Author’s response to reviews

Title: SALIVARY CREATININE AS A DIAGNOSTIC TOOL FOR EVALUATING PATIENTS WITH CHRONIC KIDNEY DISEASE

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Responses to reviewer feedback

Dear Editor

Thank you for the constructive critique and for the opportunity to submit a revised manuscript. We list the comments and our responses below.
Thank you and regards
Haly Holmes, on behalf of the authors

Editor Comments:

1. Please rename the section 'Ethical considerations' to 'Ethics approval and consent to participate'. For Consent to Participate, please state clearly whether written informed consent was obtained from the participants in this section.

Response: The suggested edits have been made at the end of the Methods section. Written informed consent was obtained from all participants.
Reviewer 1:

2. While describing the epidemiology of CKD in Africa, it might be good to reference another quite recent systematic review on this issue (Abd ElHafeez et al. BMJ Open. 2018 Jan 10;8(1):e015069.)

Response: Thank you, we have cited this paper as reference 4.

3. The sentence "Stages 1 and 2 (GFR above and below 90 ml/min/1.73m2 are diagnosed only when there are other markers of kidney damage present (e.g. proteinuria)" is wrong and must be properly corrected. CKD stage 2 can be diagnosed with eGFR 89-60 even if no urinary abnormality is present (as correctly stated afterwards).

Response: We have used the KDIGO 2012 definition of CKD, which requires evidence of kidney damage (proteinuria, imaging abnormalities, functional or histological abnormalities, etc.) for the diagnosis of CKD when the eGFR is ≥ 60 ml/min/1.73 m2. This will apply to stage 1 and 2 CKD. See reference 3.

4. Etiology of CKD must be provided and possible differences in salivary creatinine according to type of disease investigated. It would have been interesting to investigate whether salivary creatinine may correlate also with other anthropometric and lab parameters, as in some cases serum creatinine does. I'm thinking about BP, PTH, inflammation, urea, electrolytes, uricemia, age, BMI, CKD vintage…

Response: We agree that it will be interesting to investigate the relationship between salivary creatinine and various clinical and laboratory variables. The present study has not focused on investigating this relationship. We have added a note to the limitations section.

5. A more detailed summary table containing the key characteristics of individuals participating into the study is necessary.

Response: Included in paper as Table 1.

6. It would be great if the Authors may provide some additional figures, e.g. about the linear relationship between serum and urinary creatinine.

Response: Additional figures added as Figs x …

7. The lack of a direct (ioexol scan) rather than an estimated (eGFR) renal function measurement as reference standard should be more emphasized as one of the key limitation of this study. Similarly, on page 6 line 36 it is wrong that serum creatinine can be considered a gold standard for assessing renal function as a long series of well-established factors (e.g. muscle mass, diet, age…) may influence the reliability of this biomarker.

Response: Thank you for these comments. We have emphasized this limitation and corrected the statement that suggests that creatinine is a gold standard method.
Reviewer 2:

8. The table with clinical characteristics of patients would be of interest (other comorbidities, age or BMI).

Response: Thank you, we have included this as Table 1.

9. There are no information how the blood samples were processed after collection. Regarding the saliva processing, centrifugation should be reported in g not RPM (or type of rotor and centrifuge should be stated). Were the samples centrifuged at room temperature or at 4°C?

Response: We have added more information around the handling of the saliva and blood samples to the Methods section.

10. It would be interesting to point out what was the add-on value of the present study to the former ones. Indeed, more markers as is urea, uric acid, or NGAL as new markers of kidney failure would be appropriate to analyze as a part of the results and would greatly increase the significance of the paper. Similarly, in the discussion part, more information about the other markers should be added, discussed with the rationale why the authors focused only on creatinine. Indeed, the sensitivity and specificity of a combined palette of salivary markers should be calculated and discussed.

Response: Thank you for this comment. While the analysis of other markers would be very interesting, it was beyond the scope of the present study. We have added a paragraph on salivary urea and a note that newer markers (and combinations of markers) should be examined in future studies.

Reviewer 3:

11. I would be very interested to see the distribution of the salivary creatinine measurements and a comparison to that of serum creatinine. Histograms with small ranged bins and a linear regression plot (and not just the function) would be a good addition (in essence Table 2 as a plot). Further I believe it would be good to comment in more detail in the implications of the findings.

Response: Thank you very much for these comments. A histogram and linear regression plot has been added to the paper, as suggested. The implications of our findings are that we have confirmed and contributed to the existing data supporting the diagnostic potential of salivary creatinine as a non-invasive tool to estimate GFR. Our study population (from a CKD clinic) was not representative of that which would be seen in a population screening programme and further studies are needed in such settings, where most participants would be expected to have normal or near-normal renal function.