Effects of correcting metabolic acidosis on muscle mass and functionality in chronic kidney disease: a systematic review and meta-analysis

Wesley J. Visser[1]* [ID], Elma E.M. van de Braak[2], Anneke M.E. de Mik - van Egmond[1], Anna C. van der Burgh[3,4], Nicole M. de Roos[2], Inez Jans[5], Iris van der Hoef[6], Joanne F. Olieman[1], Ewout J. Hoorn[4] & David Severs[4]

[1]*Department of Internal Medicine, Division of Dietetics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands;* [2]*Division of Human Nutrition, Wageningen Centre for Food Sciences, Wageningen University, Wageningen, The Netherlands;* [3]*Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands;* [4]*Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center, Rotterdam, The Netherlands;* [5]*Department of Dietetics, Hospital Gelderse Vallei, Ede, The Netherlands;* [6]*Department of Dietetics, Hospital St. Antonius, Nieuwegein, The Netherlands*

Abstract

Metabolic acidosis unfavourably influences the nutritional status of patients with non-dialysis dependent chronic kidney disease (CKD) including the loss of muscle mass and functionality, but the benefits of correction are uncertain. We investigated the effects of correcting metabolic acidosis on nutritional status in patients with CKD in a systematic review and meta-analysis. A search was conducted in MEDLINE and the Cochrane Library from inception to June 2023. Study selection, bias assessment, and data extraction were independently performed by two reviewers. The Cochrane risk of bias tool was used to assess the quality of individual studies. We applied random effects meta-analysis to obtain pooled standardized mean difference (SMD) and 95% confidence intervals (CIs). We retrieved data from 12 intervention studies including 1995 patients, with a mean age of 63.7 ± 11.7 years, a mean estimated glomerular filtration rate of 29.8 ± 8.8 mL/min per 1.73 m^2, and 58% were male. Eleven studies performed an intervention with oral sodium bicarbonate compared with either placebo or with standard care and one study compared veverimer, an oral HCl-binding polymer, with placebo. The mean change in serum bicarbonate was +3.6 mEq/L in the intervention group and +0.4 mEq/L in the control group. Correcting metabolic acidosis significantly improved muscle mass assessed by mid-arm muscle circumference (SMD 0.35 [95% CI 0.16 to 0.54], $P < 0.001$) and functionality assessed with the sit-to-stand test (SMD -0.31 [95% CI -0.52 to 0.11], $P = 0.003$). We found no statistically significant effects on dietary protein intake, handgrip strength, serum albumin and prealbumin concentrations, and blood urea nitrogen. Correcting metabolic acidosis in patients with CKD improves muscle mass and physical function. Correction of metabolic acidosis should be considered as part of the nutritional care for patients with CKD.

Keywords   Kidney disease; Metabolic acidosis; Muscle; Nutritional status; Physical function

Introduction

In patients with chronic kidney disease (CKD), nutritional status, body composition, and muscle mass are closely linked to morbidity, mortality, and quality of life.[1,2] In addition, the loss of muscle mass is associated with a decrease in physical performance, worse quality of life, and increased hospitalization rates.[1,3–5]

Multiple CKD-related factors increase protein breakdown and decrease protein synthesis, leading to loss of muscle

mass.[1] With progression of CKD, there is a decline in spontaneous protein intake.[6] Furthermore, patients with non-dialysis dependent CKD may be encouraged to adhere to a protein-restricted diet due to concerns of hyperfiltration-related disease progression.[7]

Metabolic acidosis is common in patients with advanced CKD, especially when glomerular filtration rate (GFR) falls below 20 mL/min.[8] Metabolic acidosis acts as a potent stimulator of protein catabolism by triggering two systems responsible for intracellular protein degradation, caspase-3 and the ubiquitin–proteasome systems (UPS),[9] and by promoting insulin and growth hormone resistance.[10] Animal models and observational studies of patients with CKD suggest that metabolic acidosis contributes to a negative protein balance and that correction of metabolic acidosis may provide benefit.[9–14] The effect of correcting metabolic acidosis on nutritional status of patients with CKD is unknown. Therefore, we performed a systematic review and meta-analysis to determine the effect of correcting metabolic acidosis on nutritional status in patients with CKD.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] The search strategy was performed independently by two authors (W. V. and E. B.). We conducted an electronic literature search in both MEDLINE and the Cochrane Library from inception to June 2023. The search strategy and PRISMA checklist are provided in the Supporting Information. The study is registered at INPLASY as inplasy202350085.

Studies were eligible for inclusion if they included adult patients (≥18 years of age) with non-dialysis dependent CKD, if they used any type of intervention focused on correcting metabolic acidosis compared with a control group with or without placebo, and if they reported any kind of parameter that indicated nutritional status. As nutritional status can contain a wide range of parameters, a classification system was used based on Gibson et al.[16]: dietary protein intake, body composition, physical function, and biochemical parameters.

