Moderator’s view: Higher serum bicarbonate in dialysis patients is protective

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ABSTRACT

Several observational studies have reported an association between higher serum bicarbonate level and high mortality risk in dialysis patients. However, in such studies mere discovery of associations does not allow one to infer causal relationships. This association may be related to inadequate dietary protein intake that may lead to less acid generation and hence a higher serum bicarbonate level. Since undernutrition is a strong predictor of death in hemodialysis patients, the observed association may be an epiphenomenon and not a biologically plausible relationship. Higher protein and fluid intake between two subsequent hemodialysis treatments may lead to lower serum bicarbonate level. This low bicarbonate level may appear protective, as patients with higher food intake and better appetite generally exhibit greater survival. In the contemporary three-stream proportioning system of hemodialysis treatment, the bicarbonate concentrate is separate from the acid concentrate, and the contribution of the acid concentrate organic acid (acetate, citrate or diacetate) to the delivered bicarbonate pool of the patient is negligible. The concept of ‘total buffer’ that assumes that the combination of bicarbonate and acetate concentrations in the dialysate are added equally as bicarbonate equivalents is likely wrong and based on the misleading notion that the acetate of the acid concentrate is fully metabolized to bicarbonate in the dialysate. Given these uncertainties it is prudent to avoid excessively high or low bicarbonate levels in dialysis patients.

Keywords: acetate, acid concentrate, death, hemodialysis, metabolic acidosis

INTRODUCTION: OVERVIEW OF THE POINT/COUNTERPOINT PAPERS

In the debate as to whether higher serum bicarbonate is protective in dialysis patients, Misra [1] asserts that given the high prevalence of metabolic acidosis in dialysis patients, dialysate administration of bicarbonate is needed to maintain acid–base balance [1]. Misra agrees that in observational studies both a high and low pre-dialysis serum bicarbonate level is associated with adverse outcomes but that the mortality of high bicarbonate level disappears when adjustment for the confounding effects of nutritional status is undertaken, whereas low bicarbonate maintains its mortality association [1]. Debating against the aforementioned position, Chauveau et al. [2] agree that metabolic acidosis is frequent in advanced chronic kidney disease (CKD), with deleterious consequences on nutritional status, bone and mineral status, inflammation and mortality; however, they assert that a mild degree of metabolic acidosis in dialysis patients is associated with a better nutritional status and a higher protein intake and hence with greater survival, and refer to the dietary acid load from ingestion of animal-based protein [2]. They mention that a high predialysis serum bicarbonate concentration is an alarming finding and likely a sign of inadequate dietary protein intake and suggest that a high serum bicarbonate concentration would not imply optimal dialysis treatment [2]. Both groups of authors rebut each other’s points of view briefly and appear to have reached some common ground.

INTERPRETING REPORTED ASSOCIATIONS BETWEEN BICARBONATE AND MORTALITY

In epidemiologic studies, also known as observational studies, an association is not the same as causation. Mere discovery of associations does not allow one to infer causality [3]. In 1965 Sir Austin Bradford Hill established a number of criteria, which, if fulfilled, would strengthen—but not prove—the possibility of a causal relationship [4], including (i) temporal relationship, (ii) strength of association, (iii) dose response, (iv) consistency, (v) biologic plausibility, (vi) experimentation, (vii) specificity,
(viii) biologic coherence and (ix) analogy. Pharmacoepidemiologic studies using conventional survival analyses are subject to major limitations when examining associations of risk factors or therapeutic interventions, say a given vitamin D analogue [5] or erythropoiesis-stimulating agents [6], with higher mortality, since these associations may be created artificially through sources of bias and errors, including the ‘confounding by medical indication’. Some observational studies may describe an apparent association between a higher blood level of a given measure (or more frequent use of a given therapeutic intervention) and poor outcomes under certain pathologic conditions. Because this pathologic condition itself can both cause poor outcomes and at the same time result in high blood levels of the measure (or may prompt more likely or more frequent use of certain therapeutic interventions), it is possible that the found association of the blood level (or intervention) with death is due to ‘reverse causation’ [7].

The relevant example relates to certain reported associations between higher serum bicarbonate level (or potentially more likely, the use of alkaline-producing interventions) and higher mortality in hemodialysis patients, whereby the association may be truly causal (as shown in Model 1 in Figure 1) or an epiphenomenon (as shown in Models 2 and 3). Since inadequate dietary protein intake may lead to a higher bicarbonate level and since undernutrition is a strong predictor of death in hemodialysis patients, an artificial association between higher serum bicarbonate level and death risk is created due to this confounding [8]. On the other hand, if the administration of higher alkaline-producing substances happens more frequently in hemodialysis patients with more severe acidosis, and since acidosis per se is associated with poorer outcomes, an artificial association between the administration of the alkaline-producing substances and death can be observed as a result of this ‘confounding by medical indication’ (Figure 1).

