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## The effects of different treatments for metabolic acidosis in non-dialytic chronic kidney disease: A systematic review and meta-analysis

*Efeito de diferentes tratamentos para acidose metabólica na doença renal crônica não dialítica: uma revisão sistemática e meta-análise*

### Abstract

**Objective:** The objective of this review was to evaluate which treatments are used to treat metabolic acidosis in Chronic Kidney Disease (CKD) and their effects on disease progression. **Methods:** A systematic review was carried out, using the PRISMA protocol, of randomized clinical studies in the following databases: Science Direct, Cochrane Library, and National Library of Medicine-PubMed. The inclusion criteria were original articles from randomized clinical trials with dietary intervention with an alkaline fruit and vegetable diet, oral alkali supplementation, or any combination used to treat metabolic acidosis in patients with non-dialysis-dependent CKD. **Results:** A total of seven studies were included in this review. All studies used some oral alkali as treatment, with sodium bicarbonate being the main alkali administered, and 57% (n=4) used an alkaline diet that was either in line or not with oral alkali. All interventions improved the metabolic acidosis condition. As for the Glomerular Filtration Rate (GFR), a delay in the decline of GFR was found in 57% (n=4) of the studies after improvement in metabolic acidosis. **Conclusions:** The treatment of metabolic acidosis, when added to dietary interventions, obtained more favorable results on the progression of CKD by improving, in addition to serum bicarbonate, other parameters of interest, such as blood pressure, plasma urea, calcium, phosphatemia, urinary sodium, urinary potassium, urinary albumin, and LDL. Thus, the data support the use of an alkaline diet in treatments to treat metabolic acidosis in patients with CKD.

**Keywords:** Chronic Kidney Disease. Renal insufficiency. Metabolic Acidosis. Glomerular Filtration Rate. Alkaline Diet. Bicarbonate.

### Resumo

**Objetivo:** O objetivo desta revisão foi avaliar quais os tratamentos utilizados para correção da acidose metabólica na doença renal crônica (DRC) e os efeitos sobre a progressão da doença. **Método:** Realizou-se revisão sistemática utilizando o protocolo PRISMA, de estudos clínicos randomizados nas bases de dados *Science Direct*, *Cochrane Library* e *National Library of Medicine-PubMed*. Os critérios de inclusão foram artigos originais de estudos clínicos randomizados com intervenção dietética com dieta alcalina à base de frutas e vegetais, suplementação de álcali oral ou qualquer combinação usada para tratar acidose metabólica em pacientes com DRC não dependentes de diálise. **Resultados:** Foram incluídos sete estudos nesta revisão, todos utilizando algum álcali oral como tratamento, sendo o bicarbonato de sódio o principal álcali ministrado e 57% (n=4) utilizaram dieta alcalina em consonância ou não com álcali oral. Todas as intervenções obtiveram melhora no quadro de acidose

metabólica. Quanto à taxa de filtração glomerular (TFG), constatou-se retardo no declínio da TFG em 57% (n=4) dos estudos após melhora da acidose metabólica.

**Conclusões:** O tratamento da acidose metabólica quando somado a intervenções dietéticas, obteve resultados mais favoráveis sobre a progressão da DRC por melhorar, além do bicarbonato sérico, outros parâmetros de interesse, como pressão arterial, ureia plasmática, calcemia, fosfatemia, sódio urinário, potássio urinário, albumina urinária e LDL. Assim, os dados apoiam o uso da dieta alcalina nos tratamentos para correção da acidose metabólica em paciente com DRC.

**Palavras-chave:** Doença renal crônica. Insuficiência renal. Acidose metabólica. Taxa de filtração glomerular. Álcalis. Dieta. Bicarbonato.

