To:

Editorial Office

World Journal of Nephrology

Invited Review 12278

Why do young people with chronic kidney disease die early?

Dear Editor,

Thank you very much for considering our article and giving us the opportunity to submit a revised manuscript. We would also like to thank the reviewers for their constructive and insightful feedback. All points raised by the reviewers have been addressed.

For your convenience, we have provided an annotated version highlighting changes requested in red as well. We have also provided this appendix, which incorporates a copy of your reviewers' comments with our specific responses on a point-by-point basis.

Reviewer 1:
References are not in conformity with the journal's style.

The reference style has been adjusted to conform to the style of the journal.

It will be nice if the authors can define the abbreviations in Figure 5. These definitions should be part of legend to the Figure.

We agree with the reviewer that this will make the figure easier to follow for the reader and have supplied the abbreviations in the figure legend as follows:

(Apo)A-I	Apolipoprotein A-I
ABCG1	adenosine triphosphate–binding cassette transporter G-1 protein
LCAT	lecithin–cholesterol acyltransferase
SR-B1	scavenger receptor B1
PON1	paraoxonase-1
LRP	lipoprotein-like receptor
VEC	vascular endothelial cells
MCP-1	monocyte chemoattractant protein-1

Reviewer 2:

The review article by Kumar et al., titled "Why do young people with CKD die early?" focuses on the causes to which CKD patients die. The topic itself is interesting, although it has been extensively addressed in the literature. A mere compilation of possible causes of death with no critical analysis and no effort to connect them and extract a valuable underlying meaning (such as in this article) is of not much interest. In addition, authors seem to try and find a specific niche, in an otherwise threadbare topic, among young CKD patients. However, this is only a superficial aim, as no specific information is offered on your patients, and even less in comparison to adult or aged patients. Most strikingly, the conclusions do not even mention young patients at all. So, what is the point of addressing death causes among young CKD patients? The authors should reconsider their article in order to profit from the review work done, in order to make it show and offer some relevant analysis.

The aim on this article is to provide a concise summary of the traditional and non-traditional risk factors that contribute to the early death of young patients with CKD. The precise interplay between the factors remains to be elucidated. We have included some more detail in our conclusion to highlight the patient cohort that we are considering:

“Cardiovascular disease is the most important cause for the high morbidity and mortality seen in patients with chronic kidney disease, especially younger people. . . . . This will, hopefully, curb the excessive morbidity and mortality which seems to be particularly pronounced in young dialysis patients. Data from implantable loop recorders may give further insights to the precise events which result in sudden cardiac death and allow development of strategies to predict risk and reduce events.”

Reviewer 3:

In collecting the evidence that microalbuminuria predicts greater mortality in CKD, it might have been noted that the American Diabetes Association advises that the term no longer be used because of the reality that at least one-half of diabetic patients with microalbuminuria either revert to normoalbuminuria or do not progress.

This point, raised by reviewer 3, has been alluded to in the text as follows:

These drug classes have reduced progression of diabetic renal disease by reversing microalbuminuria to normoalbuminuria. Further long-term epidemiological studies are necessary to define its extent and enduring impact.

Good that the factors that may be influencing survival in CKD are collected and discussed. But, how vague the data are and the need for long term objective studies might have been emphasized.

We have added a sentence in the conclusion to highlight this point:

"A better appreciation of the interplay and relative contribution of the various mechanisms discussed, along with new pathogenetic mechanisms yet to be discovered over the next few years, will enable new therapies to be developed."

Reviewer 4:
It is an interesting review. Just a couple of suggestions: 1- Under the subheading of cardiorenal syndrome, different aspects of cardiovascular disease in patients with kidney failure has been discussed. This includes increased risk of mortality, coronary events, arrhythmias and sudden cardiac death with worsening kidney function. Even though the bidirectional effect of heart failure and kidney failure is a major concept in cardiorenal syndrome, the text under this subheading does not truly explain cardiorenal syndrome. The text under this subheading would benefit from a modification in a way that describes cardiorenal syndrome more accurately. Increased sudden cardiac death in patients with kidney failure has been addressed later (Pages 12 and 13) and does not need to be mentioned here.

As recommended by reviewer 4, we have added a more detailed explanation of the cardiorenal syndrome, highlighting the bidirectional effect of heart failure and kidney failure. We have removed the text pertaining to sudden cardiac death so as to avoid repetition.

"The bidirectional effect of heart failure and kidney failure is a key concept in the cardiorenal syndrome [26]. In the context of a failing heart due to pump failure, pressor systems (the sympathetic nervous system and renin-angiotensin-aldosterone axis) are activated to maintain the haemodynamic status quo[26, 27]. Increased glomerular filtration pressure, achieved by efferent vasoconstriction helps to maintain glomerular filtration rate in low-output states, but the increased vascular resistance decreases kidney perfusion. Over time, this causes tubular hypoxic damage, renal cell apoptosis and replacement fibrosis, which leads to loss of nephron mass and to progressive renal dysfunction. Conversely, as chronic kidney disease progresses, the sympathetic nervous system is overactivated as a result of renal

ischaemia, raised angtiotensin II levels and suppression of nitric oxide, causing hypertension, left ventricular hypertrophy and progressive left ventricular dilatation. Cardiac myocyte dysfunction and fibrosis, so-called 'CKD cardiomyopathy', is believed to be the predominant pathophysiological mechanism. This may be compounded by salt and water overload caused by raised angiotensin II levels leading to elevated central venous pressure and organ congestion"

2- The adverse effects of hemodialysis on cardiovascular system has been mentioned. It would be helpful to compare it with those of peritoneal dialysis, which has different hemodynamic and possibly different inflammatory effects.

We agree with the reviewer that some discussion relating to peritoneal dialysis would be of interest to the reader, and have added this to the text:

"Treatment by peritoneal dialysis confers survival advantage over haemodialysis, at least in the first few years, before risk equalises[19, 20]. Nevertheless, cardiovascular disease still poses the greatest risk in peritoneal dialysis (PD) patients[21, 22] . This patient group shares similar cardiovascular risk factors to haemodialysis patients but they typically gain more weight (due to the high glucose load and insulin resistance) and demonstrate higher levels of chronic inflammation in response to exposure to non-physiological peritoneal dialysis fluid and episodes of peritonitis[21]. However, relatively little randomised trial data is available pertaining to cardiovascular risk factors/outcome in peritoneal dialysis patients and so much of the discussion below relates to haemodialysis patients."

Thank you for considering our re-submitted manuscript for publication.

Yours sincerely

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