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in older people with CKD?

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Abstract

Metabolic acidosis is common in advanced chronic kidney disease, and has been associated with a range of physiological derangements of importance to the health of older people. These include associations with skeletal muscle weakness, cardiovascular risk factors, and bone and mineral disorders that may lead to fragility fractures. Although metabolic acidosis is associated with accelerated decline in kidney function, end stage renal failure is a much less common outcome in older, frail patients than cardiovascular death. Correction of metabolic acidosis using bicarbonate therapy is commonly employed, but the existing evidence is insufficient to know whether such therapy is of net benefit to older people. Bicarbonate is bulky and awkward to take, may impose additional sodium load with effects on fluid retention and blood pressure, and may cause gastrointestinal side effects. Trial data to date suggests potential benefits of bicarbonate therapy on progression of renal disease and nutrition, but trials have not as yet been published examining the effect of bicarbonate therapy across a range of domains relevant to the health of older people. Fortunately, a number of trials are now underway that should allow us to ascertain whether bicarbonate therapy can improve physical function, quality of life, vascular, bone and kidney health in older people, and hence decide whether any benefits seen outweigh adverse effects and additional treatment burden in this vulnerable group of patients.

Introduction

Chronic kidney disease (CKD) becomes more common with increasing age [1], and although the proportion of patients with advanced CKD (glomerular filtration rate [GFR] <30 mL/min/1.73 m^2) is a relatively small proportion of the total, population ageing and age-specific increases in prevalence [2, 3] are likely to combine to increase overall numbers in future. Managing CKD in older people presents a different set of challenges to management in younger people – the presence of multimorbidity, polypharmacy, impaired homeostasis across multiple organ systems, and differences in patients' expectations and the aims of therapy all combine to produce a situation in which the existing evidence base for treatment is often of limited help [4]. Metabolic acidosis becomes more common with advancing CKD, and emerging evidence links acidosis to a range of outcomes that are highly relevant to the healthcare priorities of older people, including effects on bone and mineral metabolism, cardiovascular health and kidney disease progression. Intuitively, correction of acidosis should be beneficial. In this review, we examine the effects of CKD-associated metabolic acidosis on health and physical function in older people, and consider whether the current evidence is sufficient to support a net benefit of treatment across a range of outcomes that are important to older people with CKD.

Observational data

How common is acidosis?

Fixed (non-volatile) acids, notably sulphuric and phosphoric acids, accumulate as a normal consequence of protein metabolism and of intake in the diet. The kidney maintains acid-base balance by eliminating excess acid: this is achieved by reclamation of filtered bicarbonate and through ammoniagenesis. These processes become impaired in kidney disease, resulting in acidosis. Acidosis is not usually measured directly in epidemiological studies, but is inferred by the presence of a low

serum bicarbonate concentration. At all ages, acidosis becomes more common with declining GFR [5], with a marked increase in the prevalence of acidosis as GFR falls below 45 mL/min/1.73 m^2; recent data [6] from a representative CKD cohort showed that 13% of those with eGFR 30-59 mL/min/1.73m^2 had a serum bicarbonate concentration <22 mmol/L, rising to 37% of those with eGFR 15-29 mL/min/1.73m^2. Similar rates have been shown in other cohorts, depending on the population and the bicarbonate concentration cutoffs used to define acidosis.

It is less clear whether older people are more or less likely to have low serum bicarbonate concentrations than younger people; in the study by Raphael et al [6], older age was associated with a slightly higher serum bicarbonate. However, other studies have found either no effect [7], that older age is associated with increased rates of low bicarbonate [8], or that younger age is associated with increased rates of low bicarbonate [5, 9]. Other factors that have been shown to impact on serum bicarbonate concentrations include medications (e.g. diuretics, renin-angiotensin system blockers) [6, 8]. This is important as rates of concomitant medication use by older people with CKD are high, and are hence likely to have an effect on how commonly low bicarbonate levels occur. Variations in dietary acid load may also have an effect. Amongst >30,000 individuals enrolled in the National Health and Nutrition Examination Survey (NHANES), the prevalence of acidosis (serum bicarbonate <22 mmol/L) was decreased amongst older compared to younger individuals with low GFR: the authors postulate that this could reflect increased thiazide diuretic usage in older people [5].