## INTRODUCTION

Chronic kidney disease (CKD) involves several changes affecting kidney structure and function, with multiple causes and prognostic factors. The main risk factors for CKD are diabetes, hypertension, obesity, a family history of CKD, smoking, and prolonged use of nephrotoxic medications such as antibiotics, painkillers, chemotherapy, antihypertensives, and anticoagulants.<sup>1,2</sup>

Anyone who, regardless of the cause, has a glomerular filtration rate (GFR)  $< 60$  mL/min/1.73m<sup>2</sup> or a GFR  $> 60$  mL/min/1.73m<sup>2</sup> associated with at least one marker of parenchymal kidney damage that has been present for at least three months is considered to have CKD.<sup>3</sup> With decreased GFR, the decline in renal capacity to synthesize ammonia and excrete hydrogen ions results in metabolic acidosis, with decreased serum bicarbonate concentration  $< 22$  mEq/L. The increase in metabolic acidosis contributes to reduced GFR, among other deleterious effects.<sup>1</sup>

Metabolic acidosis is a common CKD complication at different stages, and is the cause of tissue damage, especially musculoskeletal, altered protein and endocrine metabolism, malnutrition, and chronic inflammation, contributing to increased mortality.<sup>4</sup> The acid load in the diet, even in the absence of evident acidosis, leads to detrimental effects such as a decline in GFR, in addition to bone and muscle loss.<sup>5</sup> This is due to the fact that the renal inability to excrete acids causes the intracellular medium to acidify, generating acid-base imbalance and compromising enzymatic reactions.

Acidosis treatment can improve kidney function and slow the progression of CKD. The most common treatment for metabolic acidosis is supplementation with alkalis, mostly sodium bicarbonate, which, however, may exacerbate edema and/or hypertension in CKD. Another viable alternative is an alkaline diet, based on fruits and vegetables. Foods rich in protein, such as meat and cheese, contain higher acid loads, while fruits and vegetables contain a high alkalizing potential and contribute to health in general.<sup>6</sup> Studies suggest that reducing the acid load in the diet can improve subclinical acidosis, slow the decline in GFR in animal and human models, and improve the prognosis of patients with CKD.<sup>6,7</sup>

This study aimed to evaluate, using a systematic review with meta-analysis, the treatments used to treat metabolic acidosis in non-dialytic CKD and the effects on disease progression. Thus, by grouping results from oral treatments for metabolic acidosis, the aim is to analyze which treatments are most commonly used and yield better results on acidosis and CKD progression, with effects on the serum bicarbonate level and GFR. As a primary outcome, it is expected that oral treatments will lead to an improvement in metabolic acidosis; and as a secondary outcome that this improvement will delay the decline in GFR.

## METHODS

This is a systematic review aiming to answer the following study question: "What are the most commonly used treatments for treating metabolic acidosis, and which one has the best effect on the progression of CKD in non-dialysis patients?".

The review was performed in pairs, following the PRISMA recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).<sup>8</sup> This review was registered in PROSPERO - International prospective register of systematic reviews, under number CRD42020208639.

## Search and eligibility strategy

A paired systematic search for randomized clinical trials was carried out in the following databases: Science Direct, Cochrane Library, and National Library of Medicine-PubMed. A protocol for study search and selection was developed and performed independently by the authors, using the following combined descriptors: ("Chronic kidney disease" OR "Chronic Kidney Insufficiency" OR "Renal Insufficiency" OR "Glomerular Filtration Rate") AND ("metabolic acidosis" OR "Acid-Base Imbalance") AND ("treatment") AND ("diet" OR "dietary" OR "fruit" OR "vegetables" OR "alkali" OR "low-protein diet" OR "vegetarian diet") AND ("bicarbonate" OR "Sodium Bicarbonate" OR "Alkalies" OR "oral bicarbonate" OR "bicarbonate supplementation" according to DeCS/ MeSH and with the Boolean operators AND, OR, NOT, and AND NOT, adapted for each scientific database.

The inclusion criteria were original articles from randomized clinical trials with a dietary intervention using an alkaline diet based on fruits and vegetables, oral alkali supplementation, or any combination used to treat the risk of metabolic acidosis or an established condition in CKD patients not dependent on dialysis. Metabolic acidosis was defined as serum bicarbonate <22 mEq/L, and risk for metabolic acidosis as low normal serum bicarbonate (22-24 mEq/L).

