Author's response to reviews

Title: Large kidneys predict poor renal outcome in subjects with diabetes and chronic kidney disease

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Author's response to reviews: see over
Pessac, 21/12/2009,

Dear sir,

Please find enclosed the revised version of our paper entitled: "Large kidneys predict poor renal outcome in subjects with diabetes and chronic kidney disease".

We have performed important changes, according to the review, as underlined in the point by point answers below. Our main conclusion, as depicted by the title, still stands, and we feel that the revision improves the paper. We therefore trust that it is now suitable for publication in "BMC Nephrology".

Sincerely yours

Vincent Rigalleau
ANSWERS TO REVIEWER1 (Gianpaolo Zerbini)

Thank you for your useful comments, that allow us to provide further informations:

1-There is a correlation, this is now mentioned at the end of the discussion, with one reference:
"The kidney length is correlated to the renal volume: it is indeed included in the ellipsoid formula to calculate it (Bakker, Radiology 1999)."

2-A new table 2 now gives the outcomes of type 1 and type 2 patients separately, with a brief comment in the results section "There was no significant difference between the subjects with type 1 and type 2 diabetes (gender, GFR, Albumin Excretion Rate, kidney length, HbA1C, known duration of diabetes), except for the age and the BMI as expected. Although the different outcomes only reached significance for dialysis onset for type 2, according to the restricted number of patients, the results seemed homogenous in both types of diabetes, as shown in the table 2”.

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>age</td>
<td>54±17</td>
<td>65±10°°°</td>
</tr>
<tr>
<td>BMI</td>
<td>23.6±3.4</td>
<td>29.8±4.9°°°</td>
</tr>
<tr>
<td>Kidney length</td>
<td>Small–108mm-Large</td>
<td>Small-108mm-Large</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Isotopic GFR (mL/min/1.73m²)</td>
<td>59 (20-94)</td>
<td>73 (12-209)</td>
</tr>
<tr>
<td>Albumin Excretion Rate (mg/24H)</td>
<td>98 (20-1080)</td>
<td>196 (32-2312)</td>
</tr>
<tr>
<td>Decline of e-GFR (mL/min/1.73m²/yr)</td>
<td>-0.5 (-6+8)</td>
<td>-2.0 (-8+16)</td>
</tr>
<tr>
<td>Dialysis onset</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

3-We agree that the AER should be evaluated as the mean of three urinary collections. The AER was indeed determined on two 24H urine collections during a short hospitalization, as now mentioned.
ANSWERS TO REVIEWER 2 (Scott Thomson)

Thank you for the review, we feel that it led us to improve the paper.

1-We agree that it is a good idea to provide results as a scatter plot, as done in Ref 33, so we add a new figure 1, where the patients who required dialysis during the follow-up are discriminated, according to their initial isotopic GFR and kidney length:

![Scatter plot showing kidney length vs. Glomerular Filtration Rate](image)

2-Due to the limited effective, the AER and kidney size did not significantly correlate. We agree that this may seem puzzling at first sight. The few number of normoalbuminuric patients (n=6, as now mentioned in the results section) is a plausible explanation for this. There were 15 normoalbuminuric patients in our previous study (ref35), but most of them did not have an US evaluation.

The inclusion criterion of our previous work (ref35) was a MDRD-estimated GFR below 60 (mean isotopic GFR 45), as shown on the new figure 1, this is not the same population as here (mean isotopic GFR 60).

3-Distinction micro/macroalbuminuria. As now mentioned in the results section: "The kidney length were 100±9mm in normoalbuminuric (n=6), 106±13mm in microalbuminuric (n=39), and 113±11mm in macroalbuminuric (n=30) patients (p=0.056)."

4-Role of proteinuria on progression. We agree that our previous version may have led the reader to underestimate this role. As proposed by the 4th reviewer, we improved our statistical analysis, and as now mentioned in the results section:

a) By the use of non-parametric comparison, significance is almost reached for the AER between the small and large kidney groups (p=0.052),

b) The kidney length does not remain a significant predictor after inclusion of the AER in the cox analysis.
These results are now mentioned in the results section. We add a short comment in our conclusion to avoid any mis-interpretation: "…although it does not replace the determination of the Albumin Excretion Rate."