Association with progression of renal dysfunction

Acidosis has deleterious effects on renal function, and appears to potentiate tubular injury. A range of mechanisms have been postulated, including intrarenal calcium deposition, complement activation and neurohormonal activation, reviewed elsewhere in more detail [10]. Acidosis has direct effects on muscle function, in part by leading to increased breakdown of muscle protein [11].

Several studies have linked the presence of low serum bicarbonate concentrations to accelerated decline in renal function. These associations extend even to individuals without established CKD. In the Multi-ethnic Study of Atherosclerosis (MESA) all participants had baseline GFR levels >60 ml/min/1.73 m^2, but participants with a serum bicarbonate concentrations of <21 mmol/L were 35% more likely to experience rapid (>5%/yr) decline in kidney function compared to those with serum bicarbonate concentrations of 23-24 mmol/L [12]. Similar findings apply to older people with preserved kidney function. In the Health, Aging and Body composition study [13], participants aged 70-79 years with serum bicarbonate <23 mmol/L had a more rapid decline in GFR compared to those with serum bicarbonate concentrations between 23 and 28 mmol/L; this association remained after adjustment for baseline factors including GFR.

There is still debate as to how much of these observed associations are due to bicarbonate independent of renal function. Recent pooled data from two large randomised controlled trials [14] suggested that lower baseline bicarbonate concentrations correlate with faster decline in GFR, and a higher chance of reaching kidney failure, but also found that this association disappeared after adjusting for baseline GFR. In the MDRD cohort, serum bicarbonate was not associated with progression to end-stage renal failure or death after adjustment for baseline GFR [15]. Conversely other studies [16] have found that the association between low serum bicarbonate and accelerated decline in renal function remains even after adjustment for baseline GFR.

Association with cardiovascular disease

In the cardiovascular system, acidosis has been associated with increased levels of endothelin and aldosterone [17]; acidosis may also be a driver of chronic inflammation. Together, these alterations impair endothelial function, which is itself a major risk factor for the development of atherosclerotic lesions [18]. Furthermore, aldosterone is known to be important in driving left ventricular fibrosis (a

key substrate for both arrhythmia and diastolic dysfunction), and the combined effect of increased blood pressure, worsening arterial stiffness as a result of these pathophysiological changes results in left ventricular hypertrophy – an independent risk factor for cardiovascular events that is particularly common in patients with CKD [19].

The association between serum bicarbonate concentration and vascular events appears more complicated. There is a lack of evidence of an association between low serum bicarbonate and increased vascular events from observational studies. Recent pooled data from two randomised controlled trials enrolling patients with diabetic nephropathy [14] suggested that serum bicarbonate was not associated with incident cardiovascular events or with incident heart failure events. Increased serum bicarbonate concentration may however be associated with deleterious outcomes. In the Chronic Renal Insufficiency Cohort (CRIC) [16], serum bicarbonate concentrations persistently >26 mmol/L were associated with a higher rate of both heart failure and death compared to patients with concentrations of 22-26 mmol/L. In this cohort, a previous analysis showed no association between serum bicarbonate concentrations and atherosclerotic events [20].

Any association between acidosis and cardiovascular health in CKD patients may have knock-on effects on other important domains of health in older people. Cardiovascular disease accounts for between one third to a half of change in physical function with advancing age [21], and also plays an important role in cognitive impairment, via macrovascular stroke disease, small vessel changes and via vascular risk factors for Alzheimer's disease [22].

Association with physical function

Impaired renal function is associated with worse physical function, and this association is more marked in older people. Whether this is a causal relationship however is more difficult to discern, and the contribution of different pathophysiological components (e.g. acidosis, vitamin D system

derangements, cardiovascular disease, uraemic toxins) to the impairment of physical function is difficult to disentangle.