We manually conducted a backward citation search. Two investigators (W. V. and E. B.) independently reviewed each article to confirm eligibility. In case of disagreement, consensus was achieved by consulting the other co-authors.

Study selection, data extraction, and risk of bias assessment

Two investigators (W. V. and E. B.) extracted the data independently. Titles and abstracts were screened based on predefined inclusion and exclusion criteria in the protocol (Supporting Information). Similarly, full-text articles were screened using a predefined form to extract data. These included year of publication, study design and setting, population characteristics, description of intervention and control conditions, number of patients, and baseline and follow-up outcomes of interest. We requested any relevant missing information from original study authors and received the raw data from one author.[17] The risk of bias was separately assessed by W. V. and E. B. using the Cochrane risk of bias tools for randomized trials[18] and non-randomized studies of interventions.[19] The risk of bias was scored as 'low risk', 'some concern', or 'high risk'. Discrepancies were discussed and resolved through mutual agreement.

Meta-analyses

When ≥2 comparable studies assessed an objective parameter that indicated one of the domains of nutritional status, and when means ± standard deviations (SDs) were provided or could be calculated, we included these in subsequent meta-analyses. This was the case for the following parameters: dietary protein intake, mid-arm muscle circumference (MAMC), handgrip strength (HGS), sit-to-stand time (STS time), serum albumin and prealbumin concentrations, and blood urea nitrogen (BUN), representing the four domains of nutritional status.[16] We did not perform a meta-analysis for body weight and BMI as these do not reflect body composition. If mean difference was not reported, we used the data in the original article to calculate it. If the original data were expressed with interquartile range (IQR), we estimated the SDs by either of two methods.[20] First, in case of mean difference ± SD without *P*-value or confidence interval, we used the Cochrane method to calculate the correlation coefficient and used it to calculate the SD of the change.[20] Second, when the *P*-value or confidence intervals were reported, we used the RevMan calculator tool[21] to calculate the change SD. Random effects models were applied to obtain pooled standardized mean difference (SMD) and 95% confidence intervals (CIs), and were reported as main results. Pooled results were shown in forest plots. Data were gathered and analysed using Review Manager 5.4.1. We quantified heterogeneity using the I^2 metric and used chi-squared to test its statistical significance. $I^2 \geq 75\%$ alongside a statistically significant heterogeneity was considered to indicate considerable heterogeneity.[20] Results were considered statistically significant at $P < 0.05$. Publication bias was assessed through

funnel plots for all meta-analyses and Egger test for the meta-analyses with at least five studies included using IBM SPSS Statistics version 28.

Results

Our search yielded 383 articles. After excluding duplicate records and studies that did not meet the inclusion criteria, 12 publications remained (Figure 1). The 12 included studies consist of a total of 1995 patients ranging from 20 to 740 per study, with a mean age of 63.7 ± 11.7 years, and mean eGFR of 29.8 ± 8.8 mL/min per 1.73 m^2, 58% were male. Follow-up ranged from 2 months to 3 years. Out of the 12 studies, seven were open-label,[13,22–27] two single-blind,[17,28] and three were double-blind.[29–31] Eleven studies performed an intervention with oral sodium bicarbonate compared with either placebo[17,28,29,31] or with standard care.[13,22–27] One study compared veverimer, an oral HCl-binding polymer, with placebo.[30] The mean change in serum bicarbonate was +3.6 mEq/L in the intervention group and +0.4 mEq/L in the control group. The main characteristics of the included studies are summarized in Table 1. A more detailed overview is provided in Table 2.

Risk of bias in the included studies

Ten studies were assessed to have 'low risk' of bias,[13,22–25,27–31] and two studies were assessed as 'some concerns' relating to a lack of information on inclusion and/or randomization procedures.[17,26]

Dietary protein intake

Three out of the 12 trials[13,22,25] examined the dietary protein intake before and after the intervention with sodium bicarbonate. Other studies included in this systematic review only monitored protein intake at baseline to describe the average protein intake. One study found that dietary protein intake increased significantly after sodium bicarbonate supplementation ($P = 0.007$), and normalized protein nitrogen appearance (nPNA) decreased in the intervention group and increased in the control group ($P = 0.002$).[13] In one study there was no difference in dietary protein intake[25] and in another study there was no difference in nPNA[22] between intervention and control groups. In the meta-analysis, we included only the studies that assessed protein intake with a food diary and found no significant effect of sodium bicarbonate supplementation on dietary protein intake (SMD, 0.22; 95% CI −0.23 to 0.68, $P = 0.34$, $I^2 = 76\%$, Figure S1).

