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 deterring impact on CKD progression. 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 the 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 current evidence regarding the management of the metabolic acidosis of CKD, as well as the potential benefits and adverse effects. We also offer novel therapeutic guidelines for clinicians, which include the most evidence-based range to maintain serum bicarbonate in the CKD patient population.

Ahmed AR, Lappin D. Oral alkali therapy and the management of metabolic acidosis of chronic kidney disease: A narrative literature review. World J Nephrol 2018; 7(6): 117-122 Available from: URL: http://www.wjgnet.com/2220-6124/full/v7/i6/117.htm DOI: http://dx.doi.org/10.5527/wjn.v7.i6.117

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 individuals over 45 years of age\(^\text{[1]}\). CKD management has a significant economic impact on the 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 economic evaluations of the RENAAI 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\(^\text{[2,4]}\).

There are relatively few modifiable factors in CKD management that can slow the progression of renal function decline. The management of hypertension, proteinuria and glycaemic control in patients with diabetes are the primary focuses with regards to delaying CKD progression\(^\text{[5,6]}\). 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 CKD progression\(^\text{[7-9]}\).

MA-CKD is a complication commonly seen in patients with a glomerular filtration rate (GFR) less than 30 mL/min per 1.73 m\(^2\) (CKD G4-5), and is defined as serum bicarbonate levels that are persistently less than 22 mmol/L\(^\text{[10,11]}\). It is associated with a worsening of CKD-mineral and bone disease, muscle wasting, hyperkalaemia, insulin resistance, hyperlipidaemia, and, most importantly, with the progression of CKD and increased mortality\(^\text{[7,12]}\). In Ireland, there is currently no consensus on the management of MA-CKD, such as when to initiate oral alkali therapy or introduce a less acidogenic diet. It is therefore important to assess and develop national guidelines on the complications like MA-CKD that can prove cost-effective for the health system and improve the long-term outcome of CKD patients\(^\text{[13]}\).

**MECHANISM OF INJURY**

The most commonly proposed mechanism of injury associated with MA-CKD is related to renal ammonium metabolism. As CKD progresses, there is a loss of nephrons that is coupled 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 that leads to renal fibrosis and CKD progression\(^\text{[8]}\). Animal models and some observational studies have also demonstrated that a rise in endothelin levels and activation of the intrarenal renin-angiotensin system in response to acidosis may play a role in the pathogenesis of renal fibrosis\(^\text{[14-16]}\).

**ANALYSIS OF EVIDENCE**

Animal models using alkali agents to treat metabolic acidosis have suggested a decline in CKD progression; however, the results were not consistent\(^\text{[17]}\). Numerous observational studies in human cohorts have demonstrated beneficial effects of oral alkali therapy on renal function\(^\text{[8,18,19]}\). The first randomised control trial (RCT) on this subject was published in 2009\(^\text{[7]}\). The trial involved a total of 134 patients with estimated glomerular filtration rate (eGFR) between 15-30 mL/min per 1.73 m\(^2\) and serum bicarbonate between 16-20 mmol/L. Sixty-two patients were in the intervention group, which involved supplementation with sodium bicarbonate, with the aim of maintaining a serum bicarbonate level of more than 23 mmol/L. Sixty-seven patients were in the control group and did not receive any alkali supplementation over a two-year study period\(^\text{[7]}\). 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 m\(^2\) compared to 5.93 mL/min per 1.73 m\(^2\) in the nontreated group.

Subsequently, an American RCT was published looking at this topic in 120 patients with hypertensive nephropathy who had eGFR between 60-90 mL/min per 1.73 m\(^2\)\(^\text{[20]}\). The patients were divided into three equal groups: A sodium bicarbonate intervention group, a sodium chloride group and a placebo group. All participants had normal baseline venous total carbon dioxide (equivalent to serum bicarbonate) averaging 26 mmol/L, and albuminuria of more than 300 mg/g\(^\text{[20]}\). Over five years of follow-up, there was a decrease in the rate of GFR decline of 1.47 mL/min per 1.73 m\(^2\)/year in the sodium bicarbonate group, compared to 2.05 mL/min per 1.73 m\(^2\)/year in the sodium chloride group and 2.13 mL/min per 1.73 m\(^2\)/year in the placebo group. The study demonstrated that even without overt metabolic acidosis, oral alkali therapy contributed significantly to slowing the progression of CKD.

