Author's response to reviews

Title: High prevalence of undiagnosed chronic kidney disease in Kinshasa

Authors:

Ernest K. Sumaili (skiswaya@yahoo.fr)
Eric P. Cohen (ecohen@mcw.edu)
Chantal V. Zinga (zingavchanta@yahoo.fr)
Jean Marie Krzesinski (jm.krzesinski@chu.ulg.ac.be)
Nestor M. Pakasa (nmpakasa@free.fr)
Nzaire M. Nseka (mnsekan@yahoo.fr)

Version: 2 Date: 15 June 2009

Author's response to reviews: see over
To the Editor
BMC Nephrology

re: Re-Manuscript # BMC Nephrology-8022529082614136-2009

Dear Dr Andrea Bucceri,

Thank you very much for your letter of May 18 in which you requested major modifications of our manuscript entitled "High prevalence of undiagnosed chronic kidney disease in Kinshasa".

We thank you again and the reviewers for your constructive criticisms.

We have carefully reviewed your letter as well as the reviewer’s comments and criticisms. We are thus pleased to resubmit the new version now entitled: "High prevalence of undiagnosed chronic kidney disease among at-risk population in Kinshasa. The Democratic Republic of Congo".

We have also re-submitted both a corrected version with additions underlined in red and deletions crossed out in blue, and a clean version without the corrections still marked in the text.

We addressed:

Editor in chief requests information regarding ethical committee of the Provincial Medical Inspection of Kinshasa. We confirm that ethical committee exists for the Provincial Medical Inspection of Kinshasa. Further, all rules of confidentiality were fulfilled with, including collection of information and physical examination. We have added this information in the methods section.

Reviewer 1 (Roberto Perico) requests some comment about the apparent inconsistency between screenings of specific group for CKD versus general population performed recently in Kinshasa. We agree with this reviewer’s concern. This was done as seen at p4 § 9 or last paragraph. Moreover as mentioned earlier, according to the target people of the present screening, we have changed the title.

The same reviewer requests information on from the timing of the dipstick test, in relation to the quantitative measurement for proteinuria. Furthermore, he wonders about the accuracy of 24h urine collection in the environment of Kinshasa, that may jeopardize the data and ultimately the interpretation of the results. We agree that is an important matter. We have added this weakness in the methods section as well in discussion text (pg 15 & last paragraph). In our survey, as mentioned in methods (pg 7 § 2) : Because ratio of albumin to creatinine (ACR) is not available until now in this developing country and because urine dipstick provides only a semi-quantitative estimation of proteinuria, kidney damage in stage 1 and 2 CKD in our study was identified as 24-hour urinary protein ≥ 300 mg per day. However, to minimize the inaccuracy of 24 h urine collection, we educate our patients to collect carefully urine. We have also added this limit of the study in the discussion.

Finally, the same reviewer points out that the study population was older than 18 years of age. The analysis of odd ratio of risk factor associated with CKD (Table 5) is limited to age > 50 versus <50
years. It is suggested to perform additional analysis according to the different age periods reported in Table 1. So we have performed additional analysis with four categorical of age as the following: 18 to 43, 44 to 55, 55 to 67 and > 67 years.

<table>
<thead>
<tr>
<th>Determinants</th>
<th>OR (multivariate analysis)</th>
<th>IC 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD stage ≥ 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension versus no</td>
<td>2.6</td>
<td>1.5-4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulse pressure &gt; 60 versus &lt; 60 mmHg</td>
<td>1.1</td>
<td>0.7-2.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Age 44-55 versus 18-43 years</td>
<td>0.8</td>
<td>0.4-1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Age 56-67 versus 44-55 years</td>
<td>0.7</td>
<td>0.3-1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Age &gt; 67 versus 56-67 years</td>
<td>1.08</td>
<td>0.5-2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus versus no</td>
<td>1.1</td>
<td>0.7-1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Dipstick proteinuria ≥ 1+ versus 0</td>
<td>2.1</td>
<td>1.1-3.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Herbal remedy use versus no</td>
<td>1.5</td>
<td>0.8-2.6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

We find no age effect. As expected, there are some changes in the results in multivariate analysis. Diabetes, pulse pressure are no longer a significant predictor of CKD 3+. We believed that continuous variables such as age expressed in two categories as explicative variables in logistic regression but no in four categories is useful and informative. Therefore, we think that it is better to reduce number of categorical variables of age to two as dichotomous variable already mentioned in the first version of text (Table 5).

**Reviewer 2 (Ivor Katz)**

- **Objective of study**

(1) Requests explanation about the feasibility of detecting large numbers of previously unidentified persons with or at risk for CKD. We agree with the same reviewer. This objective was not really attained. So we have added some comments in discussion as well in conclusion sections.