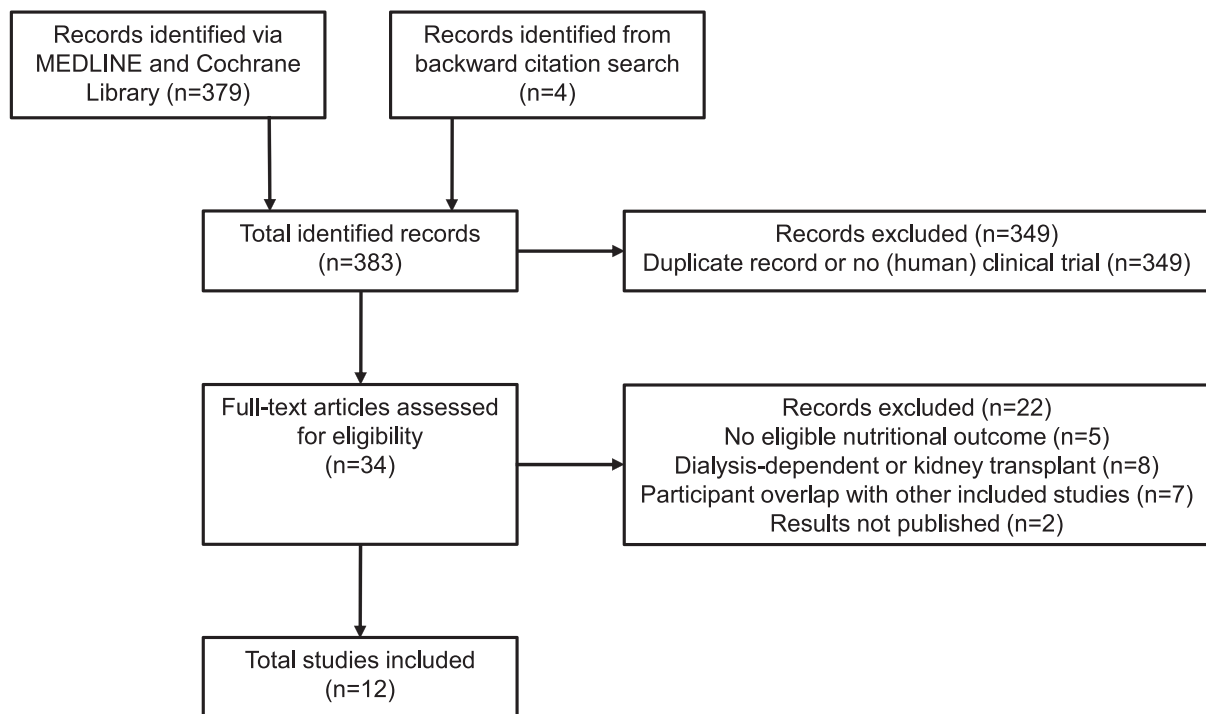

Figure 1 PRISMA flow diagram of study selection. Inclusion: Intervention study in patients with CKD focused on correcting metabolic acidosis compared with a control group with or without placebo and reporting nutritional outcomes.

Table 1 Summary of the main characteristics of the included studies

Study	*n*	Duration (months)	HCO$_3$ target value (mmol/L)	Placebo-controlled	Most important nutritional outcomes
Abramowitz M. et al.[17]	20	2	-	Yes	STS time, HGS
Alva S. et al.[23]	67	9	>23	No	MAMC, serum albumin
de Brito-Ashurst I. et al.[13]	134	24	>23	No	DPI, nPNA, MAMC, serum albumin
Di Iorio B.R. et al.[24]	740	36	24–28	No	Serum albumin
Dubey, A. et al.[25]	188	6	24–28	No	MAMC, fat mass, serum albumin, DPI, BUN
Jeong J. et al.[26]	80	12	>22	No	MAMC, serum (pre)albumin, BUN
Kendrick, J. et al.[27]	18	1.5	-	No	Catabolic and inflammation markers
Kittiskulnam P. et al.[22]	42	4	25	No	DPI, nPNA, MAMC, HGS, serum prealbumin
Mathur, R. et al.[28]	40	3	22–26	Yes	Serum albumin, BUN
Melamed, M. et al.[29]	149	24	-	Yes	STS time, HGS
Wesson, D.E. et al.[30]	217	3	22–29	Yes	KDQOL SF-36 (physical function), STS time
Witham, M. et al.[31]	300	12	>22	Yes	SPPB including 6-min walk speed, HGS, MAMC, skinfold thickness, serum albumin

DPI, dietary protein intake; HGS, hand grip strength; KDQOL SF-36, kidney disease quality of life instrument short form; LBM, lean body mass; MAMC, mid-arm muscle circumference; nPNA, normalized protein nitrogen appearance; SPPB, short physical performance battery; STS time, sit-to-stand time; BUN, blood urea nitrogen.

