Effects of Treatment of Metabolic Acidosis in CKD: A Systematic Review and Meta−Analysis

Appendix 1. SEARCH STRATEGY

Cochrane CENTRAL search strategy

ID	Search
#1	kidney disease:ti,ab,kw
#2	renal insufficiency:ti,ab,kw
#3	chronic renal disease:ti,ab,kw
#4	chronic renal insufficiency:ti,ab,kw
#5	chronic renal failure:ti,ab,kw
#6	end-stage renal disease:ti,ab,kw
#7	end-stage renal failure:ti,ab,kw
#8	kidney injury:ti,ab,kw
#9	diabetic nephropathy:ti,ab,kw
#10	diabetic nephropathies:ti,ab,kw
#11	diabetic kidney disease:ti,ab,kw
#12	hypertensive nephropathy:ti,ab,kw
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14	acidosis:ti,ab,kw
#15	metabolic acidosis:ti,ab,kw
#16	acid-base imbalance:ti,ab,kw
#17	serum bicarbonate:ti,ab,kw
#18	blood bicarbonate:ti,ab,kw
#19	total CO2:ti,ab,kw
#20	#14 or #15 or #16 or #17 or #18 or #19
#21	#13 or #20
#22	bicarbonate supplementation:ti,ab,kw
#23	alkali:ti,ab,kw
#24	alkaline:ti,ab,kw
#25	oral bicarbonate:ti,ab,kw
#26	sodium bicarbonate:ti,ab,kw
#27	potassium bicarbonate:ti,ab,kw
#28	sodium citrate:ti,ab,kw
#29	potassium citrate:ti,ab,kw
#30	calcium citrate:ti,ab,kw
#31	calcium carbonate:ti,ab,kw
#32	calcium acetate:ti,ab,kw
#33	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34	fruits and vegetables:ti,ab,kw
#35	protein-restricted diet:ti,ab,kw
#36	low-protein diet:ti,ab,kw
#37	very low-protein diet:ti,ab,kw
#38	vegetarian diet:ti,ab,kw

#39 vegan diet:ti,ab,kw
#40 #34 or #35 or #36 or #37 or #38 or #39
#41 #33 or #40
#42 renal disease progression:ti,ab,kw
#43 progression of CKD:ti,ab,kw
#44 glomerular filtration rate:ti,ab,kw
#45 estimated glomerular filtration rate:ti,ab,kw
#46 GFR:ti,ab,kw
#47 eGFR:ti,ab,kw
#48 renal function decline:ti,ab,kw
#49 eGFR decline:ti,ab,kw
#50 creatinine clearance:ti,ab,kw
#51 albuminuria:ti,ab,kw
#52 proteinuria:ti,ab,kw
#53 renal replacement therapy:ti,ab,kw
#54 kidney transplantation:ti,ab,kw
#55 dialysis:ti,ab,kw
#56 initiation of renal replacement therapy:ti,ab,kw
#57 initiation of dialysis:ti,ab,kw
#58 serum creatinine:ti,ab,kw
#59 serum cystatin C:ti,ab,kw
#60 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59
#61 mortality:ti,ab,kw
#62 cardiovascular mortality:ti,ab,kw
#63 renal mortality:ti,ab,kw
#64 hospitalization:ti,ab,kw
#65 cardiovascular event rate:ti,ab,kw
#66 heart failure:ti,ab,kw
#67 myocardial infarction:ti,ab,kw
#68 coronary artery disease:ti,ab,kw
#69 peripheral artery disease:ti,ab,kw
#70 hypertension:ti,ab,kw
#71 #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70
#72 muscle strength:ti,ab,kw
#73 mid arm circumference:ti,ab,kw
#74 tricep skin-fold thickness:ti,ab,kw
#75 nutritional status:ti,ab,kw
#76 body mass index:ti,ab,kw
#77 normalized protein nitrogen appearance:ti,ab,kw
#78 serum albumin:ti,ab,kw
#79 physical assessment:ti,ab,kw
#80 sit-to-stand test:ti,ab,kw
#81 hand strength:ti,ab,kw
#82 walking test:ti,ab,kw
#83 bone fracture:ti,ab,kw