Review articles, book chapters, guidelines, and other materials were not included, as reviewed clinical studies published by journals were prioritized, and studies with intravenous alkali interventions in acute metabolic acidosis cases were excluded. Language, year of publication, age and gender of the participants, and time of intervention were not restricted.

According to the eligibility criteria, the authors screened the studies independently, initially evaluating the title, followed by the abstract. Citations deemed potentially eligible by any of the reviewers were subjected to full-text screening. Disagreements were settled by consensus among the reviewers. The search was conducted from September 29th to October 2nd, 2020.

## Data extraction and analysis

The data of interest were extracted from the studies and organized in Chart 1, which contains information on the authors, year of publication, the purpose of the study, population characteristics (CKD number and stage), study characteristics (metabolic acidosis diagnosis, parameters assessed, number of participants per group, type and timing of interventions), main results, and main contributions measured by the authors.

**Chart 1.** Categorization matrix of the studies included in the systematic review on the effects of different treatments on metabolic acidosis in chronic kidney disease.

Author and Year	Objective	Population	Metabolic acidosis diagnosis	Intervention	Main results	Main contributions
Goraya et al., 2013 (10).	To test whether 1 year intake of fruits and vegetables or sodium bicarbonate have effects on GFR and metabolic acidosis.	71 patients with stage 4 CKD.	Serum bicarbonate < 22 mEq/L as measured by ultrafluorometry.	1-year intervention in two groups: - sodium bicarbonate (n=35); - base-inducing fruits and vegetables (n=36).	There was an improvement in metabolic acidosis in both groups. The GFR did not differ at baseline and after 1 year between the groups.	The data indicate that fruits and vegetables improve metabolic acidosis and reduce kidney damage in stage 4 CKD without producing hyperkalemia.
Goraya et al., 2014 (11).	To test whether treatment (Sodium Bicarbonate or fruit and vegetable based diet) decreases the decline in GFR and reduces Angiotensin II levels.	108 patients with stage 3 CKD.	Serum bicarbonate > 22 and <24 mEq/L, measured by ultrafluorometry.	3-year intervention in 3 groups: - standard treatment (n=36); - oral sodium bicarbonate (n=36); - base-inducing F+V fruits and vegetables (n=36).	Venous pH increased in the bicarbonate and F+V groups and blood pressure was lower in the F+V group. The GFR decreased in all three groups, but the loss was lower in the 3-year period with sodium bicarbonate or F+V.	Dietary acid reduction protects the kidneys in this population.
Jeong et al., 2014 (12).	To investigate the effects of oral sodium bicarbonate supplementation on CKD progression and nutritional indexes in patients with advanced CKD on pre-dialysis.	80 patients with stage 4 and 5 CKD.	Serum bicarbonate < 22 mEq/L.	12-month intervention in 2 groups: - oral sodium bicarbonate (n=40); - control (without alkali) (n=40).	Bicarbonate supplementation increased the total CO <sub>2</sub> serum level. The change in GFR in the intervention group was significantly lower than in the control group.	The study was a pioneer in examining the effects of bicarbonate supplementation in patients with stage 5 CKD who are not on dialysis.

**Chart 1.** Categorization matrix of the studies included in the systematic review on the effects of different treatments on metabolic acidosis in chronic kidney disease.(Continues)