Both of these studies were included in the NICE CKD guidelines, which were updated in 2014, and led the authors to recommend that medical teams should consider oral sodium bicarbonate supplementation in patients with GFR less than 30 mL/min per 1.73 m\(^2\) and serum bicarbonate levels below 22 mmol/L, a recommendation not previously seen in NICE CKD guidelines\(^\text{[21,22]}\). The KDIGO 2012 CKD guidelines also suggested using oral bicarbonate therapy in the CKD patient population, but at a serum bicarbonate value of less than 22 mmol/L. This is a lesser biochemically overt acidosis used to initiate therapy, compared to the 2014 updated NICE CKD guidelines\(^\text{[23]}\).

A shorter duration RCT (8-12 wk) consisting of 41 patients looked mainly at the effects of oral bicarbonate supplementation on thyroid function in the CKD population (GFR < 35 mL/min per 1.73 m\(^2\)) with serum bicarbonate levels less than 22 mmol/L\(^\text{[24]}\). The aim was to achieve serum bicarbonate > 24 mmol/L in the treatment group\(^\text{[24]}\). 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 a meta-analysis consisting of six 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 the non-bicarbonate therapy group. The authors of this study suggested recommendations similar to the KDIGO 2012 CKD guidelines [25].

Goraya et al [26] compared a fruit and vegetable diet with oral bicarbonate supplementation in 71 CKD G4 hypertensive nephropathy patients with serum bicarbonate levels less than 22 mmol/L who were 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 the one-year follow-up compared to baseline. Notably, 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 mmol/L vs 19.5 ± 1.59 mmol/L based on 380 CKD G4-5 participants aged 60 or older and with serum bicarbonate levels < 22 mmol/L [26]). The trial will look at the efficacy of oral sodium bicarbonate supplementation on physical performance, renal function, blood pressure, proteinuria and cost-effectiveness. Another ongoing RCT looking at renal transplant recipients with serum bicarbonate levels < 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 [27]. 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).

### Table 1 Summary of evidence

| RCT | Participants (n) | Intervention and aim | eGFR (mL/min per 1.73 m²) at baseline | Serum HCO₃ (mmol/L) at baseline | Duration (months) | Rate of Decline of eGFR (mL/min per 1.73 m²) |
|-----|------------------|----------------------|---------------------------------------|---------------------------------|------------------|---------------------------------------------|
| De Brito-Ashurst et al [7] | Total: 134 | Oral sodium bicarbonate tablets | 15-29 | 16-20 | 24 | HCO₃ group: 1.88 |
| | Intervention: 62 | to maintain serum HCO₃ > 23 mmol/L | | | | Non treated group: 5.93 |
| | | | | | | |
| Mahajan et al [27] | Total: 120 | Oral sodium bicarbonate tablets | 60-89 | 26 | 60 | HCO₃ group: 1.47 per year |
| | Intervention: 30 | | | | | Non treated group: 2.05 per year |
| | | | | | | |
| Goraya et al [28] | Total: 71 | Oral sodium bicarbonate and F and V | 15-29 | < 22 | 12 | HCO₃ and F and V groups: Preservation of eGFR |
| | Intervention: 30 | | | | | |
| Goraya et al [28] | Total: 108 | Oral sodium bicarbonate and F and V | 30-59 | 22-24 | 56 | Non treated group: 13.8 over 3 yr |
| | Intervention: 72 | | | | | |
| Disthabanchong et al [29] | Total: 41 | Oral sodium bicarbonate to maintain serum bicarbonate > 24 mmol/L | < 35 | < 22 | 2-3 | HCO₃ group: |
| | Intervention: 21 | | | | | Preservation of eGFR |
| | | | | | | Non treated group: 1.3 |

