Author's response to reviews

Title: High Serum Bicarbonate Level within the Normal Range Prevents the Progression of Chronic Kidney Disease in Elderly Chronic Kidney Disease Patients

Authors:

Eiichiro Kanda (tokyo.kyosai.kanda@gmail.com)
Masumi Ai (aivasc@tmd.ac.jp)
Masayuki Yoshida (masa.vasc@tmd.ac.jp)
Renjiro Kuriyama (icopdfirst@yahoo.co.jp)
Tatsuo Shiigai (info@shiigai-clinic.jp)

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Author's response to reviews: see over
Dear Dr. Henderson:

Thank you very much for your letter with the reviewers’ comments and for your helpful remarks concerning our paper. Included are our point-by-point responses to the reviewers’ comments, which we hope to have addressed in full. With regards to your editorial concerns, we have revised the manuscript taking your comments and suggestions into account as follows.

- Statistical Reporting
  Can you please ensure that you thoroughly revise your statistical analyses and results. You may wish to consider seeking the opinion of an expert statistician to ensure that all reporting is accurate, before submitting your revised manuscript.

  We have consulted and worked with a statistician, Dr. Masumi Ai, regarding the statistical analyses. This is included in “Authors’ contributions”.

- Copyedit
  We recommend that you copyedit the paper to improve the style of written English.

  In accordance with your recommendation, this paper has been edited by a native English speaker with scientific expertise from Myu Research Inc., Tokyo, Japan.

- General Formatting
  You now have an opportunity to ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is
important that your files are correctly formatted.

We were revised the manuscript to conform to the journal style.

**To Dr. Julia Scialla (5195612794332008_comment):**

**Major Compulsory Revisions:**

1. The use of causal language is too strong throughout the manuscript given the observational nature of the data. I recommend revising the statements that high serum bicarbonate "decreased" or "prevents" CKD progression.

   We agree with your suggestion. The expression has been toned down as you suggested.


2. I would like more information on the creation of the study population. The authors indicate that all participants had at least 2 years of follow-up (i.e. no deaths or other losses to follow-up in this period). This is unusual in clinical studies when losses to follow-up inevitably occur. Was 2 years of follow-up compulsory for inclusion in the study population? If so, this should be clearly discussed in the methods section and may be source of bias. A flow diagram may be helpful.

   I am sorry for the confusing description of our data collection. The observation period was 2 years. Data were collected until patients reached the defined outcome or changed were unable to collect their data following their transfer. Because the study population was simple, the number of patients who reached the outcome and that of those who changed hospital are described in “Results”, and a flow diagram is not used. Page 6, paragraph 2, line 12. Page 8, paragraph 2, line 8.

3. Differential rates of follow up in the two groups reported in Table 1, and "+" marks in Figure 2, suggest that censoring was present after 2 years and was much more common in the control group. The authors should discuss the reasons for these censoring events. Were deaths more common in the control group?
We agree that the censoring events need to be discussed, because of their number was large. The censoring occurred in a total of 33 patients: low-bicarbonate group, 9 (32.1%); control group, 24 (28.2%). No significant difference was observed between these two groups. However, the rate of censored observations seemed high. No death was observed as described in the Results. The reason was the change of hospital. Because Shiigai Clinic is in Ibaraki, which is far from Tokyo (it takes about two hours by train), it is difficult for patients who lived in Tokyo to continue visiting the clinic every month for years. Therefore, they changed hospital. The high rate of censored observation was described as a limitation in the Discussion.

4. Due to the presence of censoring (Comment 3), Cox models are the most appropriate method of analysis and logistic regression models are problematic. I would favor eliminating logistic models and Figure 1 and focus on the survival analysis which is more appropriate to the data type.

To focus on the results of Cox proportional hazard models, the results on ORs were eliminated. However, the logistic model is used to estimate the probability of detecting CKD progression, and the Figure 1 can show visually that the probability decreases with serum bicarbonate level within the normal range. Only Figure 1 was put in the back of the results on HRs. Page 7, paragraph 1, line 18. Page 9, paragraph 3, line 8. Page 20, paragraph 3, line 1, Figure 2.

Minor Essential Revisions:
5. The discussion mentions many other large studies with similar results. Can the authors discuss what this study adds to the others besides consistency?