#84 bone density:ti,ab,kw
#85 bone formation:ti,ab,kw
#86 bone growth:ti,ab,kw
#87 insulin resistance:ti,ab,kw
#88 #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87
#89 sleep quality:ti,ab,kw
#90 sleep apnea:ti,ab,kw
#91 sleep disorder:ti,ab,kw
#92 actigraphy:ti,ab,kw
#93 adverse effect:ti,ab,kw
#94 edema:ti,ab,kw
#95 hyperkalemia:ti,ab,kw
#96 hypernatremia:ti,ab,kw
#97 electrolyte:ti,ab,kw
#98 calcification:ti,ab,kw
#99 #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98
#100 #60 or #71 or #88 or #99
#101 #21 and #41 and #100

MEDLINE

((((((((((((((((((((kidney disease) OR "chronic kidney disease") OR renal insufficiency) OR chronic renal insufficiency) OR "kidney injury") OR chronic kidney failure) OR "end-stage kidney disease") OR "end-stage renal failure") OR diabetic nephropathies) OR "diabetic nephropathy") OR "diabetic kidney disease") OR "hypertensive nephropathy") OR acidosis) OR "metabolic acidosis") OR acid-base imbalance) OR bicarbonates) OR "serum bicarbonate") OR "blood bicarbonate") OR "total CO2")) AND ((((((((((((((("bicarbonate supplementation") OR alkalies) OR "alkali") OR "alkaline") OR "oral bicarbonate") OR sodium bicarbonate) OR "potassium bicarbonate") OR "sodium citrate") OR potassium citrate) OR calcium citrate) OR calcium carbonate) OR "calcium acetate") OR ("fruits and vegetables")) OR protein-restricted diet) OR "low-protein diet") OR "very low-protein diet") OR vegetarian diet) OR vegan diet)) AND ((("renal disease progression") OR "progression of CKD") OR glomerular filtration rate) OR "estimated glomerular filtration rate") OR "GFR") OR "eGFR") OR "renal function decline") OR "eGFR decline") OR "creatinine clearance") OR albuminuria) OR proteinuria) OR renal replacement therapy) OR kidney transplantation) OR dialysis) OR "initiation of renal replacement therapy") OR "initiation of dialysis") OR "doubling of serum creatinine") OR "doubling of serum cystatin C") OR mortality) OR "all-cause mortality") OR "cardiovascular mortality") OR "renal mortality") OR hospitalization) OR "cardiovascular events") OR heart failure) OR myocardial infarction) OR coronary artery disease) OR peripheral artery disease) OR hypertension) OR muscle strength) OR "mid-arm circumference") OR "triceps skin-fold thickness") OR nutritional status) OR body mass index) OR "normalized protein nitrogen appearance") OR serum albumin) OR "physical assessment") OR "sit-stand-sit") OR hand strength) OR "quadriceps strength") OR "leg press") OR walking speed) OR "fall-related injuries") OR bone fracture) OR bone density) OR "bone

growth") OR "bone formation") OR insulin resistance) OR "HOMA-IR") OR "sleep quality") OR "sleep disorder") OR "sleep apnea") OR actigraphy) OR adverse effects) OR electrolytes) OR hyperkalemia) OR hypernatremia) OR edema) OR "calcification")) AND (((clinical trial) OR controlled clinical trial) OR randomized controlled trial)

OUTCOMES

We included eGFR measurements that were either estimated using the Modification of Diet in Renal Disease (MDRD), or the Chronic Kidney Disease Epidemiology Collaboration (CKD−EPI) equations, or calculated using the creatinine clearance derived from a 24−hour urine collection as reported in the studies at the end of study period. The eGFR decline per year was analyzed only in trials that had a treatment duration of more than 1 year; it was calculated by dividing the overall eGFR decline (mL/min) by the treatment duration (year) of the study.