Body composition

All trials reported data on BMI or body weight. No clinically relevant changes before or after the trial nor differences between groups were found. Six out of the 12 trials[13,22,23,25,26,31] reported data on measures of body composition, specifically MAMC as a marker for muscle mass. Three of these found a significant increase in MAMC after sodium bicarbonate supplementation,[13,23,25] while three did not.[22,26,31] The meta-analysis showed a significant effect of sodium bicarbonate on MAMC (SMD, 0.35; 95% CI 0.16 to 0.54, *P* < 0.001, I^2 = 34%, Figure 2). The weighted mean difference between the groups after intervention was 0.74 [0.18–1.31] centimetres, from a weighted mean baseline MAMC of 24.0 cm. One study used multi-frequency bio-impedance analysis (MF-BIA) to determine muscle mass and found that after sodium bicarbonate supplementation, muscle mass was significantly increased (*P* = 0.04). However, the absolute changes did not significantly differ between the groups (*P* = 0.13).[22] Using double energy X-ray absorptiometry, one study found a significantly greater lean tissue mass after intervention compared with control (*P* = 0.002), while adipose tissue mass was unchanged (*P* = 0.51).[25] No other trial examined the effects of metabolic acidosis correction on adipose tissue mass.

Physical function

Five out of the 12 trials[17,22,29–31] reported data on measures of physical function. Four studies reported data on HGS, none of these found a significant effect of sodium bicarbonate supplementation.[17,22,29,31] In agreement, the meta-analysis showed no significant difference between the groups and considerable heterogeneity (SMD, −0.02 [95% CI −0.52 to 0.48], *P* = 0.94, I^2 = 83%, Figure S2). Three trials measured

STS time.[17,29,30] Abramowitz et al. tested STS time in both 5 and 10 repetitions and found improvement with sodium bicarbonate supplementation (*P* = 0.01 for five repetitions; *P* = 0.002 for 10 repetitions).[17] Wesson et al. found an improved STS time after veverimer (5 repetitions, *P* = 0.025) and no change in the placebo group (*P* = 0.063).[30] In contrast, Melamed et al. found no effect (*P* = 0.1 for five repetitions; *P* = 0.07 for 10 repetitions).[29] The meta-analysis for STS time after five repetitions showed a significant improvement after the acidosis-correcting intervention (SMD, −0.31 [95% CI −0.52 to 0.11], *P* = 0.003; I^2 = 0%, Figure 3). Weighted mean difference between the groups was −0.56 [−1.2–0.08] seconds in STS time. Three trials reported measures related to quality of life.[29–31] Witham et al.[31] recorded Kidney Disease Quality of Life Short Form (KDQOL SF-36) and the short physical performance battery (SPPB) after 3, 6, 12, and 24 months of sodium bicarbonate or no treatment. They did not find significant differences between the groups (KDQOL SF-36, *P* = 0.23; SPPB, *P* = 0.15). Melamed et al.[29] also assessed KDQOL SF-36 and found no statistically significant differences between the groups. Wesson et al.[30] used the KDQOL SF-36 question 3 (physical functioning domain) and found that the intervention group had greater quality of life related to physical functioning than the placebo group (*P* = 0.0122).

Biochemical parameters related to nutritional status

All trials reported data on biochemical measures related to nutritional status. Seven reported serum albumin concentration.[13,23–26,28,31] Of these, three found significant improvements in serum albumin levels in the intervention group.[13,23,24] However, our meta-analysis for albumin detected no significant difference between the groups (SMD, 0.19 [95% CI −0.05 to 0.42], *P* = 0.11, I^2 = 72%, Figure S3).

Table 2 Overview of all included studies with their most important outcomes and results