We agree that the importance of the control of serum bicarbonate level has been reported. However, the CKD guidelines, such as those of K/DOQI and CARI, recommend only the lower limit of the target serum bicarbonate level, but do not have recommendations about the upper limit of serum bicarbonate level in non-dialysis-dependent CKD patients. There have been no confirmatory controlled trials on the therapeutic range of serum bicarbonate levels. For example, when we treat a CKD patient whose serum bicarbonate level is 23 mEq/l, there is no evidence that helps us to decide whether we administer the same dose of sodium bicarbonate or a higher dose of sodium bicarbonate to prevent CKD progression, because there is no
determined upper limit of serum bicarbonate level. First, in this study, we showed the relationship between a high serum bicarbonate level within the normal range and CKD progression, that is, a higher level is more effective for preventing the progression of CKD, and then showed the lower and upper limits of the target serum bicarbonate levels. Page 2, paragraph 1, line 3. Page 3, paragraph 1, line 1. Page 4, paragraph 3, line 4. Page 11, paragraph 2, line 19.

6. The authors indicate that no side effects of serum bicarbonate were noted. How did the authors assess for side effects and what side effects were specifically ascertained? Given the retrospective nature of this study, I suspect that detailed ascertainment of side effects could not be performed and I would recommend removing this statement.

The statement has been removed.

7. In Table 1, it would help to indicate mean +/- SD to differentiate from n(%).

In Subjects and Methods and Table 1, mean and SD are presented as mean ± SD. Page 7, paragraph 1, line 1. Page 16, Table 1.

8. In Table 2, it is preferable to label the column with a more descriptive term, such as "difference in serum bicarbonate", as opposed to beta.

“Beta” has been replaced with "Difference in serum bicarbonate" in Table 2. Page 18, Table 2. Page 18, paragraph 1, line 1.

9. In Figure 2, it is preferable to add a risk table below the Kaplan Meier graph to show the sample size in each group over follow-up.

The risk table has been added below Figure 1. Page 20, paragraph 2, line 3.

Discretionary Revisions:
10. The analysis using propensity score does not seem to add much to the multivariable models. The propensity score involves only 3 variables and does not include many that probably are important in serum bicarbonate level but not significant due to sample size. The propensity model still involves substantial multivariable adjustment. I would consider removing this section.
The propensity models have been eliminated.

11. The study population includes a mix of participants on sodium bicarbonate supplementation (approximately 20%) versus not. These two groups address a slightly different question and it may be useful to stratify by this factor or restrict to a purely untreated group.

We agree with your very interesting suggestion. There may be some clinical and pathological differences between the treated group and the untreated group. However, because the aim of this study was to investigate the limits of the target serum bicarbonate level in CKD patients, the effect of sodium bicarbonate on CKD progression was not evaluated in this study.

12. The discussion of references 20 and 21 may be somewhat incorrect and should be reviewed. For reference 20, I believe this study indicates that for a given net acid excretion, urine pH must be lower in older adults suggesting inefficiency in acid excretion but not necessarily that net acid excretion is out of pace with intake. I am unsure of the meaning of the statement regarding ref 21 given that metabolic acidosis and retention of hydrogen ions are essentially synonymous.

Thank you very much for your suggestions. We have deleted the statement regarding reference 21. Instead, we have described the mechanisms underlying CKD progression in response to acidosis, and referred to a paper, “Net endogenous acid production is associated with a faster decline in GFR in African Americans” (Kidney Int 2012, 82(1):106-112) (ref 25). Page 12, paragraph 2.

To Dr. Donald Wesson (1412268335791251_comment):

Major Compulsory Revisions
1. The data reported by the authors support that low serum [HCO3] within the normal range is associated with worse kidney outcomes (25% eGFR reduction and/or need for dialysis. They have not shown or adequately discussed, however, the determinants of the low serum [HCO3] that might be contributing to these adverse kidney outcomes. There are a number of possibilities, some of them overlapping:
a. The lower serum [HCO₃] might indicate a higher extracellular [H+] that itself might be injurious to kidneys.

b. Higher extracellular [H+] might induce other processes, such as high levels of agents that themselves cause kidney injury.

c. Lower serum [HCO₃] might indicate higher dietary H+ intake to which the kidney response (e.g., higher NH₄⁺ production) might contribute to kidney injury.

d. An recent publication currently in online form only (Scialla JJ, et al: Net endogenous acid production is associated with faster decline in GFR in African Americans. Kid Int (2012) online at doi:10.1038/ki.2012.82) supports that higher net endogenous acid production (NEAP) is associated with faster nephropathy progression in patients, even if their serum [HCO₃] is within the normal range. Increased dietary H+ and other factors increase NAEP. Consequently, lower serum [HCO₃] might indicate higher NAEP that itself might be injurious to the kidney.

