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**Oral alkali therapy and the management of metabolic acidosis of chronic kidney disease: A narrative literature review**

Ahmed AR *et al.* Oral alkali therapy and the management of metabolic acidosis of CKD

Adeel Rafi Ahmed, David Lappin

**Adeel Rafi Ahmed*,* David Lappin,** Department of Nephrology, University Hospital Galway, Galway H91YR1, Ireland

**ORCID number:** Adeel Rafi Ahmed (0000-0002-5910-6980).

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**Correspondence to:** **Adeel Rafi Ahmed, MBChB, MRCP, Staff Physician,** Department of Nephrology, University Hospital Galway, Newcastle Road, Galway H91YR1, Ireland. adeel.r.ahmed@gmail.com

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**Abstract**

Chronic metabolic acidosis is a common complication seen in advanced chronic kidney disease (CKD). There is currently no consensus on its management in the Republic of Ireland. Recent trials have suggested that appropriate active management of metabolic acidosis through oral alkali therapy and modified diet can have a deterrent impact on the progression of CKD. The potential benefits of treatment include preservation of bone health and improvement in muscle function; however, present data is limited. This review highlights the current evidence available primarily from randomised control trials (RCTs) over the last decade in managing metabolic acidosis of CKD and outlines ongoing RCTs that are promising. An economic perspective is also briefly discussed to support decision-making.

**Key words:** Chronic metabolic acidosis; Chronic kidney disease; Oral sodium bicarbonate; Oral alkali therapy; Health economics; Serum bicarbonate

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**Core tip:** Chronic metabolic acidosis contributes to the progression of chronic kidney disease (CKD). We summarise and analyse the current evidence regarding the management of metabolic acidosis of CKD, the potential benefits and adverse effects and offer novel therapeutic guidelines for clinicians which includes the most evidence-based range to maintain serum bicarbonate at in CKD population.

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**INTRODUCTION**

The prevalence of chronic kidney disease (CKD) in the Republic of Ireland is estimated to be around 4.5% in the general population rising to around 11.6% in those over 45 years of age[1]. CKD management has a significant economic impact on a healthcare system with the cost of care inversely proportional to a decline in renal function. Thus, interventions that can delay the progression of CKD will potentially contribute to an overall decrease in cost. This relation can be seen in the economic evaluations of the RENAAL study, which demonstrated that early management of proteinuria in diabetic patients with losartan lead to a decrease in the progression to end-stage kidney disease and long-term health care costs. In fact, one of these studies was conducted in Canada, which has a public health care system relatively similar to Ireland[2-4].

There are relatively few modifiable factors in CKD management that can slow the progression of renal function decline. Primarily in practice, management of hypertension, proteinuria and glycaemic control in patients with diabetes are the focus with regards to delaying progression of CKD[5,6]. In the last decade, however, a renewed interest in the treatment of metabolic acidosis of CKD (MA-CKD) has emerged and has been identified as an independent factor causing progression of CKD[7-9].

MA-CKD is a complication commonly seen in patients with a glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m2 (CKD G4-5{Moranne, 2009 #16}) and is defined as serum bicarbonate levels that are persistently less than 22 mmol/L[10,11]{Moranne, 2009 #16}{Moranne, 2009 #16}. It is associated with worsening of CKD-mineral and bone disease, muscle wasting, hyperkalaemia, insulin resistance, hyperlipidaemia, and most importantly, with the progression of CKD and increased mortality[7,12]. In Ireland there is currently no consensus on the management of MA-CKD, in particular, when to initiate oral alkali therapy or introduce a less acidogenic diet. It is important to assess and develop national guidelines on complications like MA-CKD that can in the long term prove cost-effective for the health system and improve the outcome of CKD patients[13].

**MECHANISM OF INJURY**

The most common proposed mechanism of injury associated with MA-CKD is interlinked with renal ammonium metabolism. As CKD progresses, there is a loss of nephrons with compensatory hypertrophy of the remaining nephrons to maintain acid balance. The hypertrophied nephrons increase their capacity to produce ammonia which activates a complement pathway leading to renal fibrosis and CKD progression[9]. Animal models and some observational studies have also demonstrated that a rise in endothelin levels and activation of intrarenal Renin-Angiotensin system in response to acidosis may play a role in the pathogenesis of renal fibrosis[14-16].

