Author's response to reviews

Title: Presence of Early CKD-Related Metabolic Complications Predict Progression of Stage 3 CKD: a Case-Controlled Study

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Author's response to reviews: see over
RESPONSE TO THE REVIEWERS COMMENTS

The authors thank the reviewers for their comments. We believe that addressing the comments in the revision has strengthened the findings and conclusions of the paper.

Please note that we also submitted a COMPARISON document, using track changes, which compares the original and revised version to facilitate review.

REVIEWER 1

- Major Compulsory Revisions

This hypothesis demands the evaluation of kidney parenchymal damage, but the purpose of the study was to determine if the presence of metabolic complications were predictive of CKD progression. I believe the dissociation between hypothesis and aim is a major limitation that should be clarified.

We agree that the hypothesis should be modified to reflect the purpose of the study. We have made the following changes:

ABSTRACT: We replaced

We hypothesized that the risk of progression to stage 4 is related to the degree of parenchymal damage present at the time of entry to stage 3, reflected in the presence (or absence) of metabolic complications of CKD (anemia, worsening acidosis and mineral abnormalities).

With

We hypothesized that patients who enter stage 3 and ultimately progress have experienced greater loss of renal function, manifested by impairment of metabolic function (anemia, worsening acidosis and mineral abnormalities), than is reflected in the eGFR.

BACKGROUND: We replaced

We explored the hypothesis that future progressors can be distinguished from non-progressors in Stage 3 by assessing the degree to which there has already been a loss of functioning renal parenchyma as measured by anemia, worsening acidosis and mineral abnormalities.

With

We explored the hypothesis that compared to non-progressors, patients who enter stage 3 CKD and ultimately progress have experienced greater loss of renal function, manifested by impairment of metabolic function (anemia, worsening acidosis and mineral abnormalities), than is reflected in the eGFR at entry to stage 3.

DISCUSSION: We replaced
The purpose of this study was to design a prediction model for CKD progression using laboratory values other than eGFR based on the hypothesis that patients who enter stage 3 and ultimately progress have already sustained greater renal injury and loss of function than is reflected in the eGFR.

The purpose of this study was to design a prediction model for CKD progression using laboratory values other than eGFR based on the hypothesis that patients who enter stage 3 and ultimately progress have sustained a greater loss of renal function, manifested by impairment of metabolic function, than is reflected in the eGFR.

- Minor Essential Revisions
Data is comprehensive, but in Table 1 (or in the text) I suggest that the CKD etiology should be reported.

The etiology of CKD in these patients is either diabetes mellitus or hypertension. As described in the Methods, we removed any patient from either cohort that had any other known primary or secondary renal disease as identified in the record by an ICD9 code. That said, given the known inaccuracies of ICD9 coding some patients in our cohorts could have had one of the various primary or secondary causes of CKD without our being able to recognize this.

We have added to the LIMITATIONS section:

... although we excluded patients with known primary renal disease from the cohorts based on their ICD-9 codes, the known inaccuracy of ICD-9 coding cannot eliminate the possibility that some patients who progressed actually had a primary renal disease.

- Discretionary Revisions
Estimated GFR was not included in the predictive model, and one wonders if the inclusion of eGFR in the predictive model would have any influence on the results.

The purpose of the study was to determine if the presence or absence of metabolic complications were predictive of which patients entering stage 3 would progress to stage 4. Given that the average eGFRs of each cohort entering stage 3 were essential indistinguishable (Please see Table 3), eGFR would not be expected to be able to distinguish progressors from non-progressors. We actually did perform this analysis and found that eGFR, at entry to stage 3, was not predictive of progression.

REVIEWER 2:

This is an interesting paper where the authors try to address an important issue regarding the progression of kidney disease in terms of predictor factors as a possible tool to identify which are the patients with moderate CKD that will end up progressing to end stage renal disease and should be followed closely by a nephrologist.

