Author's response to reviews

Title: Kidney disease in patients with type 2 diabetes: prevalence and associated variables in a random sample of 2,642 patients from a Mediterranean region (Catalonia, Spain).

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

on my own behalf and on behalf of the authors of the manuscript 8110743747027738, we appreciate that you considered it. We also appreciate the excellent comments, questions and suggestions by Drs. MacIsaac, Pugliese and Lezaic that have been of great help in improving the manuscript. Please find below the answers to the editor and the reviewers, as well as the changes made in the text.

Editor

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<th>Competing interest…</th>
<th>We have changed ‘Duality of interest’ by ‘Competing interest’</th>
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<tr>
<td>Refer to the Appendix</td>
<td>We changed the text ‘Appendix’ by ‘Additional File 1’</td>
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<td>General Formatting</td>
<td>We found that the manuscript conforms to journal style</td>
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Reviewer 1. Prof Visnja Lezaic

| Methods: 1 Clearly define renal impairment. | Thank you for your suggestion. We have introduced the definitions in the abstract to enhance the reader’s understanding. It differs from the concept of Renal Impairment (GFR < 60 ml/min/1.73 m2) of Kidney disease (renal impairment and / or albuminuria). |
| Methods: 2 “…to redefine all studied patients as a groups with various combinations of eGFR and proteinuria and/or microalbuminuria” | As Dr. Lezaic proposed, we classified the patients according to the value of GFR and albuminuria (KDIGO-2011). Table 2. Page 8: ‘Patients with available creatinine and UAER were also classified according to the recent proposal of KDIGO workgroup[19].’ |
| Methods: 3 ‘It is necessary to specify how albuminuria, proteinuria and serum creatinine are measured’ | As requested by the reviewer, we added in the text the sentence that follows: (Page 7) ‘Serum creatinine was measured on a multiparameter analyzer (Cobas 711, Roche Modular System, Indianapolis, IN, USA) by the Jaffé Method with bichromatic measurements according to the manufacturer’s specifications. Albuminuria was measured by immunoturbidimetry on a Cobas 400 analyzer (Roche, Indianapolis, IN, USA).’ |
| Methods: 4 “…refer to the flow-chart scheme in the Methods” | Thank you. We added in the text: (Page 7) ‘Figure 1 shows the samples used to calculate the prevalence of the different forms of kidney disease.’ |
| Results: Table 2 is not necessary. Information about the stages of CKD patients categorization depending of GFR and albuminuria (KDIGO 2011) | We changed Table 2 and have replaced the old table 2 by the sentence (Page 9): ‘To rule out a bias attributable to patients without albuminuria data, we compared a subgroups with available albuminuria data (1,478 patients), and to the 1,164 patients not having albuminuria data. Of all variables compared (age, gender, years of evolution, HbA1c, systolic blood pressure, diastolic blood pressure and creatinine), only age showed differences (67.59 vs 68.58; p=0.03). Now, the new Table 2 shows the categorization of the patients according to KDIGO 2011.’ |
| Table 5. ‘… years of duration > 10 years and ACEI/ARB treatment…’ | Thank you. We added to the Table the number of patients (%) with type 2 DM duration 5-10 years, > 10 years, and treatment with ACEI / ARB |
Figure 1. Should be described with more detail:...statistically significant... and how many patients in each age...

According to the reviewer’s request, we added the statistical significance and the number of patients (%) of each group.

Discussion: ‘should be focused on obtained results and already published data

We included an extended review of the major epidemiological studies, with particular emphasis on the differences noted between patients with albuminuria alone versus nonalbuminuric RI. (Page 12-13)

‘The relationship between the mechanisms responsible for the development of albuminuria and renal impairment are not clear. In keeping with the most relevant studies published to date, our results show that nonalbuminuric RI is associated with female gender [9,21,25,28,29]. Nonalbuminuric RI was associated with the time elapsed from the diagnosis of diabetes, which was previously reported by Retnakavaran et al. [9]. However, Penno et al. [30] relate the duration of diabetes to both nonalbuminuric RI and albuminuria alone. Several authors showed that patients with nonalbuminuric RI have lower levels of HbA1c [9,24] and lower prevalence of obesity [28] than those with albuminuria alone, as seen in our study. According to our results, the profile of T2DM patient with nonalbuminuric RI is a woman with a diagnosis of diabetes made more than 10 years ago, low percentage of obesity, and good metabolic control measured by HbA1c. On the other hand, the patient with albuminuria alone is preferably male, with high percentage of obesity, and poor metabolic control. Diabetes duration was not significant in the latter case. There is no obvious explanation for this phenomenon other than that these diseases cause gender-specific vascular damage. We found only one study [30] comparing nonalbuminuric RI with albuminuria alone in T2DM patients. Their results are in agreement with ours in that male gender and HbA1c are associated with the presence of albuminuria alone. However, our study showed that the duration of diabetes and age are variables that differ in the two diseases whereas in the study of Penno et al. [30], age and duration of diabetes, were associated with the two forms of kidney disease. Our results may be helpful to discriminate between these two kidney diseases by taking into account the variables associated with each one of them. Several studies have reported a higher prevalence of microvascular damage (retinopathy and kidney disease) in hypertensive women [31,32], but no data have been published showing a higher prevalence of microvascular damage in women with type 2 diabetes. A recent retrospective study showed that DN appeared significantly earlier among males than females [33]. This finding may explain the gender difference we found in our cross-sectional study based on a single observation. However, different phenotypic expressions depending on gender cannot be excluded.’