However, recent data suggests an association between serum bicarbonate concentrations and physical function even in patients without advanced CKD. In cross-sectional data from a sample of 2675 patients aged 50 years and over from the NHANES cohort [23], low gait speed and quadriceps strength in older people were associated with lower serum bicarbonate. Adjustment for GFR and 25-hydroxyvitamin D concentrations did not alter the results. Similar results were obtained in another NHANES sample, examining the relationship between serum bicarbonate and estimated maximal oxygen uptake (VO_{2max}) on treadmill testing in those aged 20-49 years [24]. Again, lower serum bicarbonate was associated with lower VO_{2max} even after adjustment for GFR. Importantly for patients with CKD, low serum bicarbonate also predicts future onset of functional limitation (defined as difficulty walking quarter of a mile or climbing 10 steps) in older people [25]. Those with serum bicarbonate <23 mmol/L were 1.6 times as likely to develop limitation as those with baseline serum bicarbonate of >=26 mmol/L. even after adjustment for the presence of CKD.

Association with bone health

Acidosis affects components of bone and mineral metabolism; it promotes bone resorption by osteoclasts while inhibiting new bone formation by osteoblasts, is associated with reduced vitamin D production, and may reduce parathyroid hormone release [26-28]. The risk of fracture is of particular relevance to the health of older people. Although CKD-related mineral bone disorder (CKD-MBD) is itself a risk factor for fractures [29], advancing age is the most powerful predictor of fractures and the incidence of fragility fractures rises exponentially with increasing age. The relationship between CKD and fracture in old age is less straightforward than for younger patients; although cystatin-C based measures of GFR suggest a relationship between lower GFR and higher fracture risk [30], creatinine-based measures of renal function show a less clear cut relationship [31]. This is probably explicable on

the basis that low muscle mass is a key risk factor for falls but may also be associated with low serum creatinine concentration, hence leading to an overestimate of GFR in such individuals and masking any association between creatinine-estimated GFR and fracture risk.

Dissecting out the effect of acidosis on bone health and fracture risk from the effects of other components of mineral metabolism that are deranged in CKD is difficult; these aspects of biochemical derangement are often highly correlated. In patients without CKD, the evidence that dietary acid load is associated with bone health is weak [32], with intervention studies examining proxy measures for the development of osteoporosis such as urinary calcium excretion, and observational studies incompletely adjusting for important confounders. Analysis of the NHANES III dataset suggested that in the general population without CKD, higher bicarbonate concentrations were associated with higher bone mineral density [33]. In Japanese patients undergoing haemodialysis there was a U-shaped relationship between bicarbonate concentration and fracture risk, with both predialysis bicarbonate concentrations <20 and >22 mmol/L being associated with higher incident fracture rates than predialysis serum bicarbonate concentrations of 21-22 mmol/L [34]; similar relationships were seen between acidosis and bone mineral density in a group of patients on maintenance peritoneal dialysis [35]. There is however a paucity of studies examining the relationship between bicarbonate concentrations and fracture risk specifically in patients with CKD not receiving dialysis.

Other potential deleterious effects of bicarbonate

For many patients, bicarbonate is awkward to take. The tablets are large, and multiple tablets usually need to be taken each day. This is a particular issue for older patients, who are more likely to have dysphagia or a dry mouth, and are often taking large numbers of other medications. Use of unencapsulated bicarbonate powder is one solution to this problem, but this approach does not lend itself to accurate dosing. Sodium bicarbonate contains 6 mmol of sodium per 500 mg, and this additional sodium load might contribute to increased blood pressure and fluid overload. There is also

a possible adverse effect on vascular calcification [36]; raising the blood pH may make calcium and phosphate less soluble, thus promoting precipitation of calcium phosphate within vessel walls. Abdominal discomfort and bloating are recognized side effects listed in the Summary of Product Characteristics; this may be a result of generation of carbon dioxide in the gut via interaction with stomach acid.

What outcomes are important to older people?

Multimorbidity is common in older people; few older people present with a single condition, and the vast majority of older people will have multiple illnesses. Patients with CKD commonly suffer not only from conditions such as cardiovascular disease and diabetes mellitus (which often cause their CKD), but from conditions associated with frailty, such as falls, cognitive impairment, poor mobility and low mood, and the prevalence of such conditions increases with decreasing GFR [37]. Managing any given condition in older people, such as CKD, is thus more complex than management in younger people with less multimorbidity. In addition, many older people with CKD may have a life expectancy limited not only by CKD and cardiovascular disease, but by dementia, lung disease and frailty syndromes. The presence of multimorbidity commonly leads to polypharmacy; it is common for patients to have 6 or 7 illnesses and more than 20 medications per day to take, and this situation brings with it a major risk of side effects, drug interactions, worsening of comorbid disease, and medication burden.