QUALITY OF STUDIES

In nine studies, methods for generating the randomization sequence were of low risk, while these methods were unclear in the remainder of the studies (Figure S1). Allocation concealment was assessed as low risk in six studies, but allocation methods were unclear in another six studies. In none of the studies were participants and investigators blinded to the intervention group, and outcome assessors were blinded in only one of the 14 trials included in the analysis. Incomplete outcome data reporting was adjudicated as low risk for 10 studies and unclear for four studies. Risk of selective reporting was low for nine studies, unclear for four studies, and high risk for one study. Publication bias was tested by visual examination of the funnel plots (Figure S2 and S3) and showed no evidence of publication bias for eGFR decline.

SENSITIVITY ANALYSIS

In an analysis that excluded studies enrolling patients with low normal serum bicarbonate, similar improvement in eGFR decline was noted with oral alkali supplementation or dietary intervention (Figure S4 and S5). Similarly, in an analysis that excluded studies that compared

low protein diet to usual diet showed qualitatively similar results that favored dietary intervention (eGFR decline: MD -4.45 ml/min, 95% CI -8.00, -0.91).

Figure S1. Effects of oral alkali supplementation or dietary intervention on kidney disease progression at the end of study period in CKD patients (excluding studies that enrolled participants with low-normal serum bicarbonate levels)

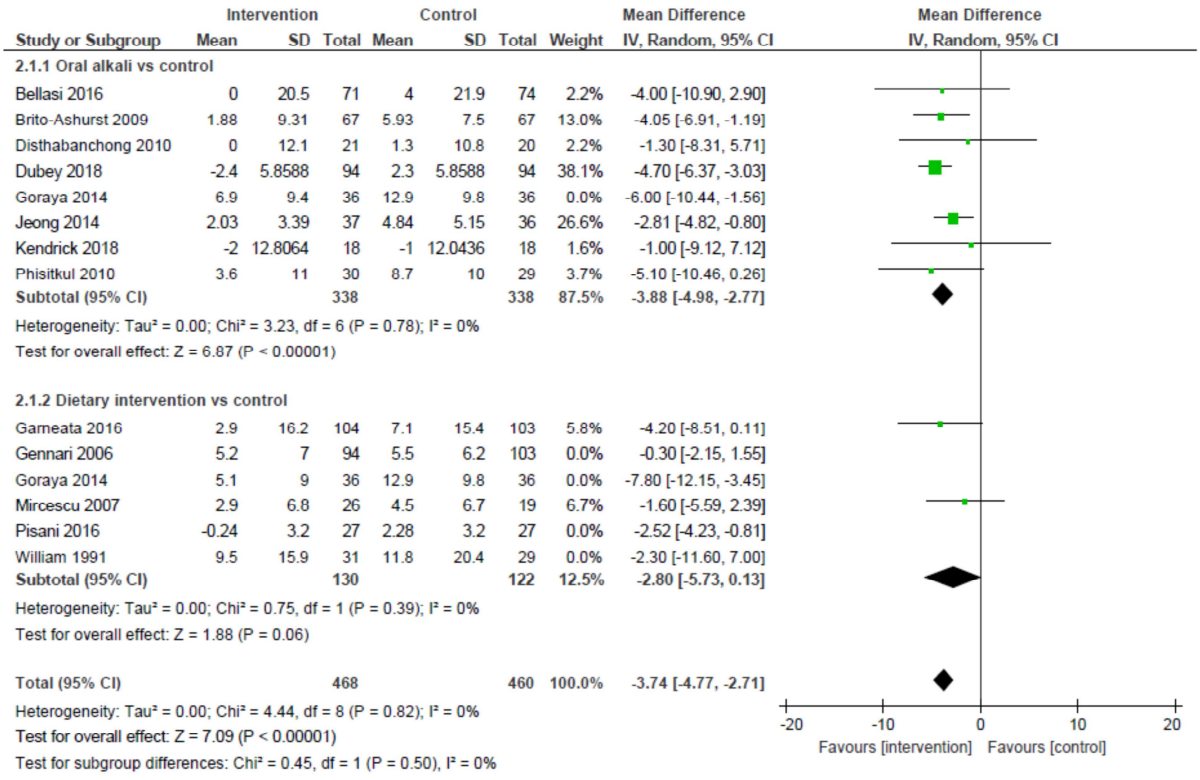

Figure S2. Effects of oral alkali supplementation or dietary intervention on eGFR slope (eGFR decline per year) (excluding studies that enrolled participants with low-normal serum bicarbonate levels)