**HYDROGEN ION HOMEOSTASIS AND METABOLIC ACIDOSIS IN RENAL FAILURE**

Daily acid production varies under different conditions and usually ranges between 50 and 70 mEq/day in healthy individuals [9]. As a rule of thumb, 1 mEq of hydrogen ion is produced per kilogram of body weight per day, and each gram of dietary protein intake leads to 1 mEq of hydrogen ion generation. The amount of daily acid production is enormous compared with the minuscule amount of hydrogen ion concentration in the extracellular fluids (40 nEq/L). The sources of acid production include loss of bicarbonate from the lower gastrointestinal tract (20–30 mEq/day); breakdown of proteins, amino acids and nucleic acids from dietary sources (20–30 mEq/day) and oxidation of carbohydrates and fats primarily in muscle cells, leading to the production of lactic acid and keto acids, respectively (10–20 mEq/day). The former mechanism can increase greatly in hypercatabolic states, whereas the latter increases under anaerobic conditions or insulin deficiency [9, 10].

The hydrogen ion homeostasis is significantly deranged in CKD patients. Metabolic acidosis almost invariably occurs in people with CKD. Although the compensatory mechanisms to mitigate the acute metabolic acidosis are normally fairly effective, the body has less tolerance for chronic metabolic acidosis in CKD and ESRD. The severity of metabolic acidosis varies widely in patients with renal failure [9, 10]. For instance, diabetic patients with CKD or ESRD are described as having less severe metabolic acidosis than their nondiabetic counterparts [9]. Metabolic acidemia interferes with a number of important functions in renal failure patients and intensifies endocrine and musculoskeletal disorders [9, 10]. Several mechanisms have been suggested that link metabolic acidosis and protein–energy wasting (PEW) in renal failure, which have been described elsewhere [9].

**FIGURE 1:** Three hypothetical ‘causal’ models of the hyperbicarbonatemia–death association in dialysis patients.
THE ROLE OF PEW IN ACID–BASE BALANCE OF CKD

Protein–energy wasting and inflammation, collectively referred to as malnutrition–inflammation complex, are among the strongest risk factors for morbidity and mortality in ESRD [9]. Although a good nutritional status may lead to greater survival, the associated higher dietary protein intake, by virtue of its acidogenic nature, invariably results in lower serum bicarbonate levels in patients with ESRD. Hence, there is little doubt that hemodialysis patients with a good appetite consume more protein and generate more acid, leading to lower serum bicarbonate, while they exhibit greater survival [11–13]. These epiphenomena are probably the underlying basis for the association between lower serum bicarbonate level and better survival observed in ESRD patients in some [14], but not all, studies [11–13].

The PEW may be a plausible cause of the reverse epidemiology of cardiovascular risk factors and other poor outcomes, such as poor quality of life and increased hospitalization and refractory anemia in dialysis patients [8, 15]. The cause of PEW in dialysis patients is not very clear, but some probable causes are discussed elsewhere [15]. Some of these factors, such as reduced food intake owing to anorexia, can be both a cause and a consequence of the PEW. Because nutritional and inflammatory conditions may be modifiable, correcting nutritional status in dialysis patients may improve outcomes and correct the reverse epidemiology.

BUFFER AND ACID CONCENTRATES FOR HEMODIALYSIS TREATMENT

As discussed above, given the ongoing acid generation and massive consumption of intrinsic bicarbonate pool in the face of failed kidneys, bicarbonate supplementation is the quintessential component of any hemodialysis therapy. Historically, as hemodialysis techniques first developed in the 1950s, bicarbonate was directly added as the main alkali during the hemodialysis treatment, but at a lower concentration than now. The use of bicarbonate, however, was associated with major technical challenges at that time, including the propensity towards calcium carbonate (CaCO₃) precipitation, high risk of bacterial contamination and need for frequent mixing and immediate use [16]. In the mid-1960s the acetate solution emerged as the chief alkali for hemodialysis treatment given that acetate would convert into bicarbonate via citric acid cycle, targeting a positive acetate balance of 3–4 mEq/L. The usual acetate solution concentration was 37 mEq/L. The use of acetate, however, was associated with certain adverse events, including hypotensive episodes especially with high-flux dialysis, recurrent headaches, nausea and vomiting, worsened metabolic academia due to bicarbonate removal from the blood and hypoxemia from suppressed ventilatory drive [16]. Since the 1990s, with the advancement of the new technology of the so-called three-stream (acid–base–water) ‘proportioning systems’, the bicarbonate is back and has replaced acetate as the alkali source. The three-stream system allows use of higher bicarbonate concentrations with the flexibility to adjust the concentration for the patient’s need given the advanced capabilities of concentrate pumping [17].