**ANALYSIS OF EVIDENCE**

Animal models have suggested a decline in the progression of CKD with the use of alkali agents to treat metabolic acidosis; however, the results were not consistent[17]. Numerous observational studies in human cohorts have demonstrated beneficial effects of oral alkali therapy on renal function decline[8,18,19]. The first randomised control trial (RCT) on this subject was published in 2009[7]. The trial involved a total of 134 patients with epidermal growth factor receptor (eGFR) between 15-30 mL/min per 1.73 m2 and serum bicarbonate between 16-20 mmol/L. 62 patients were in the intervention group involving supplementation with sodium bicarbonate with the aim to maintain a serum bicarbonate level of more than 23 mmol/L while 67 did not receive any alkali supplementation over a two-year study period[7]. One of the primary outcomes shown was a significantly lower decline in creatinine clearance in the treatment group at 1.88 mL/min per 1.73 m2 compared to 5.93 mL/min per 1.73 m2 in the nontreated group.

Subsequently, an American RCT was published looking at this topic in patients with hypertensive nephropathy, with an eGFR between 60-90 mL/min per 1.73 m2 involving a total of 120 patients[20]. The patients were divided into three equal groups, namely a sodium bicarbonate intervention group, a sodium chloride group and a placebo group. All participants had a normal baseline venous total carbon dioxide (equivalent to serum bicarbonate) averaging 26 mmol/L and albuminuria of more than 300 mg/g[20]. Over five years follow-up there was a decrease in the rate of decline in GFR at 1.47 mL/min per 1.73 m2/year in the sodium bicarbonate group compared to 2.05 mL/min per 1.73 m2/year in the sodium chloride group and 2.13 mL/min per 1.73 m2/year in the placebo group. The study demonstrated that even without overt metabolic acidosis oral alkali therapy contributed significantly in slowing the progression of CKD.

Both of these studies were included in the NICE CKD updated 2014 guidelines and it lead the authors to recommend that medical teams can consider oral sodium bicarbonate supplementation in patients with GFR less than 30 mL/min per 1.73 m2 and serum bicarbonate levels below 20 mmol/L, a recommendation not seen in the previous NICE CKD guidelines[21,22]. KDIGO 2012 CKD guidelines also suggested using oral bicarbonate therapy in CKD population, but at a serum bicarbonate value of less than 22 mmol/L, a biochemically less overt acidosis to initiate therapy compared to NICE CKD 2014 updated guidelines, and also to maintain it within a normal range unless contraindicated[23].

A further short duration RCT (8-12 wk) consisting of 41 patients looking mainly at the effects of oral bicarbonate supplementation on thyroid function in CKD population (GFR < 35 mL/min per 1.73 m2) with serum bicarbonate of less than 22 mmol/L[24]. The aim was to achieve serum bicarbonate > 24 mmol/L in the treatment group[24]. The results noted not only an improvement in thyroid function but also a preservation of GFR in the treatment group compared to a decline in GFR of 1.3 mL/min per 1.73 m2 in the control group over the time period studied.

 In 2012, a systematic review with meta-analysis consisting of 6 RCTs on oral alkali therapy and its effects on renal function found a net improvement in GFR of 3.2 mL/min per 1.73 m2 (based on 248 patients) compared to non bicarbonate therapy group with the authors suggesting a similar recommendation as KDIGO 2012 CKD guidelines[25].

Goraya *et al*[26] compared a fruits and vegetable diet with oral bicarbonate supplementation in CKD G4 hypertensive nephropathy population and serum bicarbonate of less than 22 mmol/L with a total of 71 patients, followed for one year. Markers of kidney injury, as proposed by the research team, included 8 h urine excretion of N-acetyl β-d-glucosaminidase, albumin and TGF-β all of which were lower at one-year follow-up compared to baseline and GFR was preserved in both groups. Both groups demonstrated an improvement in serum bicarbonate levels but more was seen with oral alkali supplementation ( 21.2 ± 1.3 *vs* 19.5 ± 1.59 baseline and 19.3 ± 1.9 baseline *vs* 19.9 ± 1.7 ). Interestingly, plasma potassium did not change significantly in the fruits and vegetable group (all patients were on furosemide, and patients with serum potassium more than 4.6 mmol/L were excluded).

Goraya *et al*[27] performed another RCT over a period of 3 years looking at CKD G3 hypertensive nephropathy population with serum bicarbonate (total venous CO2) between 22-24 mmol/L divided into three groups of 36 patients, oral bicarbonate supplementation group, fruits and vegetable group and standard treatment group. All three groups received an ace inhibitor with the aim to maintain a target systolic blood pressure of less than 130 mmHg. There outcome was a observed greater reduction in urinary albumin in the bicarbonate and fruits and vegetable group compared to the standard care group, reduction in N-acetyl β-d-glucosaminidase and urinary angiotensinogen in the bicarbonate and fruits and vegetable groups compared to a rise in the standard care group, and slower progression of GFR decline in the bicarbonate and fruits and vegetable group compared to standard care group.