Minor revision
- Second paragraph
- Section ‘Types of kidney disease’
- Table 4, Full explanation for abbreviations...

…’lot spelling errors’

We reviewed the Tables and found that all the abbreviations were listed at their bottoms.

The manuscript has been evaluated by American Journal Experts. However, we went through the manuscript and tried to improve some spelling errors.
Several studies on much larger cohorts have been recently published…
Cite these papers to discuss and possibly explain similarities and differences

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Also, we added the following paragraph to the text, which extends the previous discussion (pp. 12-13):

“The relationship between the mechanisms responsible for the development of albuminuria and renal impairment are not clear. In keeping with the most relevant studies published to date, our results show that nonalbuminuric RI is associated with female gender [9,21,25,28,29]. Nonalbuminuric RI was associated with the time elapsed from the diagnosis of diabetes, which was previously reported by Retnakavaran et al. [9]. However, Penno et al. [30] relate the duration of diabetes to both nonalbuminuric RI and albuminuria alone. Several authors showed that patients with nonalbuminuric RI have lower levels of HbA1c [9,24] and lower prevalence of obesity [28] than those with albuminuria alone, as seen in our study. According to our results, the profile of T2DM patient with nonalbuminuric RI is a woman with a diagnose of diabetes made more than 10 years ago, low percentage of obesity, and good metabolic control measured by HbA1c. On the other hand, the patient with albuminuria alone is preferably male, with high percentage of obesity, and poor metabolic control. Diabetes duration was not significant in the latter case. There is no obvious explanation for this phenomenon other than that these diseases cause gender-specific vascular damage. We found only one study [30]
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Minor
Prevalence of RI without albuminuria

We have calculated the prevalence of nonalbuminuric RI to total renal impairment patients.

The correlation of one condition which may present with or without albuminuria…

Thank you. We modified the comment from the multivariate analysis (p 10) as follows:

'Diabetic nephropathy patients only show gender differences and increased use of insulin.'

Reviewer 3. Prof MacIsaac.

‘…need to more clearly show what new information they have provided over and above that which was documented in the renal dysfunction in type 2 diabetes, UKPDS 74’

Thanks for your comment. We have extended the discussion to highlight the similarities and differences with the major published studies on this topic. (Page 12-13):

The relationship between the mechanisms responsible for the development of albuminuria and renal impairment are not clear. In keeping with the most relevant studies published to date, our results show that nonalbuminuric RI is associated with female gender [9,21,25,28,29]. Nonalbuminuric RI was associated with the time elapsed from the diagnosis of diabetes, which was previously reported by Retnakavaran et al. [9]. However, Penno et al. [30] relate the duration of diabetes to both nonalbuminuric RI and albuminuria alone. Several authors showed that patients with nonalbuminuric RI have lower levels of HbA1c [9,24] and lower prevalence of obesity [28] than those with albuminuria alone, as seen in our study. According to our results, the profile of T2DM patient with nonalbuminuric RI is a woman with a diagnose of diabetes made more than 10 years ago, low percentage of obesity, and good metabolic control measured by HbA1c. On the other hand, the patient with albuminuria alone is preferably male, with high percentage of obesity, and poor metabolic control. Diabetes duration was not significant in the latter case. There is no obvious explanation for this phenomenon other than that these diseases cause gender-specific vascular damage. We found only one study [30] comparing nonalbuminuric RI with albuminuria alone in T2DM.
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"… find useful if the definition for the different types of renal disease were stated in the abstract" According to Prof MacIsaac's suggestion, we added to the abstract the following text:

'Variables of renal function were defined as follows: 1) microalbuminuria: albumin excretion rate > 30 mg/g or ng/mmol, 2) Macroalbuminuria: albumin excretion rate > 300 mg/g or 35 mg/mmol, 3) Kidney disease (KD): glomerular filtration rate according to Modification of Diet in Renal Disease < 60 ml/min/1.73 m² and/or the presence of albuminuria, 4) Renal impairment (RI): glomerular filtration rate < 60 ml/min/1.73 m², 5) Nonalbuminuric RI: glomerular filtration rate < 60 ml/min/1.73 m² without albuminuria and, 5) Diabetic nephropathy (DN): microproteinuria or microalbuminuria plus diabetic retinopathy."

Definition of diabetic nephropathy


'… specific cut off for ACR are used, ie, 3.5 mg/mmol for females and 2.5 mg/mmol for males…'

Prof. MacIsaac, thanks for your comment. The authors had doubts regarding which operational definition we should use to define microalbuminuria, and we finally opted for the definition of KDIGO 2011. However, this is an important subject for future studies. Regarding this issue we added the following comment in the manuscript: (Page 11)

'In our study, as recommended by the NKF-K/DOQI the same cutoff for normal AER has been used for both sexes. In contrast, the European Societies of Cardiology and Hypertension [20] recommend adopting different normal values according to gender (<31 mg/g or 3.5 mg/mmol for men and <22 mg/g or 2.5 mg/mmol for women). So, it is possible that if we had used the European criteria, the prevalence of albuminuria would have been similar to the prevalence obtained by [12] in a similar cohort: 20.6%.'

'…new proposed classification system for chronic kidney disease…KDIGO 2011…’

According to the reviewer suggestion, we included the reference and we have prepared Table 2 according to this
classification.