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Permalink

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Journal

Seminars in Dialysis, 27(3)

ISSN

0894-0959

Authors

Chen, Joline LT
Kalantar-Zadeh, Kamyar

Publication Date

2014-05-01

DOI

10.1111/sdi.12231

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Peer reviewed

Published in final edited form as:

Semin Dial. 2014 May ; 27(3): 259–262. doi:10.1111/sdi.12231.

Is an increased serum bicarbonate concentration during Hemodialysis associated with an increased risk of death?

Joline L. T. Chen^{1,2} and Kamyar Kalantar-Zadeh^{1,2,3}

¹Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine, Orange, California

²Long Beach Veterans Affairs Healthcare System, Long Beach, California

³Dept. Epidemiology, UCLA Fielding School of Public Health, University of California Los Angeles, Los Angeles, California

Metabolic acidosis is a common complication in chronic kidney disease (CKD) and end stage renal disease (ESRD) and is known to be associated with deleterious outcomes under these conditions.^{1, 2} Consistent with this biologically plausible notion, several clinical studies have suggested that correction of acidosis and/or higher bicarbonate levels are associated with greater survival in maintenance hemodialysis (MHD) patients.^{3–5} Hemodialysis therapy can effectively correct metabolic acidosis. During each hemodialysis session, patients are exposed to both the prescribed bicarbonate bath, usually between 30–40 mEq/L, and the dry acid concentrate, which can yield up to 8 mEq/L of bicarbonate.^{6, 7} Thus, a total bicarbonate load during a single dialysis session can be quite variable.

A number of recent epidemiologic studies, however, have suggested that a higher bicarbonate bath concentration in dialysis and/or a higher level of achieved serum bicarbonate may paradoxically and counterintuitively be associated with an increased risk for death.^{8–10} These recent findings have led to an FDA advisory in 2012 and ongoing controversies and litigations.⁶ Hence, the safety of prescribed bicarbonate bath in MHD patients and the ideal target serum bicarbonate concentration are in the public spotlight. We believe that these paradoxical associations between higher serum bicarbonate concentration and poor outcomes are likely false and stem from the confounding role of better nutritional status and higher dietary protein intake, which result in acidemia but improved survival (see below). On the other hand, more profound metabolic acidosis, as a consequence of more severe protein-energy wasting and hypercatabolism, likely worsens survival chance and also prompts clinicians to prescribe higher bicarbonate concentration; hence, a misleading association may arise from the notorious “confounding by indication” (see below).

Corresponding Author: Kamyar Kalantar-Zadeh, MD, MPH, PhD, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology & Hypertension, University of California Irvine Medical Center, 101 The City Drive South, City Tower, Suite 400 - ZOT: 4088, Orange, California 92868-3217, Tel: (714) 456-5142, Fax: (714) 456-6034, kkz@uci.edu.

Potential Conflicts of Interest:

KKZ has agreed to serve as a potential expert witness for the legal proceedings involving Granuflor.

Metabolic acidosis and malnutrition-inflammation complex

Protein-energy wasting and inflammation, collectively referred to as malnutrition-inflammation complex, are among the strongest risk factors for morbidity and mortality in ESRD; they often result in metabolic acidosis as well.² Acidemia can cause a significant number of endocrine, musculoskeletal, and metabolic abnormalities in ESRD, such as insulin resistance, decreased bone mineralization, increased parathyroid hormone release, and decreased serum leptin.¹ Metabolic acidosis, per se, can lead to increased muscle protein catabolism, decreased albumin and muscle protein synthesis, insulin resistance, disturbance of endocrine homeostasis, and increased inflammation.² Whereas 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.¹¹⁻¹³ Hence, there is little doubt that MHD patients with a good appetite consume more protein and generate more acid leading to lower serum bicarbonate; they have greater survival.¹¹⁻¹³ These epiphenomena are likely the underlying basis for the association between lower serum bicarbonate level and better survival observed in ESRD patients in some,^{4, 5} but not all studies (see below for more details).