Di Iorio et al., 2017 (13).	To evaluate mortality and dialysis risk or doubled creatinine levels.	146 patients with stage 3 and 4 CKD.	Serum bicarbonate < 22 mEq /L, measured every three months by potential renal acid load and net endogenous acid production.	12-month intervention in 2 groups: - vegetarian diet + sodium bicarbonate (n=54); - oral sodium bicarbonate (n=92).	The increase in serum bicarbonate was greater among the patients on the vegetarian diet, even with decreased oral bicarbonate use. The loss of renal function was greater in the group without a vegetarian diet.	A diet lower in protein, salt, and phosphate intake should be implemented to correct metabolic acidosis.
Bushinsky et al., 2018 (14).	To evaluate the efficacy and safety of TRC101® to increase serum bicarbonate in patients with CKD and metabolic acidosis.	135 patients In stage 3 or 4 CKD and with metabolic acidosis.	Serum bicarbonate 12-20 mEq/L.	14-day intervention in 2 groups: - controlled diet + placebo (n=31); - controlled diet + oral alkali TRC101® (n=104).	TRC101® has safely and significantly increased the level of serum bicarbonate, and 35% of treated patients reached normal parameters.	The study demonstrated that TRC101® was well tolerated in patients with CKD and was effective on acidosis within just 14 days.
Wesson, D et al., 2019a (15).	To evaluate the efficacy and safety of the Veverimer® alkali as a treatment for metabolic acidosis in patients with CKD.	217 patients with CKD who are not dialysis-dependent.	Serum bicarbonate in the 12-20 mEq/L range, measured in a fasting state using an i-STAT portable blood analyzer.	12-week intervention in 2 groups: - Veverimer® - oral alkali (n=124); - placebo (n=93).	The Veverimer® group experienced the highest % increase in serum bicarbonate.	Veverimer® corrected metabolic acidosis effectively and safely. They suggest long-term studies to assess deleterious effects and CKD progression.
Wesson et al., 2019b (16).	To evaluate the efficacy and safety of the Veverimer® alkali as a treatment for metabolic acidosis in patients with CKD.	196 patients with CKD who are not dialysis-dependent.	Serum bicarbonate in the 12-20 mEq/L range, measured in a fasting state using an i-STAT portable blood analyzer.	40-week intervention in 2 groups: - Veverimer® - oral alkali (n=114); - placebo (n=82).	The change in serum bicarbonate was greater with the use of oral alkali at all time points analyzed. The decrease in GFR was slower in the intervention group.	The medication tested (Veverimer®) safely and effectively corrects metabolic acidosis in patients with CKD.

The main outcomes analyzed were the values of metabolic acidosis after the intervention, changes in GFR decline at the end of the study period, improvement in CKD clinical parameters (systolic and diastolic blood pressure, blood glucose, hyperkalemia, calcemia, phosphatemia, plasma urea and sodium, among others), and measures related to nutritional status, if present.

The primary outcome was a change in metabolic acidosis with a 95% confidence interval (95%CI). Summary measures were estimated, and subgroup analysis was performed according to the type of intervention and control performed.

For the meta-analysis, the studies were grouped according to the type of intervention and control used with the respective standard deviation values before and after the study period in relation to serum bicarbonate. The meta-analysis was calculated using a fixed random effect model, and heterogeneity was evaluated using the Chi-squared test with a significance level of  $p < 0.10$ , with its magnitude determined by I-squared (I<sup>2</sup>). The analyses were performed using the "Metan" command in the Stata software (version 11.0). Furthermore, the existence of a small-study effect was evaluated by visual inspection of the funnel plot and calculation of Egger's test.