Study	Design	Population eGFR (mL/min/1.73 m²) HCO₃⁻ (mEq/L)	Intervention Dose (mEq/kg/day) and change in serum HCO₃⁻ (mEq/L)	Most important nutritional outcomes	Main results (compared with control group)
Abramowitz et al., 2013[17]	Single centre, Single-blinded, placebo controlled	$n = 20$ eGFR 15–45, HCO₃⁻ (20–24)	Dose: 0.3, 0.6 and 1.0 mEq/kg, ascending dose each 2 week; I: 22.2 ± 2.8 to 25.5 ± 2.3 (Δ = 3.2); C: 23.0 ± 2.4 to 22.2 ± 2.8 ($P < 0.001$)	STS time; HGS; Urinary urea nitrogen excretion; Urine creatinine; Serum potassium	↑ (both 5 and 10 repetitions); n.s.; →; n.s.
Alva S. et al., 2020[23]	Single centre, open label	$n = 67$ eGFR 15–30, HCO₃⁻ (10–20)	Dose: 0.37 mEq/kg; I: 16.6 ± 3.1 to 19.8 ± 1.9 (Δ = 3.1); C: 16.84 ± 2.2 to 16.32 ± 1.8 ($P < 0.001$)	Muscle mass; Serum albumin	→; ↑; ↑
de Brito-Ashurst et al., 2009[13]	Single centre, open label	$n = 134$ CrCl 15–30, HCO₃⁻ (16–20)	Dose: 0.28 mEq/kg; I: 19.8 ± 2.2 to 24.0 ± 3.8 (Δ = 4.2); C: 19.9 ± 1.5 to 20.0 ± 2.2 ($P < 0.001$)	DPI; nPNA; LBM (assessed by MAMC); Serum albumin; Serum potassium	↑; →; ↑; ↑; →
Di Iorio et al., 2019[24]	Multi centre, open label	$n = 740$ eGFR 15–59, HCO₃⁻ (18–24)	Dose: 0.6 mEq/kg; I: 21.7 ± 2.6 to 26.1 ± 1.7 (Δ = 4.4); C: 21.4 ± 2.1 to 21.9 ± 1.9 ($P < 0.001$)	Serum albumin; Creatinine clearance; Serum potassium	↑; n.s.; n.s.
Dubey, A et al., 2020[25]	Single centre, open label	$n = 188$ eGFR 15–59, HCO₃⁻ (<22)	Dose: 0.5 mEq/kg; I: 18.1(17.7–18.8) to 23.5(22.9–24) (Δ = 5.3); C: 18.1(17.6–18.6) to 17.8(17.4–18.4) ($P < 0.001$)	LBM; Fat mass; MAMC; Serum albumin; DPI; BUN	↑; n.s.; ↑; ↑; ↑; n.s.
Jeong J. et al., 2014[26]	Single centre, open label	$n = 80$ eGFR <15 or 15–30, HCO₃⁻ (<22)	Dose: 0.58 mEq/kg; I: 18.5 ± 3.4 to 19.8 ± 3.6 (Δ = 1.3); C: 18.9 ± 4.1 to 16.5 ± 3.8 ($P < 0.05$)	MAMC; Serum prealbumin, serum albumin; Transferrin; TLC; OPNI; PTH; BUN	n.s.; n.s.; n.s.; n.s.; ↓ (CKD5 only); ↓ (CKD5 only); n.s.; n.s.
Kendrick, J. et al., 2018[27]	Single centre, cross-over, open label	$n = 18$ eGFR 15–44, HCO₃⁻ (16–21)	Dose: 0.4 mEq/kg; I: 19.3 ± 2.9 to 22.0 ± 3.1 (Δ = 2.7); C: 19.7 ± 2.3 to 19.6 ± 3.2 ($P < 0.01$)	Serum potassium; hs-CRP; IL-6; iFGF23; C-telopeptide	n.s.; n.s.; n.s.; ↑; n.s.
Kittiskulnam et al., 2020[22]	Single centre, open label	$n = 42$ eGFR 15–59, HCO₃⁻ (<22)	Dose: 0.3 mEq/kg; I: 21.2 ± 2.0 to 24.0 ± 1.4 (Δ = 2.8); C: 20.9 ± 2.3 to 20.7 ± 2.3 ($P < 0.001$)	MAMC; 3-day diet record; Muscle mass (with MF-BIA); HGS; Serum prealbumin	↑; n.s.; ↑; n.s.; n.s.

(Continues)

Table 2 (continued)

Study	Design	Population eGFR (mL/min/1.73 m²) HCO₃⁻ (mEq/L)	Intervention Dose (mEq/kg/day) and change in serum HCO₃⁻ (mEq/L)	Most important nutritional outcomes	Main results (compared with control group)
Mathur, R. et al., 2006[28]	Single centre, single-blind, placebo controlled	$n = 40$ Serum creatinine <5 mg/dL, HCO₃⁻ (22–26)	Dose: 1.2 mEq/kg I: 19.5 ± 5.5 to 22.9 ± 7.1 (Δ = 3.4) C: 19.4 ± 3.7 to 17.9 ± 4.7 ($P < 0.05$)	BUN Serum creatinine Total serum protein Serum albumin	↑ n.s. n.s. n.s.
Melamed, M. et al., 2020[29]	Multi centre, double-blind, placebo controlled	$n = 149$ eGFR 15–59, –	Dose: 0.4 mEq/kg I: 24.0 ± 2.2 to 24.4 ± 2.8 (Δ = 0.4) C: 24.1 ± 2.6 to 23.6 ± 2.6 ($P < 0.001$)	PTH STS time HGS Levels of catabolic markers	↓ n.s. n.s. n.s n.s.
Wesson, D.E. et al., 2019[30]	Multi centre, double-blind, placebo controlled	eGFR 20–40,	Dose: 6 g veverimer/day I: 17.3 ± 1.4 to 21.8 ± 1.2 (Δ = 4.5) C: 17.3 ± 1.5 to 19.0 ± 1.3 ($P < 0.0001$)	Serum potassium KDQOL SF-36 physical function STS time	↑ n.s.
Witham, M. et al., 2020[31]	Multi centre, double-blind, placebo controlled	$n = 300$ eGFR 15–30, HCO₃⁻ (<22), >60 years	Dose: 0.22 mEq/kg I: 20.6 ± 2.6 to 22.5 ± 2.6 (Δ = 1.9) C: 20.1 ± 2.5 to 21.4 ± 3.9 ($P < 0.001$)	SPPB 6-min walk speed HGS Markers of bone turnover MAMC Triceps skinfold thickness Mid-thigh circumference Serum potassium	n.s. n.s. n.s. n.s. n.s. n.s. n.s. n.s.