- **Abstract (3) and (4)**

The same reviewer suggests that the abstract should include the limitations of this study as “outlined in strengths and limitations”. We agree. We have done this in abstract (pg 2 & 2), stating that “the creatinine levels based on one random measurement …” and in conclusion (pg 2 & 4) “it appears that one out of three people in this at-risk population…”.

- **Introduction (5)**

Reviewer 2 suggests that validity of eGFR and its uses, should briefly discussed in introduction. We agree. We have done this in the introduction (page 4 & last paragraph). In addition, we think that the question of the validity of eGFR in Black race is debatable. That is because the MDRD Study formula has been adequately validated in African Americans with kidney disease (J Am Soc Nephrol 1997; 8:279-287), extrapolation to Black Africans appears justified.

- **Methods (6), (7), (8), (9) and (10)**

Reviewer 2 points out that the numbers comprising each group in results i.e. X in primary care and Y in secondary care screened should be explained. We agree and we have done that in method text (page 6 & 1).
The same reviewer further requests more information of people in stage CKD 1 and 2 and why we only did a 24-hour urinary protein measurement in 3+ combur 7 positive patients? Why we not screen any patient with proteinuria?

* As mentioned in the first version of our manuscript (page 7 & 5), we had used K/DOQI guidelines (Am J Kidney Dis 2002; 39 (Suppl 1): S1-S266 stating as the following:

The K/DOQI guidelines [20] for definition and classification of CKD were used in the present study. In brief, the CKD stages are defined as follows: stage 1, proteinuria ≥ 300 mg per day with an eGFR higher than 90 ml/min/1.73 m²; stage 2, proteinuria ≥ 300 mg per day with an eGFR of 60 to 89 ml/min/1.73 m²; stage 3, an eGFR of 30 to 59 ml/min/1.73 m²; stage 4, an eGFR of 15 to 29 ml/min/1.73 m²; and stage 5, an eGFR <15 ml/min/1.73 m².

* Regarding dipstick positive proteinuria versus 24-hour urinary protein measurement in 3+ combur 7 positive patients. We agree with this reviewer's concern. We have done that according to recent report concerning diagnosis value of dipstick protein. Indeed, Sam R et al. (Am J Nephrol 2003; 23:438-441) indicated that sensitivity 86% and specificity 88% of trace dipstick as value diagnosis of trace proteinuria to detect microalbuminuria. Also, for Konta et al. dipstick positive proteinuria are more indicative of microalbuminuria than macroalbuminuria (Clin Exp Nephrol 2007; 11:51-55). This fact because of the subjects that were trace, 1+ or 2+ positive on a dipstick protein, 61, 71 and 41% had microalbuminuria, whereas only 1, 7 and 50% had macroalbuminuria. In addition, dipstick urine analysis has imperfect accuracy in the diagnosis of persistent proteinuria.

Furthermore, another question is whether the excretion of small amounts of protein such as microalbuminuria equivalent to dipstick protein i.e. trace, +, ++ in the urine should be used to defined CKD in the absence of other findings. Therefore, it could have serious consequences on prevalence data. However, we have done results of all dipsticks abnormally urinary (in Table 3) because microalbuminuria is associated with increased risk cardiovascular but possibly CKD. Some comments are now added in discussion text (pg 10 & last paragraph).

Finally, the reviewer requests information about using eGFR measurement without validation, especially in patients with HIV as well as at least some of the eGFR validated against a gold standard like the plasma clearance of 51 Cr-EDTA or 24-hours Cr clearance. We agree with reviewer’s concern. As already mentioned, this is the main weakness of our survey. That is because of the scarcity of material and financial resources in DR Congo where the health expenditure per capita does not exceed US 1$ per year.

- Results (11), (12), (13), (14), (15), (16), (17), (18)

The same reviewer suggests some modifications in Table 1, 2, 4, 5, and 6. We agree that this is indeed an important issue. All tables concerned have been now dropped as suggested by the reviewer. Concerning the differences in proteinuria indicated in the groups in Table 2, we have added percentages of proteinuria in these groups in Table 2. We have also indicated in results text (pg 8 & last paragraph) numbers of patients in primary care and secondary care who were firstly CKD stage 1 & 2. There are also additional ones mainly the importance of findings (displayed in Table 3) regarding risk for cardiovascular disease and CKD progression in those patients with CKD3+ without or with proteinuria in discussion text (pg 10 & last paragraph).

We have also explained the discrepancy between 24 hour proteinuria and dipsticks especially in CKD stage 3 in discussion text (pg 11 & 3).

- Discussion (19), (20), (21), (22), (23), (24), (25)

Reviewer further suggested major modifications in discussion as well in strength and weakness of study. We agree. We shortened the manuscript and carefully modified discussion text along with this reviewer’s comments.

We hope the modifications will be suitable and look forward to acceptance and publication of our paper in a coming issue of BMC Nephrology.
With best regards,

Ernest K. Sumaili, M.D.; Ph.D.
Renal Unit,
University of Kinshasa, D.R. Congo.
PO BOX 123 Kinshasa XI.