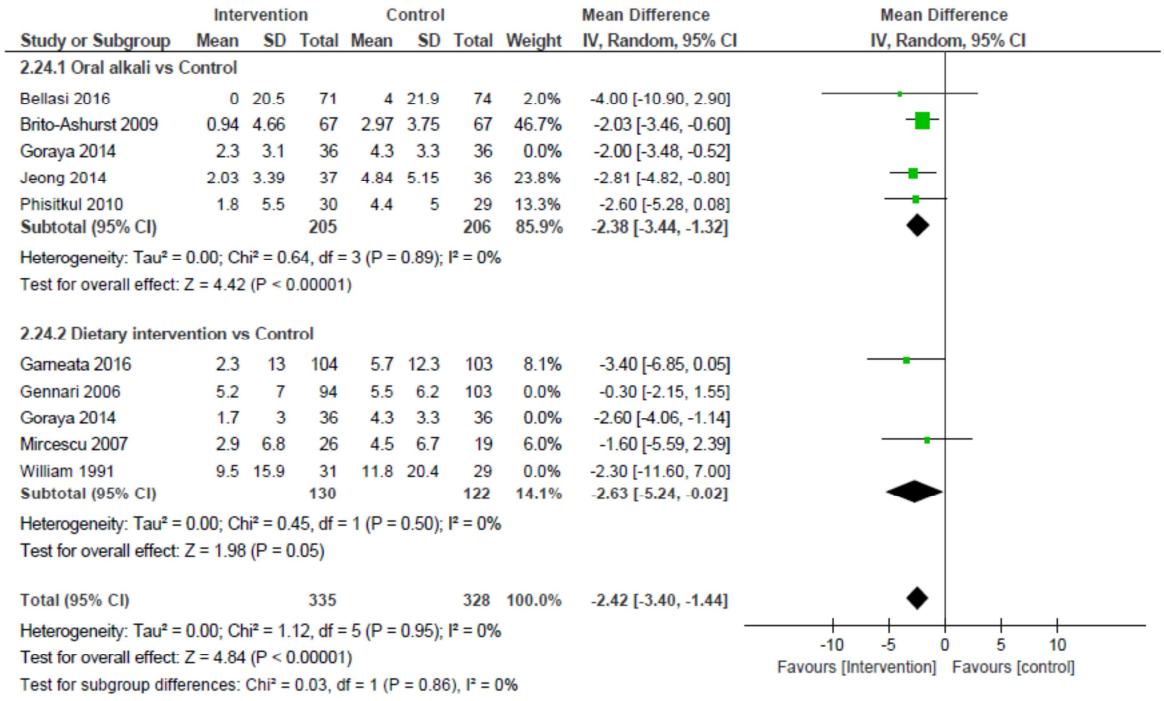

Figure S3. Assessment of risk of bias using Cochrane Collaboration Tool

Figure S4. Funnel plot for publication bias on end of-study eGFR decline

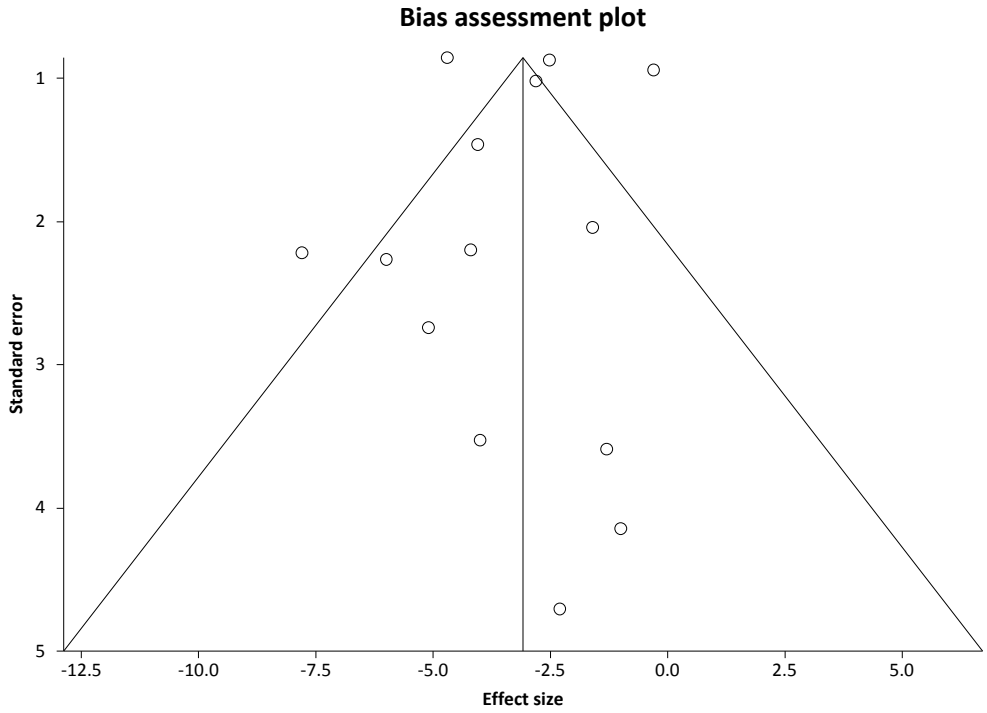

Figure S5. Funnel plot for publication bias on change in serum bicarbonate

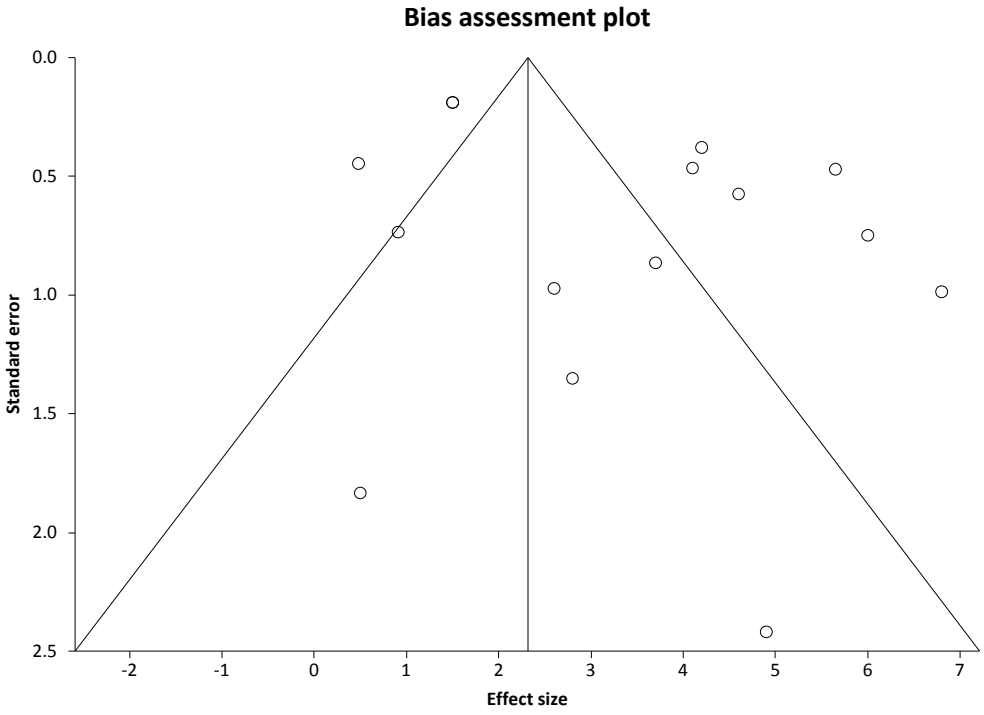

Table S1. GRADE quality of evidence

The table describes the classification of the quality of evidence according GRADE guidance

Grade	Definition
Very low quality	There is very little confidence in the effect estimate and the effect is likely to be substantially different from the estimate of effect
Low quality	There is limited confidence in the effect estimate and the true effect may be substantially different from the estimate of the effect
Moderate quality	There is moderate confidence in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
High quality	There is high confidence that the true effect lies close to that of the estimate of the effect