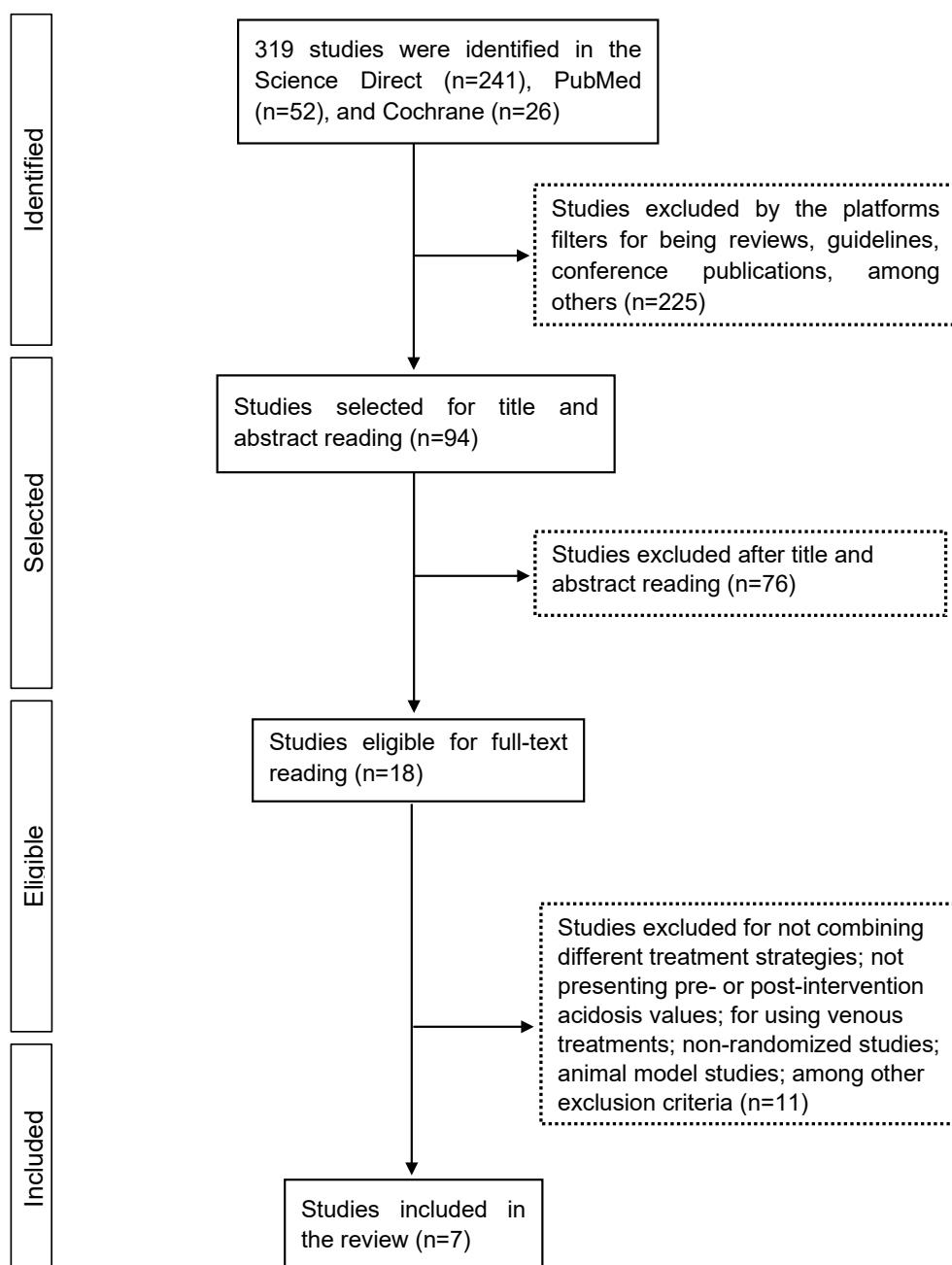
### Article quality analysis and risk of bias

The randomized clinical trials included in this review were submitted to the methodological quality analysis proposed by Jadad *et al.*<sup>9</sup> This scale consists of five questions, two of which are about randomization, two about double-blind masking, and one about losses and exclusions, where participants should check the yes or no option as an answer. Thus, the scale ranges from 0 to 5 points, according to the number of positive answers. A score lower than 3 indicates that the study has low methodological quality.