1. Major Compulsory Revisions
To classify patients with stage 3 CKD, the authors used the MDRD formula. However, it was not specified if the MDRD formula used were traceable to IDMS or not. It’s also not clear why the authors decided to use the MDRD rather than the CKD-EPI. It would be interesting to recalculate the initial study population using the CKD-EPI formula to check the number of patients who would be included by the inclusion criteria of the EGFR <60 ml/min/1.73m^2. Since the MDRD formula tends to overestimate GFR, probably a larger number of patients would be included in the study. Also, since it is an older population (mean >70 years), the use of CKD-EPI formula would be more suitable for these patients, according to recommendations of the NFK.

Regarding the measurement of creatinine: Standardization of creatinine measurements is calibrated to IDMS. We have added this sentence to METHODS.

Regarding the calculation of eGFR

The stage 3 CKD cohort used in this study was first assembled in 2009 for studied on documentation of CKD in the electronic health record (#1850). At that time the MDRD calculation for eGFR was an appropriate choice. In 2012 when we began the current investigation, we considered recalculating the eGFR based on the CKD-EPI formula. We concluded that that was not necessary because the cohorts (progressors and non-progressors) were chosen on the basis of slopes (eGFR versus time) which would be unaffected by the recalculation. Although the absolute eGFRs reported in our paper might be slightly higher using the CKD-EPI formula compared to the MDRD, the conclusion that progressors manifest subtle metabolic abnormalities compared to non-progressors remains unchanged.

We have added to the “LIMITATIONS” section the following:

... we used the MDRD formula to calculate eGFR rather than the CKD-EPI formula. Recent studies have demonstrated the MDRD calculation tends to underestimate the eGFR (#2211)#1931. However, the average MDRD eGFR values in both cohorts were significantly below 60 ml/min/1.73m^2, suggesting that patients were in stage 3 regardless of the method used to calculate eGFR. Also, the two cohorts (P and NP) were chosen on the basis of the slope of the eGFR versus time, which is largely independent of the method of calculation. Our conclusions regarding the association of presence of metabolic complications and progression are thus unaffected by the method chosen to calculate eGFR.

- In terms of progression of renal disease, regardless of cause, an important factor to be considered is the use of medications with nephroprotective effect as ACE inhibitors and ARBs. The medications were not informed in this manuscript. The use of ACE inhibitors or ARBs may have influenced the outcome of P or NP in patients with CKD stage 3. It should have been considered in the statistical analysis.

We agree that the use of nephroprotective medicines, such as ACE inhibitors, would be an important attribute to use in a predictive model for progression of chronic kidney disease. The purpose of the present study, however, was to explore the presence or absence of metabolic complications in patients entering stage 3 and the degree to which complications are predictive of progression. There are other attributes that would provide predictive value in a more complete model (such as race), which we did not explore in this study, because of our focus on metabolic complications.
However, it is possible that those patients with early metabolic complications who ultimately progressed to stage 4 were less likely to be on the nephroprotective medicines, for whatever reasons. We thus raise this possibility in the DISCUSSION.

To the DISCUSSION we added:

...we did not assess either the degree of glycemic control or the use of RAS inhibitors. If the use of RAS inhibitors was higher in patients with diabetes who did not progress, this difference could explain why some patients progressed and others did not.

- We agree. Please see comment above.

- There is no need to show figure 2. The text is sufficiently explanatory.

We will remove this figure from the paper.

- It is unfortunate not to have a larger number of PTH and vitamin D data. They are probably a better predictor of progression of renal disease than phosphorus and calcium, which will only change as a result of hyperparathyroidism.

We agree with the reviewer that PTH and Vitamin D levels would have been much better predictors of progression than either calcium or phosphorous for the reasons given above. Unfortunately, very few patients had PTH measurements reported. We are working on a CKD-decision support tool that prompts providers to measure PTH and vitamin D in patients entering stage 3.

2. Minor essential revisions
- Background (page 4, line 20): “Stage 3” should be in lowercase.
- Discussion (page 12, line 14): delete one “that”

Done.