Results project the possible statistically significant comparison between intervention group and control group. Arrows show statistically significant difference ($P < 0.05$) unless indicated otherwise.

Δ, difference between baseline end end-of-study; I, intervention; C, control; BUN, blood urea nitrogen; BW, body weight; DBP, diastolic blood pressure; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; FMD, fibromuscular dysplasia; HGS, handgrip strength; hs-CRP, high-sensitivity serum C-reactive protein; LBM, lean body mass; MAMC, mid arm muscle circumference; nPNA, normalized nitrogen protein appearance; n.m., not mentioned; n.s., no statistically significant difference; OPNI, Onodera's prognostic nutritional index; SBP, systolic blood pressure; sig., statistically significant; SPPB, short physical performance battery; STS time, sit-to-stand time; TLC, total lymphocyte count.
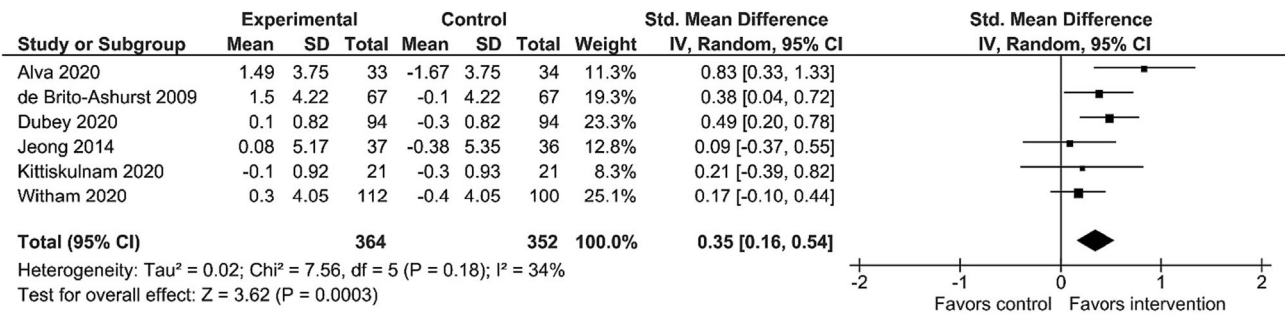
Figure 2 Effect of correcting metabolic acidosis on MAMC. IV, instrumental variable; SD, standard deviation.
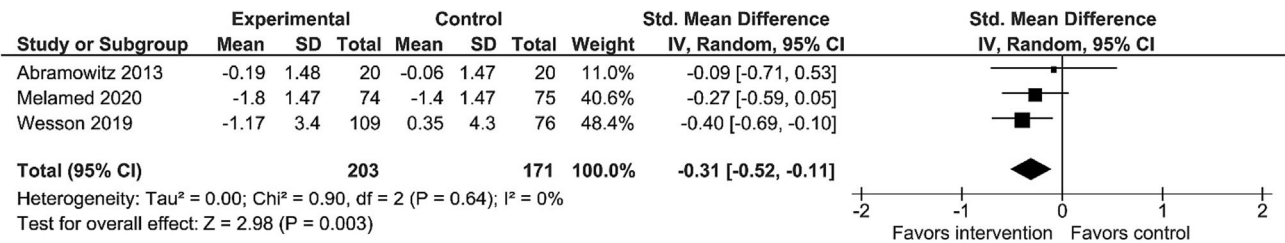

Figure 3 Effect of correcting metabolic acidosis on in STS time after five repetitions. IV, instrumental variable; SD, standard deviation.

Two trials[22,26] monitored serum prealbumin concentrations and found no significant differences between the groups. Accordingly, our meta-analysis for prealbumin detected no significant difference between the groups (SMD, 0.24 [95% CI −0.13 to 0.61], $P = 0.20$, $I^2 = 0\%$, Figure S4).