## RESULTS

A total of 319 articles were identified, of which 225 were excluded for being review articles, non-clinical studies, and conference publications, among others, resulting in 94 articles selected for the title and abstract analysis and later reading in full. The search in the Science Direct, Pubmed, and Cochrane platforms allowed the use of descriptors added to the existing filters in the platforms, allowing the exclusion of review articles, guidelines, book chapters, editorials, and other materials, and directing the search to randomized clinical trials. Thus, after directing the search, among the 94 articles selected, 18 were eligible to be read in full, and seven were included. The search flow for article selection is described in figure 1

Figure 1. Study search, selection, and inclusion flowchart.



### Selected studies' characteristics

All the included studies dealt with patients in stage 3 or 4 CKD.<sup>10-16</sup> Already established metabolic acidosis cases were prevalent, with serum bicarbonate levels under 22 mEq/L.<sup>10,12-16</sup> Only one study dealt with serum bicarbonate > 22 and <24 mEq/L,<sup>11</sup> for considering it pertinent to intervene where the threshold level is low. The intervention and control strategies in the studies were heterogeneous. All studies included the use of some oral alkali as an intervention,<sup>10-16</sup> and two studies added an alkaline diet to oral alkali.<sup>14,13</sup> The most commonly used oral alkali was sodium bicarbonate, but without any



uniformity in the dosage used in the studies. As controls, three studies used placebo alone,<sup>12,15,16</sup> three used the alkaline diet,<sup>10,11,14</sup> and one study used only oral alkali as a control.<sup>13</sup>

The alkaline diet was heterogeneous in the studies that used it. In two studies, the supply of base-inducing fruits and vegetables was increased in the diet group's intake, not to mention the daily amount of protein.<sup>10,11</sup> One study used a vegetarian diet containing 0.3-0.4g protein/kg body weight/day, and another study used a reduced protein diet (0.7 g/kg body weight/day).<sup>14</sup> The quantities of protein mentioned are lower than the usual recommendations for CKD, which are 0.8 g protein/kg body weight/day.<sup>1,3</sup>

All interventions improved metabolic acidosis in patients. The studies that used the dietary strategy, in addition to the result on metabolic acidosis, found improvement in blood pressure and other parameters of interest in CKD such as plasma urea, calcemia, phosphatemia, urinary sodium, urinary potassium, urinary albumin, and LDL cholesterol.<sup>10,11,13</sup>

Among the included studies, three evaluated the performance of alternative oral alkali<sup>14-16</sup> for the treatment of metabolic acidosis, with two studies on the same medication evaluated at different time stages.<sup>15,16</sup> Regarding this medication that was used in two studies, it is a nonabsorbed, counter-ion-free polymeric drug that binds to and selectively removes hydrochloric acid from the gastrointestinal lumen, unlike oral sodium bicarbonate therapy, which only neutralizes accumulated acid.<sup>15,16</sup> The studies declared no conflict of interest.

Regarding GFR, four studies found a lower decline in GFR after intervention and the resulting control of metabolic acidosis,<sup>11,12,13,16</sup> of which two used the alkaline diet to achieve this result.<sup>11,13</sup> In two studies, no difference in GFR was observed between the control and intervention groups during the evaluated period<sup>10,14</sup> and one study measured no effects on GFR after the intervention.<sup>15</sup>

There were patient losses in some studies due to deaths, worsening of their condition in the dialysis phase, and other complications that characterized exclusion criteria. The shortest intervention time among the selected studies was 14 days<sup>15</sup>, and the longest was three years.<sup>12</sup> The data extraction is represented in table 1.

