks Chronic Disease Innovation Centre, Mitacs and Canadian Institutes of Health Research (CIHR) (CIHR Number: 177969).

AUTHORS' CONTRIBUTIONS

D.M. is a content expert in nutritional interventions who contributed to the study conception, design, study screening, quality assessment, providing input for manuscript preparation and critically revising the manuscript. R.M. is a content expert in nutritional interventions who contributed to the study conception, design, double title and abstract and full text screening, providing input for manuscript preparation and critically revising the manuscript. N.T. is a nephrologist who provided expertise in chronic kidney disease and contributed to the conception and design of the study, quality assessment, providing input for manuscript preparation and critically revising the manuscript. S.M. is a postdoctoral fellow in nutrition who contributed to double title and abstract and full text screening, data extraction and entry, and preparation of the initial manuscript draft. A.M.A.-S. and R.R. provided content expertise in knowledge synthesis and meta-analysis and provided input for manuscript preparation and revision. N.A. is a health sciences librarian who developed the search strategy based on input from D.M., R.M., A.M.A.-S., R.R. and N.T., contributed to manuscript preparation and revision. T.F. is a health economist and biostatistician who conducted the meta-analyses and contributed to the interpretation and preparation of findings and provided input for manuscript preparation and revision. T.R. is a Masters student in nutrition who contributed to data extraction and manuscript preparation.

DATA AVAILABILITY STATEMENT

The Endnote database, as well as final extraction sheets and data regarding risk of bias assessment will be available upon request.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Hill NR, Fatoba ST, Oke JL *et al.* Global prevalence of chronic kidney disease–a systematic review and meta-analysis. *PLoS One* 2016;**11**:e0158765. https://doi.org/10.1371/journal.pone.0158765
2. Raphael KL. Metabolic acidosis in CKD: core curriculum 2019. *Am J Kidney Dis* 2019;**74**:263–75. https://doi.org/10.1053/j.ajkd.2019.01.036
3. Raphael KL. Metabolic acidosis and subclinical metabolic acidosis in CKD. *J Am Soc Nephrol* 2018;**29**:376–82. https://doi.org/10.1681/ASN.2017040422
4. Adamczak M, Surma S. Metabolic acidosis in patients with CKD: epidemiology, pathogenesis, and treatment. *Kidney Dis* 2021;**7**:452–67. https://doi.org/10.1159/000516371
5. Kraut JA, Madias NE. Metabolic acidosis of CKD: an update. *Am J Kidney Dis* 2016;**67**:307–17. https://doi.org/10.1053/j.ajkd.2015.08.028
6. Witham MD, Band M, Ahmed A *et al.* Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double-blind, placebo-controlled trial. *BMC Med* 2020;**18**:91. https://doi.org/10.1186/s12916-020-01542-9
7. Shi H, Su X, Yan B *et al.* Effects of oral alkali drug therapy on clinical outcomes in pre-dialysis chronic kidney disease patients: a systematic review and meta-analysis. *Ren Fail* 2022;**44**:106–15. https://doi.org/10.1080/0886022X.2021.2023023
8. Łoniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. *Kidney Int* 2014;**85**:529–35. https://doi.org/10.1038/ki.2013.401
9. Stevens PE, Ahmed SB, Carrero JJ *et al.* KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024;**105**:S117–314. https://doi.org/10.1016/j.kint.2023.10.018
10. Osuna-Padilla IA, Leal-Escobar G, Garza-García CA *et al.* Dietary acid load: mechanisms and evidence of its health repercussions. *Nefrologia (Engl Ed)* 2019;**39**:343–54. https://doi.org/10.1016/j.nefroe.2019.08.001
11. Scialla JJ, Anderson CAM. Dietary acid load: a novel nutritional target in chronic kidney disease? *Adv Chronic Kidney Dis* 2013;**20**:141–9. https://doi.org/10.1053/j.ackd.2012.11.001
12. Goraya N, Simoni J, Jo C-H *et al.* A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. *Clin J Am Soc Nephrol* 2013;**8**:371–81. https://doi.org/10.2215/CJN.02430312
13. Goraya N, Simoni J, Jo C-H *et al.* Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int* 2014;**86**:1031–8. https://doi.org/10.1038/ki.2014.83
14. Goraya N, Munoz-Maldonado Y, Simoni J *et al.* Fruit and vegetable treatment of chronic kidney disease-related metabolic acidosis reduces cardiovascular risk better than sodium bicarbonate. *Am J Nephrol* 2019;**49**:438–48. https://doi.org/10.1159/000500042
15. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med* 2017;**377**:1765–76. https://doi.org/10.1056/NEJMra1700312
16. Navaneethan SD, Shao J, Buysse J *et al.* Effects of treatment of metabolic acidosis in CKD: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2019;**14**:1011–20. https://doi.org/10.2215/CJN.13091118
17. Page MJ, McKenzie JE, Bossuyt PM *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. https://doi.org/10.1136/bmj.n71
18. McGowan J, Sampson M, Salzwedel DM *et al.* PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;**75**:40–6. https://doi.org/10.1016/j.jclinepi.2016.01.021
19. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC Chapter 8: Assessing risk of bias in a randomized trial [last updated October 2019]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane, 2024. Available from www.training.cochrane.org/handbook
20. Higgins JPT, Li T, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect [last updated Au-