Table S2. Key inclusion and exclusion criteria of the included studies

Reference	Key Inclusion Criteria	Key Exclusion Criteria
Oral alkali supplementation		
Bellasi, 2016	CKD stage 3b/4 patients of 18 to 80 years, serum bicarbonate <24 mEq/L	Neoplastic diseases, autoimmune diseases, chronic heart failure NYHA class III-IV, uncontrolled arterial hypertension, severe peripheral arterial disease, cerebrovascular disease, neobladder or ureterosigmoidostomy, severe metabolic acidosis or use of $CaCO_3$ in the 3-month prior to study inclusion
de Brito-Ashurst, 2009	CKD stage 4/5 patients of >18 years of age, serum bicarbonate <20 and >16 mEq/L, stable clinical condition	Malignant disease, morbid obesity, cognitive impairment, chronic sepsis, poorly controlled blood pressure (>150/90 mm Hg despite use of 4 agents), overt congestive heart failure
Disthabanchong, 2010	Patients with average serum total CO_2 for the past 6 months ≤22 mM and eGFR ≤60 mL/min/1.73 m^2	Treated for thyroid disorder, had acute illnesses or were on thyroid hormone supplement, antithyroid drugs or corticosteroids
Dubey, 2018	CKD stage 3/4 patients of 18 to 65 years, venous bicarbonate levels <22 mEq/L with a stable eGFR (defined as<5% fluctuations during a 4-week observation period)	Structural and functional anomalies of the gastrointestinal tract, decompensated chronic liver disease, decompensated heart failure, morbid obesity (BMI ≥40 kg/m^2), malignancy, chronic infections, prior bicarbonate therapy for a duration of >2 weeks or receiving immunosuppression
Jeong, 2014	CKD stage 4/5 patients with eGFR <30 mL/min/1.73 m^2 and total CO_2 <22 mEq/L	Malignant disease, liver cirrhosis, infection, sepsis, and overt congestive heart failure
Mathur, 2006	Stable, mild to moderate CKD patients with serum creatinine <5°mg/dL.	Not disclosed
Phisitkul, 2010	CKD patients of 18 years, eGFR ≥20 and <60 mL/min/1.73 m^2, hypertensive nephropathy, history of compliance with clinic visits	Known primary kidney disease, history of diabetes or fasting blood glucose ≥110 mg/dL, history of malignancy, chronic infection, clinical evidence of cardiovascular disease, peripheral edema or diagnoses associated with edema (i.e., heart failure), renal artery stenosis and/or primary hyperaldosteronism
Kendrick 2018	CKD stage 3B/4 patients with eGFR 15−44 mL/min/1.73m^2 and serum bicarbonate level of <22 and ≥16 mEq/L	significant comorbid conditions, uncontrolled hypertension, overt congestive heart failure, use of alkali therapy, use of sevelamer

Table S2. Key inclusion and exclusion criteria of the included studies (Cont'd)

