Author’s response to reviews

Title: The Role of Asprosin in Patients with Dilated Cardiomyopathy

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Version: 1 Date: 15 Aug 2020

Author’s response to reviews:

August 13, 2020
Eisuke Amiya, M.D., Ph.D.
BMC Cardiovascular Disorders
Dear Dr. Amiya,

Thank you for inviting us to submit our revised manuscript entitled “The Role of Asprosin in Patients with Dilated Cardiomyopathy” (BCAR-D-20-01031). We appreciate the thoughtful comments of the reviewers and editor and have addressed their concerns as detailed below. We hope you will now find our work suitable for publication in BMC Cardiovascular Disorders.

Reviewer #1:
I read this paper and I think that:

1. The lack of a control healthy group is a limitation of the study design. This should be discussed in a dedicated limitation section. Please provide.

   Ans:
   We have addressed this comment by revising our limitation paragraph with this sentence “In this DCM cohort study, we did not include a control healthy group.” in page 14, paragraph 4.

2. The small sample size is a further limitation of the study design. Please discuss such a point in a dedicated limitation section.
Ans:
We have addressed this comment by revising our limitation paragraph with this sentence “The small cohort might limit the statistic power and the interpretation of study results.” in page 14, paragraph 4.

3. A post-hoc sample size calculation should be calculated.
Ans:
Thanks for the comment for the post-hoc sample size calculation. Well-designed studies with prior sample size and power calculations sometimes result in statistically non-significant results. Therefore, post-experiment power and size calculations were used to explain the observed data and possibility of type II errors. However, these calculations can lead to contradictory evidence for and against the null hypothesis. Therefore, the guideline suggests to determine the values by the calculation of confidence intervals. We have calculated the confidence intervals with “ Patients with lower asprosin levels (< 210 ng/mL) were associated with increased risks of adverse clinical outcomes with a hazard ratio of 7.94 (95% CI 1.88–33.50; P = 0.005) when compared patients with higher asprosin levels (≥ 210 ng/mL)”. Our confidence interval did not contain the value of zero, then it is of little possibility that the difference between the patients with high and low asprosin levels may equal zero.

J. Neyman and E. S. Pearson (1933) On the Problem of the Most Efficient Tests of Statistical Hypotheses. Philosophical Transactions of the Royal Society of London. Series A, Containing Papers of a Mathematical or Physical Character Vol. 231: 289-337

Reviewer #2:
Wen and coworkers explored the role of asprosin in DCM. Asprosin is a novel fasting glucogenic adipokine which induces rapid glucose releases from the liver. Asprosin is also a novel therapeutic target in heart failure treatment.
The investigators hypothesized that asprosin is able to modulate cardiac mitochondrial functions and has important prognostic implications in dilated cardiomyopathy (DCM) patients. Wen and coworkers enrolled 50 patients (86% male, mean age 55 ± 13 years) with DCM and followed their 5-year major adverse cardiovascular events from 2012 to 2017. Comparing with healthy individuals, DCM patients had higher asprosin levels (191.2 versus 79.7 ng/mL, P < 0.01). During the 5-year follow-up in the study cohort, 16 (32.0%) patients experienced adverse cardiovascular events. Patients with lower asprosin levels (< 210 ng/mL) were associated with increased risks of adverse clinical outcomes with a hazard ratio of 7.94 (95% CI 1.88-33.50; P = 0.005) when compared patients with higher asprosin levels (≥ 210 ng/mL). Using cardiomyoblasts as a cellular model, the investigators showed that asprosin prevented hypoxia-induced cell death and enhanced mitochondrial respiration and proton leak under hypoxia.
The topic and hypothesis are interesting and concern a large patient population.

Questions and comments:

1. Dilatation of all four chambers of the heart was one inclusion criterion. Why was this chosen and how was the right side of the heart evaluated?
Ans:
We revised the sentence to “(2) transthoracic echocardiography evaluation showed left ventricular or biventricular systolic dysfunction and dilatation by the European Society of Cardiology guideline”, which accurately represents our exact criteria for DCM inclusion at page 5, paragraph 1. All of our DCM patients received diagnostic catheterization with coronary angiography and complete left and right side hemodynamic evaluation for the left and right side heart function.

2. I would propose language check. For example in Results, the title "Asprosin Impairs Mitochondrial Function and Accelerated Cell Death in Animal Models" should be corrected to correspond to the reported results” Treatment of asprosin significantly increased cell viability under hypoxic conditions”.
Ans:
We revised the result title to “Treatment of asprosin significantly increased cell viability under hypoxic conditions”. We also did language check to avoid any grammar error.

3. There was no significant difference in BNP concentrations between high and low asprosin concentration groups, this could be discussed.
Ans:
We agreed with reviewer and added a paragraph to discuss this point in page 13, paragraph 2: “Patients with lower or higher asprosin levels exhibited similar serum BNP concentrations. Serum BNP levels are predictors of outcomes in chronic heart failure patients[24]. However, BNP has several limitations for follow-up and diagnosis of heart failure patients[27]. BNP may be affected by renal function, body weight, and lung diseases[28]. BNP measurements alone are not sufficient to guide therapeutic decision-making in patients with heart failure[29]. The fact that patients with different asprosin levels had similar BNP concentrations in our cohort could indicate that the mechanisms linking cardiovascular outcomes in heart failure patients are different from BNP or asprosin.”

Sincerely yours,
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