In the contemporary three-stream proportioning system, in addition to purified warm water and buffer (bicarbonate) concentrate, there is a so-called acid concentrate that usually consists of acetic acid, citric acid or sodium diacetate, and that is used to prevent a rapid increase in pH from bicarbonate administration. The conventional acid concentrate also contains glucose monohydrate along with the chloride salts of sodium, calcium, magnesium and potassium [16]. By keeping the PH of the dialysate fluid <7.3, the acid concentrate prevents precipitation of carbonate salts of calcium and magnesium that could have occurred upon bicarbonate administration. As to whether there are clinically meaningful differences among the different types of acid concentrates, there have been ongoing debates with sensitive commercial angles. Citric acid likely works similar to liquid acetic acid, whereas sodium diacetate (composed of sodium acetate and acetic acid) can be handled in the form of dry acid concentrate.

The contribution of the acid concentrate to the in vivo delivered bicarbonate pool of the patient is negligible. Some experts explain this by arguing that since the organic acid (acetate, citrate or diacetate) consumes bicarbonate from the bicarbonate concentrate while it is also converted into bicarbonate, it yields a zero balance of net bicarbonate delivery. This likely misguided reasoning is based on the old (pre–bicarbonate era) concept in that acetate was administered directly as a buffer solution. Similarly, some have suggested that sodium diacetate could generates 2 bicarbonate equivalents compared with 1 bicarbonate equivalent generated by acetic or citric acid and recommend that the base concentrate should be adjusted downwards accordingly to avoid higher ‘total buffer load’ when sodium diacetate is used as the acid concentrate [16, 17]. The concept of ‘total buffer’ is likely incorrect, as it assumes that the combination of bicarbonate and acetate concentrations in the dialysate are added equally as bicarbonate equivalents. It is based on the wrong notion that the acetate of the acid concentrate is fully metabolized to bicarbonate in the dialysate. It is important to note that during hemodialysis treatment patients are dialyzed against the dialysate bicarbonate only. The erroneous concept of the ‘total buffer’ may mislead nephrologists to reduce inappropriately the bicarbonate doses prescribed for hemodialysis treatment when organic acids are used as acid concentrate. It might lead to ill-advised and potentially risky reductions in bicarbonate dosing and result in poor outcomes in hemodialysis patients.

SERUM BICARBONATE MEASUREMENTS BEFORE AND AFTER HEMODIALYSIS

Variation in serum bicarbonate concentration occurs during the interdialytic and intradialytic periods in hemodialysis patients, with the highest bicarbonate level occurring immediately after the dialysis session and the lowest immediately before the next dialysis session, known as the sawtooth pattern. Predialysis serum bicarbonate (which is often measured during the monthly dialysis blood testing) is usually determined by the endogenous acid production between two consecutive dialysis treatments, in particular dietary protein intake and endogenous protein catabolism. This may cause serum bicarbonate fluctuation amounting to
4–6 mEq/L. The rate of fluid retention between two consecutive hemodialysis treatment sessions may also play a role by virtue of a ‘dilution acidosis’ (the opposite concept of the contraction acidosis), as the retained fluid can affect prehemodialysis bicarbonate by several units (mEq/L). The posthemodialysis serum bicarbonate is influenced mostly by the hemodialysis prescription, including the administered buffer concentrate, hemodialysis treatment length and the degree of ultrafiltration, which may lead to contraction alkalosis. Hence, postdialysis serum bicarbonate is often 2–5 units higher than the prehemodialysis concentration. It is important to remember that serum bicarbonate is not measured directly. The chemistry analyzers convert bicarbonate into CO₂ and measure the total CO₂, which is 1–2 mEq/L (= 0.03 × P_CO₂) higher than the real serum bicarbonate level [9].

CONCLUSIONS

ESRD patients lack the kidney function required for hydrogen ion homeostasis. Hence, without dialysis treatment, including its bicarbonate administration, severe metabolic academia incompatible with life will eventually ensue. One of the goals of dialysis treatment is to correct metabolic acidosis by adding buffer concentrate in the form of bicarbonate. Variation in serum bicarbonate concentration occurs during the interdialytic and intradialytic periods with a sawtooth pattern. It is important to know that the bicarbonate concentration in the dialysate, known as bicarbonate or ‘buffer’ solution or concentrate, and its effect on patient serum bicarbonate is very different from the ‘acetate’ added to the dialysate, known as acid concentrate. To conclude, a higher predialysis measured serum bicarbonate level probably reflects poorer dietary protein intake, and such a higher serum bicarbonate level itself is not causally harmful, whereas a low serum bicarbonate level should be corrected in dialysis and other CKD patients. The observed associations between a higher bicarbonate concentration in the prescribed dialysate bath or addition of alkaliotic supplements to the dialysate and dialysis patient mortality are most likely due to confounding by indication and may not have biologically plausible causality. Given these uncertainties it is prudent to avoid excessively high or low bicarbonate levels in dialysis patients.

AUTHORS CONTRIBUTIONS

K.K.-Z. wrote the manuscript and its revisions and researched data and literature.

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