Two of three trials that monitored change in blood urea nitrogen (BUN) found no significant difference between groups.[25,26] In contrast, Mathur et al. observed a significantly slower rise of BUN in the intervention group than in the control group ($P < 0.05$).[28] The difference in BUN failed to reach statistical significance in the meta-analysis (SMD, −0.41 [95% CI −0.83 to 0.01], $P = 0.05$, $I^2 = 62\%$, Figure S5). Abramowitz et al. used urinary urea nitrogen excretion and found that it decreased after intervention ($P = 0.001$).[17] No other trial monitored this parameter. Three studies[17,27,29] reported changes in different catabolic markers related to inflammation and/or nutritional status (14-kDA actin fragment, ubiquitin ligases, MuRF1, IL-6, TNF-a, iFGF23, and IGF-1) but found no significant changes.

Adverse events

None of the included trials reported significant differences in the number or type of adverse events. Only one study[31] reported more frequent adverse events in the treatment group (457 vs. 400), driven in part by higher rates of gastrointesti-

nal, cardiac and respiratory adverse events but did not provide data on statistical significance. Specifically, cardiac adverse events occurred in 32 versus 19 participants. For this study, we tested significance between the groups and found no significant difference, $P = 0.08$.

Assessment of publication bias

The funnel plots indicated no outliers for the meta-analysis of dietary protein intake, MAMC, STS time, and serum prealbumin. They indicated one outlier[29] for HGS, one[25] for BUN, and two[13,23] for serum albumin concentration. For the meta-analyses with at least five studies included, we conducted the Egger test and it showed no statistical indications of publication bias (MAMC, $P = 0.273$; serum albumin concentration, $P = 0.936$, Figure S6).

Discussion

We performed a systematic review and meta-analysis of 12 studies testing the effect of correcting metabolic acidosis on the nutritional status of patients with CKD and found that it significantly improved measures of muscle mass and functionality. No statistically significant effects were found on di-

etary protein intake, HGS, serum albumin and prealbumin, and BUN.

Our hypothesis of the working mechanism is based on the notion that metabolic acidosis is one of the several factors in patients with CKD that leads to an imbalance in protein synthesis and protein breakdown, resulting in a negative protein balance. A negative protein balance leads to a decrease in muscle mass and muscle strength. The loss of muscle mass, as a result of a negative protein balance, is associated with worse quality of life, higher hospitalization rates, and mortality.[1,2] Thus, an intervention that corrects the negative protein balance can also affect muscle mass, muscle strength, quality of life, risk of hospitalization and mortality. We found a weighted mean difference between the groups after intervention of 0.74 [0.18–1.31] centimetres, from a weighted mean baseline MAMC of 24.0 centimetres. This increase in MAMC suggests that correcting metabolic acidosis helps correct the protein balance, because an increase in muscle mass will not occur in a status of negative protein balance. Higher values of MAMC indicate greater lean mass and have been associated with reduced mortality in haemodialysis patients.[32,33] The hypothesis is further supported by the fact that MAMC decreases in all control groups in the meta-analysis, suggesting that the control groups remain in a negative protein balance. Furthermore, the effect size we found is larger than in some nutritional intervention trials in patient populations with significant morbidity. For example, Bernardes et al. performed a systematic review and meta-analysis on the effect of increased energy and/or protein intake on nutritional status in obstructive pulmonary disease patients and found an increase of 0.29 cm in MAMC.[34] In HD patients, Sahathevan et al. performed a 6-month open-label randomized controlled trial with oral nutritional supplements and found an increase in MAMC in the intervention group of 0.4 cm.[35] A precise assessment of risk reduction associated with correction of metabolic acidosis in this specific patient population is impossible, but observational data from related patient populations may provide an indication. The HEMO study was a randomized controlled trial in haemodialysis patients, with a mean follow-up of almost 3 years. In this patient population with a high risk of malnutrition and mortality, a higher baseline MAMC was associated with a relative mortality risk of 0.83 per 2 cm.[32]

The hypothesis that correction of metabolic acidosis improves protein balance is further supported by the finding that a decrease in nPNA occurs with the correction of metabolic acidosis.[13,36] Similarly, Abramowitz et al. found that oral sodium bicarbonate significantly reduced urine urea nitrogen excretion.[17] Because we did not find an effect of correcting metabolic acidosis on dietary protein intake (estimated by food diaries), lower urea appearance may be attributable to a decrease in protein degradation. This is in agreement with Reaich et al., who examined the effect of correction of metabolic acidosis in patients with CKD on whole-body protein

turnover and amino acid oxidation using primed constant infusions of L-[1-13C] leucine.[14] They found that metabolic acidosis is a reversible catabolic stimulus in patients with CKD and that correcting metabolic acidosis attenuates protein breakdown. As higher BUN may indicate greater protein degradation, we would expect a decrease in BUN by correcting metabolic acidosis. The numerical decrease in BUN after sodium bicarbonate failed to reach statistical significance in the meta-analysis ($P = 0.05$), probably due to the limited sample size. An additional explanation for the effect on MAMC could be that correcting metabolic acidosis ameliorates protein degradation by improving insulin resistance.[37]