If the authors have no data to support one of the above or other mechanisms to explain the reported data, they must at least comment upon these or other possible explanations. Doing so will give insight as to how therapeutic intervention might slow nephropathy progression.

Thank you very much for your suggestions. We have described the mechanisms underlying CKD progression in response to acidosis, and referred to the paper, “Net endogenous acid production is associated with a faster decline in GFR in African Americans” (Kidney Int 2012, 82(1):106-112), and cited it as reference 25. This limitation has been described in the Discussion as the fourth limitation. Page 12, paragraph 2. Page 13, paragraph 2, line 8.

2. Can the authors comment on the urine net acid excretion in their subjects?

The urine net acid excretion is meaningful and interesting to investigate with regard to the mechanism underlying the effect of acidosis on the progression of CKD. However, we did not measure urine net acid excretion level in this study.

Minor essential revisions:
1. Please provide the dose of NaHCO₃ used for subjects being so treated.

The dose of sodium bicarbonate is shown in Table 1. Page 5, paragraph 2, line 12. Page 8, paragraph 3, line 7. Page 16, Table 1.
2. Please state if other sources of alkali, like sodium citrate, were used in the subjects.

Only sodium bicarbonate was administered to control serum bicarbonate level. Page 5, paragraph 2, line 12.

*To Sankar D Navaneethan (1193964632792501_comment):*

Major compulsory revisions:
1. The exact aim of the study is unclear. If the objective was to study the associations between low serum bicarbonate and renal outcomes, this has been studied previously and well established. In fact, authors have appropriately referenced these studies (both observational studies and RCTs).

We agree that the importance of the control of serum bicarbonate level has been reported. However, the CKD guidelines, such as those of K/DOQI and CARI, recommend only the lower limit of the target serum bicarbonate level, but do not have recommendations about the upper limit of serum bicarbonate level in non-dialysis-dependent CKD patients. There have been no confirmatory controlled trials on the therapeutic range of serum bicarbonate levels. For example, when we treat a CKD patient whose serum bicarbonate level is 23 mEq/l, there is no evidence that helps us to decide whether we administer the same dose of sodium bicarbonate or a higher dose of sodium bicarbonate to prevent CKD progression, because there is no determined upper limit of the serum bicarbonate level. In this study, we showed the relationship between a high serum bicarbonate level within the normal range and CKD progression, that is, a higher level is more effective for preventing the progression of CKD, and then showed the lower and upper limits of the target serum bicarbonate levels. Page 2, paragraph 1, line 3. Page 3, paragraph 1, line 1. Page 4, paragraph 3, line 4. Page 11, paragraph 2, line 19.

2. Authors have mentioned that they conducted propensity analysis but they did not provide additional details relating to this. For example, did they use matching technique? How did the standardized difference plot differ before and after matching? What was the propensity score and what was the C-statistic of the model? It would be better to provide complete details of the propensity analyses and elaborate on this.
Considering your comment, statements about the propensity models have been eliminated.

3. Serum bicarbonate changes over time. It would be better to consider time-dependent models.

We agree that time-dependent models are better for this study. However, the design of this study and dataset were not appropriate for time-dependent models.

4. Were patients followed-up even after they were started on dialysis or were they censored. Please clarify as the methods section state that patients were censored at the end of follow-up.

I am sorry for the confusing description of our data collection. The observation period was 2 years. Data were collected until patients reached the defined outcome or changed were unable to collect their data following their transfer. Because the study population was simple, the number of patients who reached the outcome and that of those who changed hospital are described in “Results”. Page 6, paragraph 2, line 12. Page 8, paragraph 2, line 8.

5. Table 1. Please consider including only those with low-bicarbonate and those with normal bicarbonate group.

Patients were included in this study when their serum bicarbonate levels were within the normal range (normal range, 21 to 32 mEq/l). Because all the patients in this study had normal levels of serum bicarbonate, we defined serum bicarbonate level to be low when it fell in the lower 25th percentile of serum bicarbonate level (25.5 mEq/l). The inclusion criteria have been described in Subjects and Methods. Page 5 paragraph 2, line 4.

Minor revision:
6. Quality of the figures could be improved.

Figures 1 and 2 have been revised. A risk table has been added below Figure 1. The format of the figures was changed from JPEG to TIFF. Page 20, paragraph 2, line 3.
We thank the reviewers for the very thorough but fair review and hope that the revisions address all your concerns.

Sincerely,

Eiichiro Kanda, M.D. M.P.H. Ph.D.
Department of Nephrology,
Tokyo Kyosai Hospital