RCT: Randomised control trials; eGFR: Estimated glomerular filtration rate; F and V: Fruits and Vegetables
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 (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 a loss of calcium and an exacerbation of bone fragility. The preservation of bone health and the stabilisation of parathyroid hormone by the correction of metabolic acidosis has been demonstrated in a few studies. Furthermore, a decrease in protein degradation is seen, at a biochemical level, with an increase in muscle mass and an improvement in physical function.

POTENTIAL ADVERSE EFFECTS

There has always been a concern regarding the worsening of hypertension, fluid overload and congestive heart failure (CHF) after the administration of oral sodium-based alkali supplementation in the CKD population due to sodium loading. These potential theoretical adverse effects have not been proven in a clinical setting, although a majority of participants in the RCTs were excluded if uncontrolled hypertension or clinically overt CHF was present. In one RCT, blood pressure was noted to be similar between the bicarbonate and standard care groups, with no CHF-related hospitalisation, and a similar increase in the use of diuretics and antihypertensive agents over the course of the study. Goraya et al. reported a similar finding, with no significant difference in blood pressure between the standard care and bicarbonate-treated groups, and a similar requirement for enalapril. Two RCTs by Goraya et al. also demonstrated that 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 affecting blood pressure, and may become widely available in the near future. A plausible risk of increased vascular calcification exists once an acidic environment has been resolved with oral alkali supplementation. However, there is currently a scarcity of studies to conclusively demonstrate this phenomenon.

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 fruit and vegetable diet reduced the overall acid load and had a renoprotective effect. Two interesting observations can be noted. Firstly, the RCT with serum bicarbonate levels < 22 mmol/L in the CKD G4 hypertensive nephropathy population did not achieve the desired aim of serum bicarbonate levels of > 22 mmol/L with fruits and vegetables. Despite this, however, the urinary indices of renal injury were lower and GFR was preserved. Secondly, the RCT on the CKD G3 hypertensive nephropathy population with serum bicarbonate levels between 22-24 mmol/L, above the current treatment guidelines, also demonstrated a slower progression of GFR decline and a reduction in urinary indices of renal injury with oral alkali supplementation. Even when oral alkali therapy was used in patients with CKD G2 and normal serum bicarbonate levels, a decline in the reduction of GFR was observed. These findings correlate with the understanding that, at a biochemical level, with an increase in muscle mass and an improvement in physical function.

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

Based on the current evidence, it can be suggested that the CKD population maintain a serum bicarbonate level above 22 mmol/L, and that oral alkali therapy should be utilised to achieve this, especially in CKD G4-G5 patients. 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 of CHF or hypertension requiring more than three agents to control.

The upper limit of serum bicarbonate levels once on oral alkali therapy is still speculative, with limited data available. In one cohort study, a serum bicarbonate level of > 26 mmol/L was associated with increased mortality and a risk of heart failure, while another study on haemodialysis patients demonstrated an association with increased mortality when serum bicarbonate levels were > 27 mmol/L. Maintaining serum bicarbonate levels between 22-26 mmol/L in the CKD population would be 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.

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

A 1 mg dose 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 preparation is optimized 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, one-half of 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 of sodium bicarbonate tablets (including enteric-coated tablets) is approximately 0.1-0.15 Euros. 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. Current evidence suggests that it contributes to renal function decline, and that 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 practices currently hold very diverse opinions on managing MA-CKD. The recommendations offered here can be used as a basis to develop more detailed guidelines in the Republic of Ireland and around the world. Larger ongoing RCTs highlighted in this review will perhaps provide more conclusive evidence.

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P- Reviewer: Keramati MR, Raikou VD, Sakhaee K, Stollic RV
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