The editor-in-chief Aging Pathobiology and Therapeutics

RE: reviewers' comments.

We thank the reviewer for their work in reviewing our manuscript. We tried to address their comments and add the required information to the manuscript.

Reviewer #1:  
Weizhan Wang (Department of Emergency, Harrison International Peace  
Hospital)  
  
This review clearly summarized the pathogenesis, risk factors, and possible  
management strategies of cardiovascular disease in CKD. Since the CKD and  
CVD can pose a huge threat to human health, such review can provide an  
important reference for the prevention and treatment of CKD and CVD. I  
suggest the acceptance of this article. The minor revision is that please  
replace some of the older literature with more recent literature. Thank you.

Thank you for your valuable feedback. We are happy that the review can provide essential information about this significant topic.

We added more recent literature and replaced the old ones. We changed the color of the numbers of new references to Red.

Reviewer #2:  
Hongzhi Liu (Department of Vascular and Endovascular Surgery, Henan  
Provincial People's Hospital)  
  
This review entitled "Cardiovascular Aging in Patients with Chronic Kidney  
Disease: Pathogenesis and Potential Therapeutics" submitted by Alkhayyat et  
al. summarizied the pathogenesis, risk factors, and possible management  
strategies of cardiovascular disease in CKD. The content is interesting.  
However, some revisions are required.

Thank you for your valuable comments. We tried to address all of them  
  
Introduction  
--The full name of CKD should be mentioned on its first appearance.

Thank you for your observation. We mentioned it.

--Paragraph 3, from line 41, more referenced should be cited in this paragraph.

Thank you for your comment. More recent references have been added to the paragraph.

TRADITIONAL RISK FACTOR  
--Page 7, line 175, Abbreviations of Diabetes mellitus should be added here.

Thank you for your observation. We added them.

--Line 196, The reason why obesity is related to CKD and CVD should be  
briefly specified.

Thanks for your comment. We added a new paragraph to illustrate this relationship in depth. We changed the color of the new edits to red.

“ Obesity is a major precursor to diabetes and HTN. Moreover, it raises the risk of CKD and CVD [74, 75]. Obesity can have a direct impact on the heart, both pathologically and hemodynamically via increase myocardial fibrosis and volume excess [76]. In addition, obesity raises the risk of CVD through augmenting renal hyperfiltration and low-grade systemic inflammation [77]. Adipokines are a type of cytokine produced by cells such as adipocytes, macrophages, and lymphocytes, primarily in white adipose tissue. Depending on their relationship with the body’s inflammatory response, adipokines can have either anti-inflammatory or pro-inflammatory effects. Most adipokines are pro-inflammatory, including IL-6, TNF-α, A-FABP, PAI-1, resistin, leptin, and MCP-1. These pro-inflammatory adipokines are associated with metabolic and vascular complications related to obesity. In cases of obesity, an increase in white adipose tissue from visceral deposits causes a shift towards pro-inflammatory molecules, which can activate mechanisms that lead to vascular calcification and arterial stiffness[78].

Dyslipidemia promotes the development and progression of VC by several pathways, one of which may be linked to cellular senescence. Modified low-density lipoprotein (LDL), triglyceride-rich lipoproteins (TRLs), and dysfunctional high-density lipoprotein (HDL) are the three primary types of pro-atherogenic lipids and lipoproteins. They can cause the senescence of several types of VC cells, such as endothelial cells (ECs), VSMCs, and adipose-derived mesenchymal stem cells (AMSCs). These senescent cells have a slower replication rate, more inflammation, and reactive oxygen species (ROS), all of which contribute to the development and progression of VC. Senescent ECs reduce endothelial integrity and permeability, allowing oxidized LDL to be retained and finally leading to VC[79].”