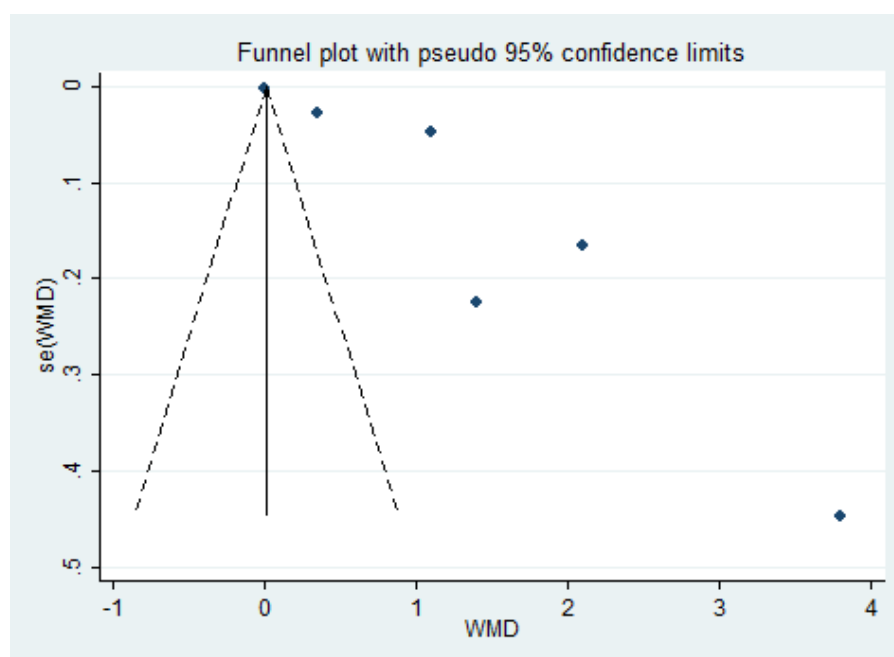
Regarding the quality analysis of randomized clinical trials, according to the method proposed by Jadad et al.,<sup>9</sup> two studies were classified as of low methodological quality due to their scores on the scale, mostly due to the fact that they were not double-blind and failed to address the methodology, exclusions, and losses appropriately.<sup>12,13</sup>

For the meta-analysis, it was possible to group six studies into four groups according to the type of intervention and control used (figure 2), as follows; Group 1: Intervention with oral alkali and control with placebo;<sup>12,16</sup> Group 2: Oral alkali intervention and control with alkaline diet;<sup>10,11</sup> Group 3: Oral alkali intervention + alkaline diet and control with oral alkali only<sup>13</sup>, and Group 4: Oral alkali intervention + alkaline diet and control on alkaline diet only.<sup>14</sup> One study was not included because it lacked the data needed for meta-analysis<sup>15</sup>.

The interventions were found to have a clustered effect on metabolic acidosis compared to their controls (1.25 95%CI 0.82 - 1.68). The heterogeneity was significant ( $p < 0.001$ ). In the group analysis, a positive effect could be observed in Group 1, which was expected since it concerned treatment with oral alkali compared to placebo. In Group 2, the intervention did not differ from the control, and both were able to increase serum bicarbonate and cause a protective effect, demonstrating the potential of diet as a treatment. In Groups 3 and 4, the oral alkali intervention in addition to diet was more positive than controls that used only one of the two strategies.

The funnel plot (figure 3) showed that the studies in this review are imprecise in their outcome estimates, indicating the need for further studies in this area.

**Figure 3.** Funnel plot. Intervention and control analysis in the treatment of metabolic acidosis.



## DISCUSSION

The interventions were effective on metabolic acidosis in all studies at different time stages. The alkaline diet proved to be as effective as medication treatment, demonstrating that adequate nutrition favors the control of metabolic acidosis and should be used as an alternative treatment.<sup>11-13</sup>

The use of oral alkalis as a treatment to correct metabolic acidosis in CKD is a common clinical practice, easy to handle, generally inexpensive, and with fast results, being the most recommended by nephrology guidelines. One of the studies showing only 14 days of oral alkali admission demonstrated the correction of metabolic acidosis, but it is worth noting that the intervention was added to the use of an alkaline diet, thus improving the results of the treatment.<sup>14</sup>

However, caution is required regarding overtreatment that increases serum bicarbonate beyond the normal range, as high bicarbonate concentrations (> 26 mEq/L) seem to be associated with an increased risk of death, regardless of the level of renal function.<sup>6</sup> In a meta-analysis on treatments for metabolic acidosis in CKD, interventions with oral alkalis (sodium bicarbonate and/or sodium citrate) were associated with worsening edema and hypertension or the need for increased antihypertensive therapy.<sup>17</sup>

The use of the alkaline diet, either in the intervention or control, achieved favorable results, as it affected other clinical parameters of interest for CKD, such as blood pressure control, calcemia, plasma urea, sodium, potassium and phosphate control, and protein intake, emphasizing that dietary modifications and restrictions are relevant clinical practices to slow the progression of CKD.