gust 2023]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane, 2024. Available from www.training.cochrane.org/handbook
21. Higgins JPT, Li T, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect [last updated August 2023]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane, 2024. Available from www.training.cochrane.org/handbook
22. Garneata L, Stancu A, Dragomir D *et al.* Ketoanalogue-supplemented vegetarian very low–protein diet and CKD progression. *J Am Soc Nephrol* 2016;**27**:2164. https://doi.org/10.1681/ASN.2015040369
23. Pathak M, Dwivedi SN, Deo S *et al.* Which is the preferred measure of heterogeneity in meta-analysis and why? A revisit. *Biostat Biometrics Open Acc* 2017;**1**:1–7.
24. Goraya N, Simoni J, Munoz Maldonado Y *et al.* Dietary acid reduction with fruits and vegetables better prevents transition of stage 3 CKD to stage 4 than oral NaHCO3. *J Am Soc Nephrol* 2017;**28**:233.
25. Goraya N, Munoz-Maldonado Y, Simoni J *et al.* Treatment of chronic kidney disease-related metabolic acidosis with fruits and vegetables compared to NaHCO3 yields more and better overall health outcomes and at comparable five-year cost. *J Ren Nutr* 2021;**31**:239–47. https://doi.org/10.1053/j.jrn.2020.08.001
26. Garneata L, Mocanu CA, Mocanu AE *et al.* FO012 Vegetarian severe hypoproteic diet supplemented with keto-analogues for predialysis chronic kidney disease patients: the influence on long term prognosis. *Nephrol Dial Transplant* 2019;**34**:gfz096.FO012. https://doi.org/10.1093/ndt/gfz096.FO012
27. Gennari FJ, Hood VL, Greene T *et al.* Effect of dietary protein intake on serum total CO2 concentration in chronic kidney disease: Modification of Diet in Renal Disease study findings. *Clin J Am Soc Nephrol* 2006;**1**:52–7. https://doi.org/10.2215/CJN.00060505
28. Mircescu G, Gârneaţă L, Stancu SH *et al.* Effects of a supplemented hypoproteic diet in chronic kidney disease. *J Ren Nutr* 2007;**17**:179–88. https://doi.org/10.1053/j.jrn.2006.12.012
29. Williams P, Stevens M, Fass G *et al.* Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *QJM Int J Med* 1991;**81**:837–55.
30. Pisani A, Riccio E, Bellizzi V *et al.* 6-tips diet: a simplified dietary approach in patients with chronic renal disease. A clinical randomized trial. *Clin Exp Nephrol* 2016;**20**:433–42. https://doi.org/10.1007/s10157-015-1172-5
31. Levin A, Stevens PE, Bilous RW *et al.*Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
32. Hultin S, Hood C, Campbell KL *et al.* A systematic review and meta-analysis on effects of bicarbonate therapy on kidney outcomes. *Kidney Int Rep* 2021;**6**:695–705. https://doi.org/10.1016/j.ekir.2020.12.019
33. Liu W, Li L, Zhang X *et al.* Efficacy and safety of veverimer in the treatment of metabolic acidosis caused by chronic kidney disease: a meta-analysis. *Front Pharmacol* 2021;**12**:643128. https://doi.org/10.3389/fphar.2021.643128