The results of our meta-analyses suggest that correction of metabolic acidosis improves physical function assessed with STS time, but not when assessed with HGS. This seems somewhat contradictory, though an explanation for the fact that we only found significant effect on STS time but not on HGS could be because both assess physical function, but on different components. HGS is used to assess muscle strength, whereas the STS time requires a combination of muscle power, speed, and balance control.[38] This explanation is supported by Grgic et al. who showed that supplementation with sodium bicarbonate acutely improves peak anaerobic power, anaerobic capacity, and performance in endurance runs, but could not find significant differences in muscle strength.[39] Yee et al. found that STS time better represents physical function in sarcopenia rather than muscle strength (assessed with HGS) and suggested that poor outcome on STS time may be due to a reduction in muscle quality.[40] In addition to effects on muscle quality, differential effects of metabolic acidosis on different muscle fibre types could also be a part of the explanation.

We found no significant effect of correcting metabolic acidosis on serum albumin and prealbumin concentrations. These findings are in line with the systematic review of Roderick et al. who examined the benefits and harms of treating metabolic acidosis with published data up to October 2005.[41] They found no RCTs in patients with CKD and identified three trials in dialysis patients, and found no significant effect on serum albumin concentrations. Despite its wide use as an index of nutrition in patients with CKD, there is insufficient evidence to conclude that nutritional interventions raise serum albumin in patients with CKD with hypoalbuminaemia.[42] The serum albumin concentration should therefore be considered an unreliable isolated marker of nutritional status and its variance may be better explained by chronic inflammation rather than changes in nutritional status.[42]

Differences in participant and study characteristics may explain some of the variation in outcomes. Studies with a statistically significant effect tended to have lower serum bicarbonate concentrations at baseline, a greater increase in serum bicarbonate after treatment and the lowest MAMC values at baseline (weighted mean MAMC at baseline

23.0 cm vs. 25.3 cm). We could not find an additional explanation from study duration and medication dosage.

The optimal target range of serum bicarbonate concentrations for intervention studies is currently uncertain. In our analysis, most of the studies in which bicarbonate supplementation had a positive effect on parameters of nutritional status raised serum bicarbonate concentration to 23.5–26 mmol/L. Importantly, bicarbonate supplementation may slow CKD progression, even in individuals with serum bicarbonate concentrations of 22–24 mmol/L.[13,24,43–47] In our analysis, we found no difference in the number and type of adverse events between control and intervention groups, including in the incidence of congestive heart failure. This is in line with the findings of a recent meta-analysis, which suggest that sodium bicarbonate is unlikely to raise blood pressure or cause fluid retention.[48] It is unknown whether attaining higher serum bicarbonate concentrations yields further clinical benefits or induces harm. Animal studies suggest that metabolic acidosis inhibits vascular calcification and that alkalosis may enhance it.[49,50] In a large population-based cohort study of diuretic nonusers, serum bicarbonate >25 mmol/L was associated with higher aortic pulse pressure.[51] However, a cross-sectional study in an elderly population failed to demonstrate an association between acidity and arterial stiffness measured by pulse wave velocity.[52] In the absence of more definitive evidence, we suggest adhering to the 2020 KDOQI guidelines, which prudently suggest maintaining serum bicarbonate levels at 24–26 mmol/L.[7]

Our analysis was restricted to studies in which intervention consisted of sodium bicarbonate or the oral HCl binder veverimer. Importantly, nutritional interventions may also correct metabolic acidosis. Goraya et al. showed that increased intake of fruits and vegetables yielded better overall health outcomes than did oral sodium bicarbonate.[53] Unfortunately, they did not measure nutritional parameters. Apart from effects on correction of metabolic acidosis, fruits and vegetables have additional beneficial effects on the nutritional status of patients with CKD, including improved intake of vitamins and fibre. Because interventions with fruits and vegetables have been shown to correct metabolic acidosis

with low risk of developing hyperkalemia, we advocate for further research focusing on the effect of plant-based nutritional interventions to correct metabolic acidosis and their effect on nutritional status and safety.

This review and meta-analysis has some limitations. First, the studies included were limited and heterogeneous in design and number of patients. Between the studies, there were large differences in dosages and target values, sample size, and duration. In the included studies, no specific nutritional regimen was enforced and in some of the studies the protein intake at baseline was lower than recommended. Second, the total number of included studies per meta-analysis was relatively small. Even though our analyses suggest a low risk of a significant influence on outcomes by bias and heterogeneity we cannot completely exclude it because of the relatively low number of included studies.

In conclusion, this study shows that correcting metabolic acidosis with sodium bicarbonate or veverimer in patients with CKD has a positive and clinically meaningful effect on muscle mass and physical function. This suggests that correcting metabolic acidosis may deserve a more prominent place in efforts to preserve or improve the nutritional status of patients with CKD.

Conflict of interest

None.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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