When directly comparing the two treatments, oral alkali use or alkaline diet use, the studies showed that both increased serum bicarbonate, demonstrating the potential of the diet as a viable treatment option.<sup>10-11</sup> The meta-analysis demonstrated that the studies that used oral alkali along with the alkaline diet had better results regarding metabolic acidosis than the use of one of these treatments in isolation.

Dietary modification leads to positive feedback since the dietary pattern and urinary pH are closely related. The protein and industrialized diet acidify the plasma, which contributes to deleterious effects on the kidney even in healthy

individuals.<sup>18</sup> However, plenty of fruits and vegetables are relatively high in potassium; thus, patients with kidney failure should receive comprehensive dietary advice.<sup>6,10</sup> The studies that used fruit and vegetable-based diets did not report hyperkalemia, even with increased use of potassium-rich foods.<sup>10,11,13</sup>

In a study<sup>5</sup> it was found that approximately half of the American patients with GFR < 30 mL /min/ 1.73 m<sup>2</sup> had metabolic acidosis, whose correction was aimed at mitigating the decline in GFR. Some studies included in this review measured a lower decline in GFR in the groups that had elevated serum bicarbonate,<sup>11-13,16</sup> demonstrating the effect of treating metabolic acidosis on CKD progression. The alkaline diet was helpful in achieving this outcome in the studies that used it as a treatment.<sup>11,13</sup>

Intervention time may be an important variable for the clinical outcome of interest. The studies that reported the best results on the decline in GFR had interventions of longer duration. In contrast, the studies that had shorter intervention times recorded no effects on GFR, with one study having an intervention time of 14 days<sup>14</sup>, and another of three months.<sup>15</sup>

Correcting metabolic acidosis contributes to a better CKD outcome, as acidosis causes nutritional and physiological changes, such as the loss of bone mass due to the release of calcium phosphate from the bone into the circulation, which assists in buffering acidosis, but also results in worsening hyperphosphatemia; multiple endocrine disturbances such as hyperglycemia, hyperinsulinemia, hyperglucagonemia, elevated GH (Growth Hormone) and catecholamines, increased levels of cytokines, and with it a loss of quality of life and a faster progression of kidney failure.<sup>19</sup>

## Limitations

The search for articles showed that the subject is not widely studied, which highlights the relevance of studies in this field. Several studies identified in the search were review articles or non-randomized studies, and when randomized failed to meet the inclusion criteria because they addressed other parameters of interest in CKD, other than the direct treatment for the correction of metabolic acidosis.

The studies included in this review, although being randomized clinical trials on the treatment of metabolic acidosis in CKD, presented data heterogeneity, time and type of interventions, with the use of different alkalis and dosages, combined or not with an alkaline diet. The methods for diagnosing metabolic acidosis and measuring it after the interventions differed in the studies. One study failed to provide the mean values of serum bicarbonate at the end of the interventions, which precluded its inclusion in the meta-analysis.

## CONCLUSION

The data support that the correction of metabolic acidosis is positive in CKD and support the use of alkaline diets based on fruits and vegetables and with protein restriction as an option for the treatment of metabolic acidosis, combined or not with oral alkalis, depending on the patient progression, in order to maximize improvement in the clinical picture and quality of life with delayed CKD progression.

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**Contributors**

Trivellato PT and Machado JC worked on the methodological planning, study search and selection, and article writing and review; Moreira TR worked on the methodological planning, statistical analysis, and article review; Cotta RMM worked on the methodological planning, orientation, and article review.

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