Reference	Key Inclusion Criteria	Key Exclusion Criteria
Dietary intervention		
Garneata, 2016	Adult CKD stage 4+ patients (eGFR <30 mL/min/1.73m^2), stable renal function for at least 12 weeks before enrollment (defined as a reduction in eGFR <4 mL/min per year, proteinuria <1 g/g urinary creatinine, good nutritional status as indicated by an SGA score A/B, and serum albumin >3.5 g/dL)	Poorly controlled arterial blood pressure (>145/85 mm Hg), relevant comorbidities (diabetes mellitus, heart failure, active hepatic disease, digestive diseases with malabsorption, or inflammation/anti-inflammatory therapy), uremic complications (pericarditis or polyneuropathy), or feeding inability (anorexia or nausea)
Gennari, 2006	Patients of 18 to 70 years, serum creatinine 1.2 to 7.0 mg/dL (women), or 1.4 to 7.0 mg/dL (men), or a creatinine clearance rate of <70 mL/min/1.73 m^2, mean arterial pressure ≤125 mm Hg	Diabetes mellitus requiring insulin, urine protein excretion rates of 10 g/day or more, weighed 160% of standard body weight
Mircescu, 2007	Adult CKD stage 4+ patients (eGFR <30 mL/min/1.73m^2), stable renal function for at least 12 weeks before enrollment (defined as a reduction in eGFR <4 mL/min per year, proteinuria <1 g/g urinary creatinine, good nutritional status as indicated by an SGA score A/B, and serum albumin >3.5 g/dL)	Poorly controlled arterial blood pressure (>145/85 mm Hg), relevant comorbidities (diabetes mellitus, heart failure, active hepatic disease, digestive diseases with malabsorption, or inflammation/anti-inflammatory therapy), uremic complications (pericarditis or polyneuropathy), or feeding inability (anorexia or nausea)
Pisani, 2015	CKD patients of more than 18 Years, eGFR ≤45 mL/min/1,73 m^2, dietary protein intake 0.7-0.9 g/kg/day, stable throughout hospital stay	Inability to perform correct 24-hours urine collections, malignancies, treatment with immunosuppressive drugs, congestive heart failure (NYHA class III-IV), proteinuria >3,5 g/24 hours
Williams, 1991	Patients aged < 70 years; chronic renal failure (males: plasma creatinine > 150 umol/L; females: > 130 umol/L) with evidence of deteriorating renal function on serial plasma creatinine or creatinine clearance estimations; plasma creatinine <900 umol/L and plasma phosphate <2.0 mmol/L	Not disclosed

Table S2. Key inclusion and exclusion criteria of the included studies (Cont'd)

Reference	Key Inclusion Criteria	Key Exclusion Criteria
Oral alkali supplementation and dietary intervention		
Goraya, 2014	CKD patients of ≥ 18 years, nonmalignant hypertension, eGFR 30 to 59 mL/min/1.73m^2, macroalbuminuria, plasma total CO_2 >22 mM and < 24 mM, able to tolerate ACE inhibition, no diabetes or cardiovascular disease	Known primary kidney disease or findings consistent thereof, history of diabetes or fasting blood glucose ≥ 110 mg/dL, history of malignancy, chronic infection, clinical evidence of cardiovascular disease, peripheral edema or diagnoses associated with edema (i.e., heart failure), plasma potassium level >4.6 mEq/L, taking or inability to stop taking drugs (other than ACE inhibitors) that limit potassium excretion

Table S3. Effects of oral alkali supplementation on kidney disease progression endpoints in CKD patients

Outcomes	No. of Studies	No. of Patients	Effect Estimate [95% CI]	P values	I^2 (95% CI)%
eGFR decline (mL/min/1.73 m^2)	8	748	MD -4.0 [-5.1, -2.9]	<0.001	0 (0-56)
eGFR decline per year (mL/min/1.73 m^2/year)	5	483	MD -2.3 [-3.1, -1.4]	<0.001	0 (0-64)
Urinary ACR (mg/g)	2	131	MD -48 [-76, -19]	<0.001	0 (NA)
Progression to ESKD	2	174	RR 0.34 [0.08, 1.39]	0.13	64 (NA)

MD: Mean difference; RR- Relative risk; ESKD- end stage kidney disease; ACR- Albumin:creatinine ratio; NA- available

Table S4. Effects of dietary intervention on kidney disease progression endpoints in CKD patients

Outcomes	No. of Studies	No. of Patients	Effect Estimate [95% CI]	P values	I^2 (95% CI)%
eGFR decline (mL/min/1.73 m^2)	5	575	MD -2.8 [-4.9, -0.6]	0.01	65 (0-80)
eGFR decline per year (mL/min/1.73 m^2/year)	5	581	MD -1.9 [-3.0, -0.7]	0.002	11 (0-68)
Urinary ACR (mg/g)	1	72	MD -61 [-105, -17]	0.007	NA
Progression to ESKD	2	260	RR 0.33 [0.18, 0.61]	<0.001	0 (NA)

MD: Mean difference; RR- Relative risk; ESKD- end stage kidney disease; ACR- Albumin:creatinine ratio; NA- not available

Table S5 Effects of oral alkali supplementation on change in biochemical measurements