34. Ko GJ, Obi Y, Tortoricci AR *et al.* Dietary protein intake and chronic kidney disease. *Curr Opin Clin Nutr Metab Care* 2017;**20**:77. https://doi.org/10.1097/MCO.0000000000000342
35. Banerjee T, Crews DC, Wesson DE *et al.* High dietary acid load predicts ESRD among adults with CKD. *J Am Soc Nephrol* 2015;**26**:1693–700. https://doi.org/10.1681/ASN.2014040332
36. Xu K, Cui X, Wang B *et al.* Healthy adult vegetarians have better renal function than matched omnivores: a cross-sectional study in China. *BMC Nephrol* 2020;**21**:268. https://doi.org/10.1186/s12882-020-01918-2
37. Dinu M, Colombini B, Pagliai G *et al.* Effects of vegetarian versus Mediterranean diet on kidney function: findings from the CARDIVEG study. *Eur J Clin Invest* 2021;**51**:e13576. https://doi.org/10.1111/eci.13576
38. Świątek Ł, Jeske J, Miedziaszczyk M *et al.* The impact of a vegetarian diet on chronic kidney disease (CKD) progression–a systematic review. *BMC Nephrol* 2023;**24**:1–8. https://doi.org/10.1186/s12882-023-03233-y
39. Craddick SR, Elmer PJ, Obarzanek E *et al.* The DASH diet and blood pressure. *Curr Atheroscler Rep* 2003;**5**:484–91. https://doi.org/10.1007/s11883-003-0039-5
40. Guo R, Li N, Yang R *et al.* Effects of the modified DASH diet on adults with elevated blood pressure or hypertension: a systematic review and meta-analysis. *Front Nutr* 2021;**8**:725020.
41. Krupp D, Esche J, Mensink GBM *et al.* Dietary acid load and potassium intake associate with blood pressure and hypertension prevalence in a representative sample of the German adult population. *Nutrients* 2018;**10**:103. https://doi.org/10.3390/nu10010103
42. St-Jules DE, Goldfarb DS, Sevick MA. Nutrient non-equivalence: does restricting high-potassium plant foods help to prevent hyperkalemia in hemodialysis patients? *J Ren Nutr* 2016;**26**:282–7. https://doi.org/10.1053/j.jrn.2016.02.005
43. Rhee CM, Ahmadi S, Kovesdy CP *et al.* Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. *J Cachexia Sarcopenia Muscle* 2018;**9**:235–45. https://doi.org/10.1002/jcsm.12264
44. Li A, Lee H-Y, Lin Y-C. The effect of ketoanalogues on chronic kidney disease deterioration: a meta-analysis. *Nutrients* 2019;**11**. https://doi.org/10.3390/nu11050957
45. Rughooputh MS, Zeng R, Yao Y. Protein diet restriction slows chronic kidney disease progression in non-diabetic and in type 1 diabetic patients, but not in type 2 diabetic patients: a meta-analysis of randomized controlled trials using glomerular filtration rate as a surrogate. *PLoS One* 2015;**10**:e0145505. https://doi.org/10.1371/journal.pone.0145505
46. Kelly JT, Rossi M, Johnson DW *et al.* Beyond sodium, phosphate and potassium: potential dietary interventions in kidney disease. *Semin Dial* 2017;**30**:197–202. https://doi.org/10.1111/sdi.12580
47. Nagami GT, Kraut JA. Regulation of acid-base balance in patients with chronic kidney disease. *Adv Chronic Kidney Dis* 2022;**29**:337–42. https://doi.org/10.1053/j.ackd.2022.05.004

Received: March 18, 2024; Editorial decision: August 13, 2024