Minor revisions
P6 "of kidney size" is now written
P9 prognostic
P9 are likely to undergo
P9 its outcome replace "it"
This is not the same population as ref 35, as previously shown.

Discretionary
Our conclusion now mentions that kidney size does not replace the AER.
ANSWERS TO REVIEWER 3 (Daniel Teta)

Thank you for the revision, your questions allow us to provide interesting informations.

1-Although this was not the main topic of the present study, we agree that indications about predictors of renal outcome are of interest. We now provide further informations in the methods section, with a new reference 15:
"The care program objectives included glycemic control according to the French 1999 recommendations (HbA1c < 8.0%, if possible 6.5% without severe hypoglycemia in type 2, and < 7.0% in type 1), but also control of associated factors such as hypertension (objective: < 130/80 mmHg) and dyslipidemia (objective: LDL-cholesterol < 1.3 g/L). We have previously reported (15) that we could obtain significant reductions of HbA1C (-0.7%, 40% of the patients reached the objective), LDL-Cholesterol (-0.4 g/L, 70% of the patients reached the objective), and blood pressure (-10mmHg systolic, 54% of the patients reached the objective, -5mmHg diastolic, 95% of the patients reached the objective - 75% were on ACE inhibitors, Ang2 receptor inhibitors, or both), and the Albumin Excretion Rate decreased by -40%.

2-The % reaching the objective are now mentionned, we also provide the reduction of the AER, as mentionned in the previous §.

3-As now mentionned in the results section: "The decline of e-GFR did not significantly correlate to the kidney size (r=0.15, p=0.20)."

4-The min:1 (unfortunately one of our patients died 1 month after inclusion…), max:84 and the end of the follow-up (Dec 2008) are now mentionned in the method section.

5-Our message is that the kidney size is still an interesting information in advanced CKD, we keep cautious and do not go further, as reflected by our last phrase: "…although it does not replace the determination of the Albumin Excretion Rate."

Minor revisions

1-Followed, born are corrected
2-CKD stages are now stated in the new table 3.
3-The number of patients at each follow-up endpoints are now reported on the new figure 2.
Thank you for the statistical advise, we have performed these changes and we agree that it improves our analysis.

1-We agree that microalbuminuric patients with GFR>60 are not usually evaluated by US: their number is therefore limited in our study, and we now give indications about the outcome of this group of especial interest, at the end of the results section: "Twenty-one subjects had microalbuminuria (30-300mg/24H) and an isotopic GFR > 60 mL/min/1.73m²; none of them required dialysis during the follow-up. Although the difference was not significant, the MCQ-eGFR declined faster for the eleven subjects with the largest (>109mm) kidneys: -4.2 mL/min/1.73m² (-14+-16), vs -2.3 (-6+-5) for the 10 subjects with the smaller kidneys."

2 and 3-The data (GFR, creatinine and AER are now presented as median (range) and compared by non-parametric tests. We agree that this was justified, it leads to noticeable changes as reflected in the abstract: " Serum creatinine were initially smaller (Small kidneys: 125 (79-320) µmol/L, Large: 103 (50-371), p<0.05), but significantly increased in the "large kidneys" group at the end of the follow-up (Small kidneys: 129 (69-283) µmol/L, Large: 140 (50-952), p<0.005 vs initial)." But our main conclusion that the outcome is worst in the patients with large kidneys, still stands.

4-The difference in kidney length between the 3 strates was not far from significance (p=0.08, as now mentionned in the results section), so this does not puzzle.

5-The numbers of remaining subjects are now mentionned on the figure 2.

6-As now mentionned in the results section : "The influence of the kidney length did not remain significant after adjustment for the AER." We agree that this must not be neglected, and we add in our conclusion: "although it does not replace the determination of the Albumin Excretion Rate."

7- We now provide further informations about the treatment of hypertension in our patients, in the methods section: "We have previously reported (15) that we could obtain significant reductions of HbA1C (-0.7%, 40% of the patients reached the objective), LDL-Cholesterol (-0.4 g/L, 70% of the patients reached the objective), and blood pressure (-10mmHg systolic, 54% of the patients reached the objective, -5mmHg diastolic, 95% of the patients reached the objective - 75% were on ACE inhibitors, Ang2 receptor inhibitors, or both), and the Albumin Excretion Rate decreased by -40%. "

ANSWERS TO REVIEWER 4 (Peter Rossing)