Outcomes	No. of Studies	No. of Patients	Effect Estimate [95% CI]	P values	I^2 (95% CI)%
Serum bicarbonate (mEq/L)	9	788	MD 3.7 [2.4, 5.1]	<0.001	93 (90-95)
Serum potassium (mEq/L)	3	279	MD -0.24 [-0.91, 0.43]	0.48	93(83-96)
Serum calcium (mg/dL)	6	530	MD -0.17 [-0.41, 0.07]	0.16	55(0-79)
Serum phosphate (mg/dL)	6	530	MD -0.09 [-0.28, 0.09]	0.31	0(0-59)
Serum albumin (g/L)	4	435	MD 0.67 [-1.10, 2.45]	0.46	78(0-90)
Serum PTH (pg/mL)	2	76	MD -22 [-126, 81]	0.67	42(NA)
Mid-arm muscle circumference (cm)	3	395	MD 0.3 [-0.2, 0.9]	0.24	0(0-73)

MD: Mean difference; NA-Not available

Table S6. Effects of dietary intervention on change in biochemical measurements and mid-arm muscle circumference

Outcomes	No. of Studies	No. of Patients	Effect Estimate [95% CI]	P values	I^2 (95% CI)%
Serum bicarbonate (mEq/L)	6	644	MD 2.7 [0.9, 4.5]	0.002	93(88-95)
Serum potassium (mEq/L)	2	279	MD -0.01 [-0.20, 0.18]	0.92	34(NA)
Serum calcium (mg/dL)	2	252	MD 0.52 [0.29, 0.75]	<0.001	0(NA)
Serum phosphate (mg/dL)	3	306	MD -1.21 [-2.42, 0.01]	0.05	77(0-91)
Serum albumin (g/L)	3	306	MD 0.30 [-1.54, 2.14]	0.75	61(0-87)
Mid-arm muscle circumference (cm)	2	252	MD 0.1 [-0.5, 0.7]	0.78	0(NA

MD: Mean difference; NA- Not available

Table S7. Effects of oral alkali supplementation/dietary intervention on kidney disease progression endpoints in CKD patients using fixed effects method

Outcomes	No. of Studies/ Comparisons	No. of Patients	Effect Estimate [95% CI]	P values	I^2 (95% CI)%
End-of-study eGFR decline (mL/min/1.73 m^2)	13 / 14	1,329	MD -3.1 [-3.9, -2.3]	<0.001	39(0-66)
eGFR decline per year (mL/min/1.73 m^2/year)	9 / 10	1,028	RR -2.1 [-2.8, -1.4]	<0.001	0(0-53)
Progression to ESKD	4	434	RR 0.30 [0.19, 0.48]	<0.001	17(0-73)
Urinary ACR (mg/g)	2 / 3	167	MD -51 [-76, -27]	<0.001	0(0-73)

MD: Mean difference; RR- Relative risk; ESKD- end stage kidney disease; ACR- Albumin:creatinine ratio

Table S8. Effects of oral alkali supplementation/dietary intervention on change in biochemical measurements using fixed effects method

Outcomes	No. of Studies/ Comparisons	No. of Patients	Effect Estimate [95% CI]	P values	I^2 (95% CI)%
Serum bicarbonate (mEq/L)	14 / 15	1,378	MD 2.3 [2.1, 2.5]	<0.001	93(91-95)
Serum potassium (mEq/L)	4 / 5	522	MD -0.02 [-0.07, 0.04]	0.52	88(73-93)
Serum calcium (mg/dL)	8	782	MD -0.06 [-0.17, 0.04]	0.26	82(64-89)
Serum phosphate (mg/dL)	9	836	MD -0.19 [-0.36, -0.02]	0.03	59(0-78)
Serum albumin (g/L)	7	741	MD -0.06 [-0.25, 0.12]	0.50	68(0-84)
Serum PTH (pg/mL)	2	76	MD -34 [-105, 36]	0.33	42(NA)
Mid-arm muscle circumference (cm)	5	647	MD 0.2 [-0.2, 0.6]	0.29	0(0-64)

MD: Mean difference; NA- not available