How then should we manage the competing demands of multiple illnesses in older patients with CKD? One key principle is to focus on what outcomes are important to older people themselves; surveys consistently report that physical function and quality of life are key outcomes for older people [38], and thus our interventions should be geared towards improving these outcomes. Preventing declines in renal function *per se* may be a lower priority for some patients, although a build-up of uraemic toxins may contribute to the association seen between impaired renal function and frailty and poor physical function shown in observational studies.

The majority of older people with CKD will not develop kidney failure or require renal replacement therapy. Death from cardiovascular disease outstrips kidney failure by a factor of 6 in those aged 65 years and over with a baseline GFR <60 mL/min/1.73m^2; death from any cause (before reaching kidney failure) was 13 times as common as reaching kidney failure in this cohort [39]. Hence reducing the high rates of cardiovascular disease seen in CKD in older people is another key outcome. Preventing fractures – both by improving muscle function and by ameliorating osteoporosis and related CKD-MBD – is another key target for intervention for older people.

Ideally, any intervention for older people with CKD should therefore be tested across these multiple domains, and should show benefits to physical function and quality of life, reduce net cardiovascular risk and improve CKD-MBD. Interventions that reduce the rate of decline in renal function without impacting favourably on these other outcomes are unlikely to provide the benefits that older patients wish to see from their treatment. So what does the intervention data accrued for bicarbonate therapy to date show when measured against these domains?

Intervention data

A small number of trials have been published examining the effect of interventions designed to ameliorate the effects of acidosis, but very little has been published that is of direct relevance to older patients. A single centre randomised controlled trial, performed in the UK, of 134 patients with GFR <30 mL/min/1.73 m^2 provides perhaps the most relevant current evidence [40]; two years supplementation with a mean of 1.8 g/day oral sodium bicarbonate led to significant increases in serum bicarbonate (25 mmol/L vs 20 mmol/L, p<0.001), significantly fewer patients (7% vs 33%, p<0.001) developing kidney failure (defined as a creatinine clearance of <10ml/min/1.73m^2), together with improvements in anthropometric measures. Reassuringly, no difference in blood pressure

between bicarbonate and placebo groups was seen. However, patients in this trial were comparatively young, with a mean age of 55 years, and were overwhelmingly of Asian or African origin.

A smaller, more recent Korean trial [41] also tested the effect of 3 g/day of oral sodium bicarbonate versus placebo in patients with GFR <30 mL/min/1.73 m^2 and baseline serum bicarbonate <22 mmol/L. The decline in renal function appeared slower with intervention in those with GFR 15-29 mL/min/1.73 m^2, but not in those with GFR <15 mL/min/1.73 m^2 over the 12 month follow up period. A nutritional index derived from serum albumin and the lymphocyte count showed improvement in the intervention group relative to controls in the GFR <15 mL/min/1.73 m^2 subgroup, as did body weight. No changes were noted with treatment for mid-arm muscle circumference however, arguing against this being due to changes in lean mass. In this trial, a difference in blood pressure was seen, albeit non-significant due to the small size of the trial; the intervention group blood pressure increased by 5/2.5 mmHg relative to controls after 12 months of follow-up. Again, patients in this trial were relatively young (mean age 54 years), and measures of physical function or quality of life were not reported.

Current trials in this area

What trials are currently underway, and will these trials help us to decide if bicarbonate therapy is of overall net benefit to older patients with CKD and acidosis? Table 1 shows trials that are currently recruiting, with a particular focus on the age targets and outcomes being collected. The trials currently in progress cover a range of ages and a range of categories of renal dysfunction. Most trials are targeting patients with normal or only slightly low serum bicarbonate concentrations; only the BiCARB trial is targeting patients exclusively with low serum bicarbonate (<22 mmol/L).

