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Response letter

The review article written by Farooqi and Dickhout is a thorough revision of co-morbid diseases associated with AKI. Suggestions: Page 5 first paragraph: According to AKIN, AKI is defined the way the authors transcribe, but the time frame of creatinine rise is missing.

We thank the reviewer for their comment, the manuscript has been revised to incorporate the time frame of creatinine rise to "According to the Acute Kidney Injury Network (AKIN), Acute Kidney Injury (AKI) is an abrupt loss in kidney function within 48 hours, as defined by an increase in serum creatinine of 26.4 μmol/L (0.3 mg/dL) or more; a percentage increase in serum creatinine of more than 50% from baseline; or a reduction in urine output, oliguria (< 0.5 mL/kg hourly for > 6 h)."

At the end of the first paragraph, it would be illustrative to complete the concept by adding the average percentage of subjects who require renal replacement in ICUs Page 6.

We thank the reviewer for their suggestion. This comment has been addressed by incorporating information regarding the average percentage of subjects requiring renal replacements in the ICU to "On average 5% of patients in the ICU with severe AKI require Renal Replacement Therapy (RRT)".

In the second paragraph please add the limitations and pitfalls of using creatinine as the molecule to assess kidney function. In this regard, please write a short comment on TIMP-2 and IGFBP-7 (Ronco C. Blood Purif 2014;38:I–II DOI: 10.1159/000368919). It will be illustrative.

We thank the reviewer for their suggestion and have addressed this by incorporating detailed information about the pitfalls of using creatinine as a molecule to assess renal function. The following information has been added, "Creatinine is not ideal in the early detection of AKI, as damage to the renal tubules can be insufficient to cause

a change in creatinine. Additionally, in more extensive cases of tubular injury, there exists a lag time between the injury and subsequent increase in serum creatinine".

Furthermore a new paragraph has been added to the body of the research paper on the biomarkers TIMP-2 and IGFBP-7 as novel concepts in the early diagnosis of AKI with an added emphasis on NEPHROCHECK, "In addition to the KDIGO criteria, biomarkers have become a novel concept for the early diagnosis of AKI. A combination of two urinary cell-cycle arrest biomarkers, insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) have been used to predict the risk of moderate and severe AKI (defined by stages 2 and 3 respectively according to the KDIGO classification of AKI). These biomarkers have been said to perform better than existing markers such as NGAL, KIM-1, IL-18, L-FABP and Cystatin C. In AKI, these biomarkers localize in the site of injury where they are involved in the process of the G1 cell-cycle arrest, which acts to prevent cells from continuous division when DNA is damaged. Two independent multicenter cohort studies conducted by Bihorac et al. and Kashani et al. allowed for the development of the FDA approved NEPHROCHECK® Test system. The test system is comprised of assays for TIMP-2 and IGFBP-7, which is to be used in conjunction with clinical evaluations. This system is used as a clinical aid in the risk assessment for moderate to severe AKI within 12 hours of patient assessment. As such, these new advancements allow for the early detection of AKI."

Reviewer's code: 00503196
Reviewer's country: Greece
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The review paper with the title <<Comorbid disease processes associated with increased incidence of acute kidney Injury>> based on literature claims to clarify different obscure points on renal injury in patients with comorbid diseases such as diabetes, cancer, cardiac surgery and HIV infection. The authors describe the pathogenesis of AKI very well and the relation to the above described diseases. However the diseases described as causes of AKI are a few of all the causes so the title has to be adapted according to the text.

We thank the reviewer for raising this point. The following comment has been taken into consideration and addressed by altering the title from "Comorbid disease processes associated with increased incidence of acute kidney injury" to "Major comorbid disease processes associated with increased incidence of acute kidney injury".

Also there are a number of publications in 2015 concerning the subject and it would be better if they were added to the text. Please see the new references to address this comment.

We thank you for your suggestion; we added new references such as information on novel biomarkers TIMP-2 and IGFBP-7 and the development of the NEPHROCHECK test system.

As well in a number of references the year of publication is missing. (references 2,4,8,14,15,16,17,19,20,24,27,29,30,32,33,35,42,43,44,45,46,47,53,54,56,57,69,70,76) reference 78 pages are missing.

Thank you for bringing this to light, we have adjusted the references accordingly.

Response to editor in chief

1. *Revision with data:*
   With thanks to the reviewer, as this is a review article, no original research data has been included.

2. *Shorten the article:*
   We thank the reviewer for this suggestion and have shortened the article, in the following ways: we shortened the introduction, the section on ***Pathogenesis and co-morbid disease processes in AKI***. Further, we have shortened and revised the following sections: introduction to ***Co-morbidities and AKI***, ***Diabetes-associated AKI***, ***Cancer-associated AKI***, ***Cardiac surgery-associated AKI*** and ***Human immunodeficiency virus-associated AKI.***