Serum bicarbonate level, prescribed bicarbonate bath, and clinical outcomes

Despite basic research that indicated adverse catabolic response to metabolic acidosis, several epidemiologic studies in MHD patients have shown that improved metabolic acidosis does not correlate linearly with better clinical outcome. In 1990, Lowrie *et al* reported a U shaped relationship between baseline serum bicarbonate and mortality.⁸ The authors reported a higher risk of death when serum bicarbonate was < 17.5 mEq/L or > 25 mEq/L. A decade later, an analysis of 7,000 dialysis patients in the *Dialysis Outcomes and Practice Patterns Study* (DOPPS) by Bommer *et al* also demonstrated a U shaped association between mortality and pre-dialysis serum bicarbonate level.⁹ Low (< 17 mEq/L) and high (> 27 mEq/L) bicarbonate levels both correlated with worse survival in univariate analyses. Notably, however, after adjustment for comorbidity, nutritional factors, and dialysis adequacy, the apparent association between metabolic alkalosis and mortality became non-significant.

More recently, Tentori *et al* examined the relationship of dialysate bicarbonate concentration with mortality using the DOPPS database of 17,000 MHD patients followed between 2002 and 2011.¹⁰ While no association between mortality and prescribed bicarbonate bath was found in univariate analyses, the investigators found a slightly (8%) higher mortality risk among patients prescribed high dialysate bicarbonate concentration after multivariate adjustment. Curiously, the higher risk in mortality was driven by a marked increase in infectious mortality, and not by cardiovascular events, a finding against the expected mechanism of action of high bicarbonate associated metabolic alkalosis if it were indeed a real cause of death.

Whereas the authors attributed the higher mortality to the high dialysate bicarbonate concentration, the presence of a significant confounding by indication bias is a more likely

explanation.¹⁴ It is likely that high bicarbonate bath was prescribed to treat more severe metabolic acidosis, driven by underlying processes such as more profound protein-energy wasting and inflammation, which often lead to poorer survival. The two aforementioned DOPPS studies are, hence, flawed given their lack of fundamental information on the true reason as to why certain dialysate bathes were used and given deficient data on post-dialysis bicarbonate and blood pH, dietary intake, and nutritional and inflammatory status of these patients, among others.

Is there a reverse epidemiology in the relationship between serum bicarbonate and mortality?

In 2005, the role of protein-energy wasting and inflammation in confounding the relationship of acidosis with mortality in MHD patients was more systematically and thoroughly examined using the database of approximately 56,000 US American MHD patients followed between 2001 and 2003; these results were initially published in form of an abstract with a subsequent peer-reviewed paper.^{3, 4} The investigators of this landmark study reported that in unadjusted analysis, an “acidotic” range of serum bicarbonate (17–22 mEq/L) exhibited better survival, whereas a “normal to alkalotic” bicarbonate range (23–27 mEq/L) was associated with higher all-cause and cardiovascular mortality. However, these associations reversed almost entirely after multivariate adjustments, first for case mix and then for markers of nutritional status and inflammation (Figure 1). Indeed in the fully adjusted model, a serum bicarbonate level greater than 23 mEq/L was associated with best survival whereas acidemic ranges of bicarbonate (<22 mEq/L) was incrementally associated with higher death risk. Several years later a similar phenomenon was reported in non-dialysis dependent (NDD) CKD populations.¹⁵

Therefore, although high bicarbonate levels may *appear* to be associated with increased mortality in CKD and MHD patients, this paradoxical association likely an epiphenomenon with little to no biologic plausibility since it is almost entirely due to the overwhelmingly confounding impact of the nutritional status on survival. The MHD patients with significant malnutrition and lower protein intake likely take smaller amounts of acidogenic foods resulting in a higher level of serum bicarbonate at the pre-dialysis time when the blood draw usually happen in MHD patients. Thus, the apparent pre-dialysis alkalemia is likely an indicator of poor protein intake from the underlying anorexia and protein-energy wasting and infers poor prognosis. Meanwhile, the MHD patients with more profound metabolic acidosis and even lower serum bicarbonate levels due to hypercatabolism and muscle and fat wasting remain at higher risk for death; these patients are often prescribed higher bicarbonate baths, resulting in the misleading observation that show an arbitrary link between the higher prescribed bicarbonate bath and worse survival.