There are a few RCTs currently ongoing or recruiting which may further shed light on the effectiveness of oral alkali therapy in preserving renal function and other potential benefits such as improvement in muscle strength and cardiac function[28-32]. The Bicarb Trial is perhaps the most comprehensive of the current ongoing RCTs involving multiple United Kingdom centers with 380 CKD G4-5 participants aged 60 or older and serum bicarbonate < 22 mmol/L[29]. The trial will look at physical performance, renal function, the effect on blood pressure, proteinuria and cost-effectiveness. Another ongoing RCT looking at Renal Transplant recipients with serum bicarbonate < 22 mmol/L and GFR between 15-89 mL/min per 1.73 m2 could potentially enhance our understanding of the benefits of treating metabolic acidosis on transplant physiology[32]. It will also cover a cohort of patients(Renal Transplant Recipients) that have not formally been studied regarding chronic metabolic acidosis. The results of these RCTs are highly anticipated (Table 1).

**OTHER POTENTIAL BENEFITS**

CKD patients have a higher risk of fractures compared to the general population largely due to a decrease in 1,25 hydroxylation of calcidiol F(25-OH-vitamin D) and secondary hyperparathyroidism. Bone is also used as a buffer for excess hydrogen ions in chronic metabolic acidosis, which leads to loss of calcium and exacerbation of bone fragility[33].

Preservation of bone health and stabilisation of parathyroid hormone by the correction of metabolic acidosis has been demonstrated in a few studies[34-36]. Furthermore, a decrease in protein degradation is seen, at a biochemical level, with an increase in muscle mass and an improvement in physical function[7,37-39].

**POTENTIAL ADVERSE EFFECTS**

There has always been a concern regarding worsening of hypertension, fluid overload and congestive heart failure (CHF) after the administration of oral sodium based alkali supplementation in CKD population due to sodium loading. These potential theoretical adverse effects have not been proven in a clinical setting, although a majority of the participants in the RCTs were excluded if uncontrolled hypertension or clinically overt CHF was present[7,25]. In one of the RCT’s blood pressure was noted to be similar between the bicarbonate group and standard care group with no CHF related hospitalisation and a similar increase in the use of diuretics and antihypertensive agents over the course of the study[7]. Goraya *et al*[27] reported a similar finding with no significant difference in blood pressure between standard care compared to bicarbonate treated group and a similar requirement for enalapril. Two RCTs by Goraya *et al*[26,27] also demonstrated a fruit and vegetable diet allowed better blood pressure control compared to both bicarbonate supplementation and standard care.

TRC 101, a novel sodium-free, non-absorbed hydrochloric acid binder has shown efficacy in alleviating MA-CKD without effecting blood pressure and may become widely available in the near future[40].

A plausible risk of increased vascular calcification, once an acidotic environment has been resolved with oral alkali supplementation exists, however, currently there is a scarcity of studies to conclusively demonstrate this phenomen[41].

**RECOMMENDATIONS**

An appraisal of current evidence is necessary for the appropriate management of MA-CKD, which could have a significant impact on CKD care in Ireland.

A few RCTs demonstrated that a fruits and vegetable diet reduced the overall acid load and had a renoprotective effect[26,27]. Two interesting observations can be noted, one of the RCT with serum bicarbonate < 22 mmol/L in CKD G4 hypertensive nephropathy population did not achieve the desired aim of serum bicarbonate of > 22 mmol/L with fruits and vegetables. However despite that the urinary indices of renal injury were lower as well and GFR was preserved[26]. Secondly, the RCT on CKD G3 hypertensive nephropathy population with serum bicarbonate between 22-24 mmol/L, above the current treatment guidelines, also demonstrated a slower progression of GFR decline and reduction in urinary indices of renal injury[26,27]. Even when Oral alkali therapy was used in patients with CKD G2 and normal serum bicarbonate, a decline in the reduction of GFR was observed[20]. These findings correlate with the understanding that western, high animal meat diets are indirectly renotoxic due to their overall acid inducing effect and alkaline agents, either fruits and vegetables or oral sodium bicarbonate, help neutralize this excess acid [42,43].

It can be postulated that fruits and vegetables associated with an alkaline effect incorporated into a diet will be renoprotective at any CKD stage because of their ability to buffer acid. However, CKD G4-G5 patients have a tendency towards hyperkalemia and all the patients in the RCT involving CKD G4-G5 and fruits and vegetables were on furosemide thus the use of high potassium containing fruits and vegetables in this category remains controversial[26].