Most trials are designed and powered to show differences in renal function, or to explore surrogate markers of renal damage. The BiCARB trial [42] aims specifically to examine the impact of bicarbonate

on physical function and quality of life. The trial by Hostetter will examine sit to stand time – a powerful predictor of falls and functional impairment in older people, and will also examine grip strength, which is known to predict death, hospitalisation, and future need for care in older people. The Use of Bicarbonate in Chronic Renal Insufficiency (UBI) trial [43] will collect data on lean body mass (mostly represented by muscle), which although not a measure of function, is related to impairment as seen in studies of sarcopenia [44]. Thus the current batch of trials should provide evidence not only to test whether bicarbonate therapy slows the decline in renal function, but of perhaps greater relevance to older people, may show whether bicarbonate therapy improves physical function and quality of life.

Although none of the trials currently underway will be large enough to show differences in all-cause mortality or cardiovascular events, the high rate of such events in patients with CKD might allow for such a signal to be detected in pooled analyses – for example, if the rate of a composite endpoint such as cardiovascular event or death was 30%, a pooled sample of 2100 patients would have approximately 80% power to detect a 25% difference in event rate. Even in the absence of such a signal, the current trials should be able to ascertain whether bicarbonate therapy causes blood pressure to rise, and whether episodes of fluid overload are more common.

Conclusion

Several lines of evidence from basic science and observational studies suggest that metabolic acidosis in patients with CKD has deleterious effects. Acidosis may adversely affect cardiovascular health, muscle function and bone health as well as accelerating decline in renal function, and impairments in these organ systems would be expected to have an adverse impact on physical function and quality of life – key outcomes for older people. There are however few intervention studies to date to show whether these observational data translate into relevant health gains for older people with CKD, and there is concern that side effects or even adverse cardiovascular effects of bicarbonate

supplementation could negate any putative benefits. Until such data are available, it will remain unclear if bicarbonate therapy in older CKD patients is of net benefit; fortunately, a number of trials are currently underway (including one targeted specifically at older CKD patients with acidosis) that should give some much-needed answers to these questions.

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Table 1. Trials currently in progress testing the effect of bicarbonate supplementation in chronic kidney disease

Trial reference and name	Age range (yrs)	Bicarbonate at entry (mmol/L)	eGFR at entry (mL/min/1.73 m^2)	Dose	Primary outcome	Secondary outcomes	Target n	Follow up time
ISRCTN09486651 (BiCARB)[42]	>= 60	<22	<30	3g/day vs placebo	Short Physical Performance Battery	Quality of life (KDQoL and EQ5D); decline in renal function, bone turnover markers, BP, BNP	380	2 yrs
NCT01640119 (UBI)[43]	>=18	>=18	<45	Up to 4g/day; titrated to serum bicarbonate of 24-28mmol/L vs usual care	Commencement of renal replacement therapy, or death	Renal function, PTH, calcium, phosphate, albuminuria, lipids and homocysteine; bone turnover markers, blood pressure, lean body mass by bioimpedance	728	3 yrs
EuDRACT 2012-001824-36 (SoBIC)[45]	>=18	<21	15-44	Up to 5g/day; Titrated to keep serum bicarbonate >24 mmol/L vs titrated to keep serum bicarbonate >20 mmol/L	Decline in renal function	Death, recommendation to start renal replacement therapy, bone turnover markers	200	2 yrs
NCT01452412	>=19	20-25	15-45	0.4mEq/Kg ideal body wt/day vs placebo	Insulin resistance, bone mineral density, sit to stand speed, renal tubular function markers	Insulin sensitivity by clamp, grip strength, renal function, PTH, albuminuria, calcium, phosphate, 1,25OHD	150	1 yr
Pending registration: (BASE trial)	18-85	20-28	20-44 or 45-59 + ACR >100 mg/g	0.5 vs 0.8 mEq/Kg lean body wt/day	Adherence to dose	Urinary ammonium excretion	192	28 wks

NCT01574157	>=18 with Type 2 diabetes	22-28	15-89 + ACR >30 mg/g	0.5 mEq/Kg lean body wt/day vs placebo	Urinary TGF-beta	Urinary complement components	74	6 mths
NCT02031770	40-70	16-19	15-29	2-3x/day dosing to raise serum bicarbonate to >=23 mmol/L vs usual care (crossover design)	Brachial artery flow-mediated dilatation	-	20	14 wks

ACR: Albumin/Creatinine ratio. BP: Blood pressure. BNP: B-type natriuretic peptide. PTH: parathyroid hormone, TGF-beta: transforming growth factor beta

1,25OHD: 1,25-hydroxyvitamin D