Management of Metabolic Acidosis in MHD

Whereas there are no large interventional clinical trials examining the effect of higher bicarbonate bath or oral alkali supplementation on outcomes of MHD, epidemiologic studies and some smaller clinical trials provide some guidance on management of metabolic acidosis in this patient population. Vashistha *et al* examined the use of bicarbonate bath,

time-averaged pre-dialysis serum bicarbonate levels, and mortality in a national cohort of more than 160,000 ESRD patients between 2001–2007.⁵ The authors found that 40% of the 110,000 MHD patients in the US had inadequate correction of uremic metabolic acidosis with serum bicarbonate < 22 mEq/L and 36% of patients dialyzed against a bicarbonate bath of 39 – 40 mEq/L still had a bicarbonate level < 22 mEq/L. After accounting for case mix and nutritional and inflammatory markers, a pre-dialysis bicarbonate level < 24 mEq/L was associated with a higher risk for death irrespective of dialysis modality, while a serum bicarbonate concentration >25 mEq/L was not associated with increased death risk.

In another study in a registry of 405 critically ill patients who received bicarbonate based continuous renal replacement therapy, treatment related alkalemia and metabolic alkalosis were not associated with increased mortality, whereas persistent acidosis was linked with poorer survival.¹⁶ Among other studies in dialysis dependent patients, a small single center study followed 164 MHD patients who were treated with oral bicarbonate for 1 year.¹⁷ During the trial period, the patients appeared to have improved acid-base status, less intradialytic hypotension, and fewer hospitalizations. Among ESRD patients treated with peritoneal dialysis (PD), a clinical trial comparing a high versus low level of lactate in peritoneal dialysate found that patients treated with higher amount of base had better nutritional status and markers, such as higher body weight, greater mid-arm circumference, and fewer hospitalizations.¹⁸ In another study where PD patients were prescribed oral bicarbonate, those who achieved a serum bicarbonate level of 26 – 28 mEq/L showed better subjective global assessment scores, higher normalized protein catabolic rate and fewer hospitalizations.¹⁹ Several interventional studies examining the effect of oral bicarbonate or base-inducing food types have reported improvement of muscle strength and a delay of renal disease progression among NDD-CKD patients.^{20–22}

Conclusion

Clinical practice guidelines from the *National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiatives (KDOQI)* recommend treatment of metabolic acidosis to achieve a serum bicarbonate levels of at least 22 mEq/L.²³ Notwithstanding some inconsistent data likely representing the epiphenomenon of greater survival associated with the combination of low serum bicarbonate levels and higher protein intake, well conducted epidemiologic studies have demonstrated adverse outcomes of patients with serum bicarbonate levels < 22 mEq/L; hence, we recommend physicians adhere to the KDOQI guideline in treating metabolic acidosis. While no large-scale interventional trials have evaluated clinical outcomes of alkali supplementation or bicarbonate bath prescription in ESRD patients, nephrologists must be aware of the potential flaws and nuances of recent observational studies as we apply the literature to clinical practice. Whereas mild pre-hemodialysis acidemia is often a reflection of higher dietary protein intake and may require no change in the prescribed bicarbonate bath, a more profound acidemia that is (usually from hypercatabolism or other comorbid states) may prompt the prescription of higher bicarbonate bath, leading to the confounding by indication in some observational studies that misleadingly report an association between prescribed higher bicarbonate bath and mortality.

A higher serum bicarbonate level immediately prior to the hemodialysis treatment session may be a surrogate of inadequate dietary protein intake and possibly a sign of poor appetite and inadequate protein intake. In these cases, physicians should pay attention to the underlying cause of variation in pre-dialysis serum bicarbonate levels, such as protein-energy wasting and inflammation, and focus on treatment to improve nutritional status and protein intake, instead of blaming a high serum bicarbonate level as a “cause” of higher death risk under such conditions.

