Author’s response to reviews

Title: The Association between Oxidative Stress and Endothelial Dysfunction in Early Childhood Patients with Kawasaki Disease

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Francesca Dickens

Editor, BMC Cardiovascular Disorders

RE: Manuscript for BMC Cardiovascular Disorders #BCAR-D-17-00368R4 by T. Ishikawa et al.

Dear Dr. Dickens,

Thank you very much for your email. We have completely revised our manuscript according to the suggestions made by the Reviewers. Based on the suggestion from the Reviewers, we have changed the title from “The Association between Oxidative Stress and Premature Atherosclerosis in Early Childhood Patients with Kawasaki Disease” to “The Association between Oxidative Stress and Endothelial Dysfunction in Early Childhood Patients with Kawasaki Disease”.

Our responses to the Reviewers are presented below.

Thank you for your consideration of the revised version of our manuscript.
Respectfully yours,

Takamichi Ishikawa, MD, PhD.

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Reviewer #1

Thank you very much for your comments on our article. We have revised the manuscript according to your comments and suggestions as follows.

Points 1 and 2
We very much appreciate and agree with your comment. We repeatedly imply that Kawasaki disease causes early onset of atherosclerosis, which is a specific histological diagnosis involving plaque-formation. However, it was our original intention to state the word “arteriosclerosis” rather than “atherosclerosis”, which is a physiological state. Therefore, first, we changed the title from “The Association between Oxidative Stress and Premature Atherosclerosis in Early Childhood Patients with Kawasaki Disease” to “The Association between Oxidative Stress and Endothelial Dysfunction in Early Childhood Patients with Kawasaki Disease”. Second, we changed “atherosclerosis” to “arteriosclerosis” in the Abstract (page 2, line 8), Background (page 4, lines 15 and 26), and Conclusion (page 19, line 22).

Point 3
We appreciate your suggestion. In this study, the FMD in Group 1 was lower than in Group 2. However, this difference did not reach significance. This result differed from that of our previous study (Ishikawa T, et al. J Pediatr. 2013; 163(4): 1117-21). One possible reason for this result is
the duration of fever in the Group 1 patients in the present study, which was shorter than that in the previous study. Another likely reason is the small sample size in this study. We have added text to the Discussion noting the sample size as a limitation.

Point 4

Thank you for your comment. As you point out, there is no statistical difference in the level of ROM between Groups 1 and 2. However, there was a significant correlation between ROM and %FMD (Figure 2). Moreover, In-ROM and total fever duration was independently associated with %FMD (Table 4). We believe that the duration of fever is as important with CAL as without CAL in regard to endothelial dysfunction and the genesis of arteriosclerosis. Therefore, the patients with prolonged fever during KD should be take care regarding arteriosclerosis, even if they have no CAL. It was our intention in this study to emphasize this latter point.

Point 5

Thank you for your question and comment. We performed coronary angiography in all ten patients in Group 1, but not in the remaining 15 children without CAL. We have now expanded this point in the Results. We agree with the importance of coronary angiography in the evaluation of atherosclerosis or arteriosclerosis, and have included this point as a limitation in the Discussion.

Point 6

We agree with your comment. This was a small study of only 25 children with KD and 25 controls, so the findings should be considered as preliminary. We have now included this factor as a limitation in the Discussion.

Thank you once again for your consideration of the revised version of our manuscript.

Respectfully yours,

Takamichi Ishikawa, MD, PhD.
Reviewer #2

Thank you very much for your comments on our article. We have revised the manuscript according to your comments and suggestions as follows.

Major:

Point 1

We very much appreciate your suggestion. As you indicate, a prospective study is defined as one that follows subjects over time. A more accurate description of this study is cross-sectional, since only one time point is involved. Therefore, we have deleted the words “prospective study” in the Abstract and Methods to avoid the misleading the reader.

Point 2

Thank you very much for your comments. As you point out, we did not follow the participants to investigate atherosclerosis. Rather, we assessed the association between oxidative stress and endothelial function, but not atherosclerosis, over the study period. Therefore, we have changed the title from “The Association between Oxidative Stress and Premature Atherosclerosis in Early Childhood Patients with Kawasaki Disease” to “The Association between Oxidative Stress and Endothelial Dysfunction in Early Childhood Patients with Kawasaki Disease”. In addition, we repeatedly imply that Kawasaki disease causes early onset of atherosclerosis, which is a specific histological diagnosis involving plaque-formation. However, it was our original intention to state the word “arteriosclerosis” rather than “atherosclerosis”, which is a physiologic state. Therefore, we have changed “atherosclerosis” to “arteriosclerosis.” in the Abstract (page 2, line 8), Background (page 4, line 15 and 26), and Conclusion (page 19, line 22).
Point 3

Thank you very much for your comments. The intervals applied for checking the CAL were based on the guideline published by the Japanese Circulation Society, and were not essential in this study. Therefore, we have deleted the sentence stating the intervals for checking CAL.

Point 4

We agree with your comment. The fact that patients are not receiving the same treatment may affect the results of the present study. In particular, additional treatment such as steroid and infliximab and plasma exchange may have influenced the data. We have now included this point as a limitation in the Discussion.

Minor:

Thank you for your suggestion. We have had our manuscript reviewed by a native English speaker and have completely revised our manuscript.

Thank you once again for your consideration of the revised version of our manuscript.

Respectfully yours,

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