Based on the current available RCTs evidence, It can be suggested to maintain a serum bicarbonate above 22 mmol/L in CKD population, and oral alkali therapy should be utilised to achieve this especially in CKD G4-G5 patients[7,20,24-27]. Since none of the RCTs included uncontrolled hypertension and overt CHF patients, clinical judgment should be used when initiating oral alkali therapy in patients with an underlying history CHF or hypertension requiring more than three agents to control[7,20,26,27,37].

The upper limit of serum bicarbonate once on oral alkali therapy is still speculative with limited data available. In one cohort study, a serum bicarbonate of > 26 mmol/L was associated with increased mortality and risk of heart failure and another study on haemodialysis patients demonstrated an association with increased mortality when serum bicarbonate > 27 mmol/L[44,45].

Maintaining serum bicarbonate between 22-26 mmol/L in CKD population would be the closest to the evidence base available at the moment. In four of the RCTs an average of 0.3 mEq/kg per day to 1 mEq/kg per day of oral sodium bicarbonate was used to achieve the desired aim of serum bicarbonate levels > 22 mmol/L[7,20,26,27,37].

 It is further suggested that dieticians in renal units get involved in designing a program for CKD G1-G3 regardless of serum bicarbonate that incorporates fruits and vegetables to reduce the overall acid load and commence community programs to promote this.

**DOSING AND COST**

Thus a 1mg of sodium bicarbonate approximately equates to 0.0123 mEq. A 600 mg sodium bicarbonate tablet contains 7.4 mEq of bicarbonate, and the usual commencing dose is 600 mg three times daily. In a 70 kg patient this is approximately 0.3 mEq/kg per day. Three additional tablets may have patient compliance issues as sodium bicarbonate can lead to abdominal bloating. However until better preparations, and other formulations including sodium citrate are commonly available, oral sodium bicarbonate tablets will need to be titrated as required to achieve the desired serum bicarbonate levels between 22-26 mmol/L. An unconventional approach is to utilise natural baking soda (sodium bicarbonate) of which one teaspoon is equal to approximately 5000 mg of sodium bicarbonate thus ½ a teaspoon mixed in water should produce 2500 mg which is equivalent to 31 mEq (2500 x 0.0123) of sodium bicarbonate. The cost per 600 mg sodium bicarbonate tablet ( including enteric coated tablets) is approximately 0.1-0.15 euros, and if used at 0.3 mEq/Kg per day, it would cost 109-170 euros/year ( for a 70 kg patient).

**CONCLUSION**

MA-CKD is a complication that is often overlooked in clinical practice. The current evidence base suggests it contributes to renal function decline and an appropriate management would lead to better CKD outcomes in terms of renal function preservation, muscle function, bone health and economic burden. Oral alkali therapy has the potential when combined with other known interventions like blood pressure control and glycaemic control to prolong the time before reaching end-stage renal disease. Irish nephrology practice currently holds a very diverse opinion on managing MA-CKD. The recommendations offered here can be used as a bases to develop more detailed guidelines in Republic of Ireland and around the world. Further larger ongoing RCTs highlighted in this review will perhaps provide a more conclusive evidence.

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**Table 1 Summary of evidence**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **RCT**  | **Participants (*n*)**  | **Intervention and aim**  | **eGFR (mL/min per 1.73 m2)****baseline**  | **Serum HCO3 (mmol/L) at baseline** | **Duration (mo)**  | **Rate of Decline of eGFR (mL/min per 1.73 m2)**  |
| De brito-ashurst *et al*[7] | Total: 134 Intervention: 62  | Oral sodium bicarbonate tablets to maintain serum HCO3 > 23 mmol/L | 15-29 | 16-20 | 24  | HCO3 group: 1.88non treated group: 5.93 |
| Mahajan *et al*[20] | Total: 120Intervention: 30 | Oral sodium bicarbonate tablets | 60-89 | 26 | 60 | HCO3 group: 1.47 per year Non treated group: 2.05 per year  |
| Goraya *et al*[26] | Total 71Intervention: 30 | Oral sodium bicarbonate and Fruits and vegetable  | 15-29 | < 22 | 12 | HCO3 and F and V group: Preservation of eGFR |
| Goraya *et al*[27] | Total : 108Intervention: 72 | Oral sodium bicarbonate and fruits and vegetables  | 30-59 | 22-24 | 36 | Non treated group: 13.8 over 3 yrHCO3: 5.4 over 3 yrF and V:5.4 over 3 yr |
| Disthabanchong *et al* [24] | Total: 41Intervention: 21 | Oral sodium bicarbonate to maintain serum bicarbonate > 24 mmol/L | < 35 | < 22 | 2-3 | HCO3 group: Preservation of eGFR non treated group: 1.3 |

RCT: Randomised control trials; eGFR: Epidermal growth factor receptor.