To conclude, a higher pre-dialysis measured serum bicarbonate level likely reflects poorer dietary protein intake and that such a higher serum bicarbonate level itself is not causally harmful, and indeed all things equal a low serum bicarbonate level <24 mEq/L should be corrected in dialysis and other CKD patients. Moreover, we also believe that the observed associations between a higher bicarbonate concentration in the prescribed dialysate bath or addition of alkalotic supplements to the dialysate and MHD patient mortality is most likely due to confounding by indication and has little if any causality.

Acknowledgments

Support:

This work was supported by KKZ’s research grants from the NIH/NIDDK (K24-DK091419 and R01-DK078106) and a philanthropic grant from Mr. Harold Simmons.

References

1. Kopple JDKZK, Mehrotra R. Risk of chronic metabolic acidosis in patients with chronic kidney disease. *Kidney International*. 2005; 67:S21–S7. [PubMed: 15882309]
2. Kalantar-Zadeh KMR, Fouque D, Koppe JD. Metabolic acidosis and malnutrition-inflammation complex syndrome in chronic renal failure. *Seminars in dialysis*. 2004; 17(6):455–65. [PubMed: 15660576]
3. Wu D, Kilpatrick RD, Dadres S, McAllister CJ, Kopple JD, Kalantar-Zadeh K. Association between serum bicarbonate and death in hemodialysis patients: is it better to be acidotic or alkalotic? *Hemodialysis International*. 2005; 9(1):87.
4. Wu DSC, Regidor DL, McAllister CJ, Kopple JD, Kalantar-Zadeh K. Association between serum bicarbonate and death in hemodialysis patients: is it better to be acidotic or alkalotic? *Clinical Journal of American Society of Nephrology*. 2006; 1(1):70–8.
5. Vashistha TK-ZK, Molnar MZ, Torlen K, Mehrotra R. Dialysis modality and correction of uremic metabolic acidosis: relationship with all-cause and cause-specific mortality. *Clinical Journal of American Society of Nephrology*. 2013; 8(2):254–64.
6. FDA. [accessed 01/14/2014] FDA Safety Communication: Dialysate Concentrates and Alkali Dosing Errors with Hemodialysis. 2012. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm305477.htm>
7. Meyers K. Dialysate Bicarbonate: the case for foot dragging. *American Journal of Kidney Disease*. 2013; 62(4):650–2.
8. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis*. 1990; 15(5):458–82. [PubMed: 2333868]
9. Bommer JLF, Satayathum S, Keen ML, Goodkin D, Saito A, Akiba T, Port FK, Young EW. Association of predialysis serum bicarbonate levels with risk of mortality and hospitalization in the dialysis outcome and practice patterns study (DOPPS). *American Journal of Kidney Disease*. 2004; 44(4):661–71.

10. Tentori FKA, Robinson B, Morgenstern H, Zhang J, Sen A, Ikizler TA, Rayner H, Fissell RB, Vanholder R, Tomo T, Port FK. Association of dialysate bicarbonate concentration with mortality in the dialysis outcomes and practice patterns study (DOPPS). *American Journal of Kidney Disease*. 2013; 62(4):738–46.
11. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *American Journal of Clinical Nutrition*. 1998; 68:576–583. [PubMed: 9734733]
12. Adeva MM, Souto G. Diet-induced metabolic acidosis. *Clinical Nutrition*. 2011; 30:416–21. [PubMed: 21481501]
13. Remer T. Influence of nutrition on acid-base balance-metabolic aspects. *European Journal of Nutrition*. 2001; 40:214–20. [PubMed: 11842946]
14. Salas M, Hofman A, Stricker B. Confounding by indication: an example of variation in the use of epidemiologic terminology. *American Journal of Epidemiology*. 1999; 149(11):981–3. [PubMed: 10355372]
15. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. *Nephrol Dial Transplant*. 2009; 24 (4): 1232–7. [PubMed: 19015169]
16. Demirjian S, Teo BW, Paganini EP. Alkalemia during continuous renal replacement therapy and mortality in critical ill patients. *Critical Care Med*. 2008; 36(5):1513–7. [PubMed: 18434895]
17. Checherita IADC, Ciocalteu A, Lascar I, Budala L. Oral treatment of metabolic acidosis in hemodialyzed patients and the implications on the hemodynamic status. *Romanian Journal of Morphology & Embryology*. 2013; 54(3):539–43. [PubMed: 24068401]
18. Stein A, Moorhouse J, Iles-Smith H, et al. Role of an improvement in acid-base status and nutrition in CAPD patients. *Kidney Int*. 1997; 52(4):1089–95. [PubMed: 9328950]
19. Szeto CC, Lai KN. Metabolic acidosis and nutritional status of patients receiving continuous ambulatory peritoneal dialysis (CAPD). *Int J Artif Organs*. 1998; 21(4):192–5. [PubMed: 9649058]
20. Goraya NSJ, Jo C, Wesson D. Dietary acid reduction with fruits and vegetables or sodium bicarbonate reduces kidney injury in individuals with moderately reduced GFR due to hypertensive nephropathy. *Kidney International*. 2011; 81:86–93. [PubMed: 21881553]
21. Abramowitz MKMM, Bauer C, Raff AC, Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. *Clinical Journal of American Society of Nephrology*. 2013; 8(5):714–20.
22. de Brito-Ashurst IVM, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of chronic kidney disease and improves nutritional status. *Journal of American Society of Nephrology*. 2009; 20:2075–84.
23. Foundation NK. Clinical practice guidelines for nutrition in chronic renal failure. *American Journal of Kidney Disease*. 2000; 35(suppl 2):S1–S140.

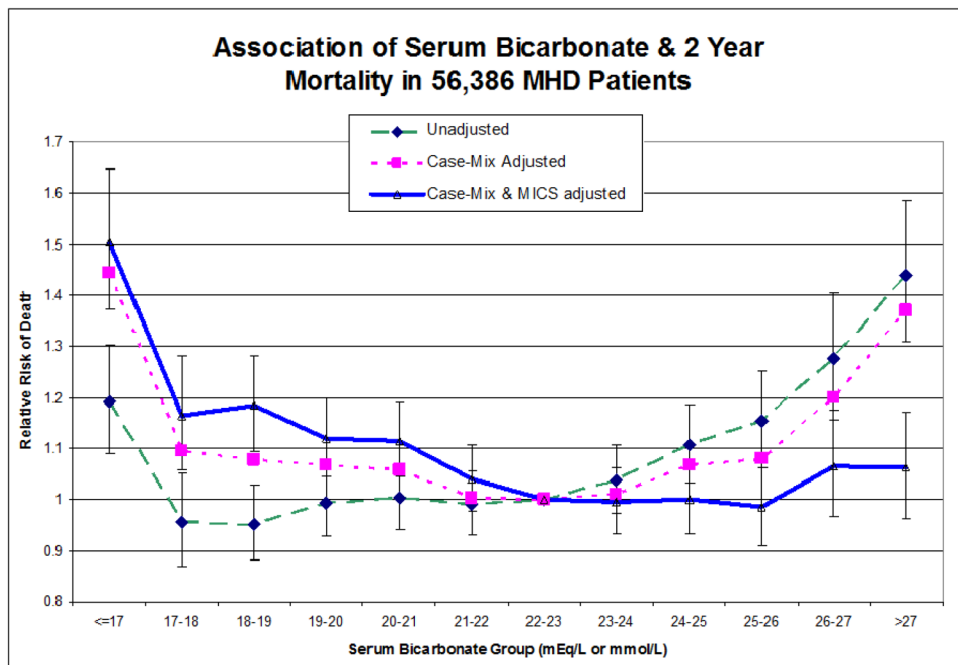


Figure 1.

Multivariate adjustment may change or even reverse the naïve association between serum bicarbonate level and survival in MHD patients. Adopted from Wu D et al, *Hemodialysis International* 2005 (oral abstract presentation during the 2005 Annual Dialysis Conference)³ and Wu et al, *Clin J Am Soc Nephrol* 2006 (full manuscript).⁴
MICS: Malnutrition-inflammation complex syndrome.