Author's response to reviews

Title: High Pericardial and Peri-Aortic Adipose Tissue Burden in Pre-Diabetic and Diabetic Subjects

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Version: 2 Date: 19 September 2013

Author's response to reviews: see over
The Biomed Central Editorial Team

Please kindly find this revised manuscript entitled “The Relation of Pre-diabetes and Region-specific Visceral Adipose Tissue: Quantified by Multi-Detector Computed Tomography” that we are submitting for possible publication in “BMC Cardiovascular Disorders”. Thank you for the opportunity to further revise our manuscript. We appreciate the expert comments of the reviewers, which have been invaluable to us. We have since then made appropriate changes in the manuscript as suggested and incorporated edited changes as suggested in another mark-up version and, further responded in a point by point fashion to these comments in the rebuttal letter.

Please allow me to assure you that the information within this manuscript has not previously been submitted for publication nor has it been published in whole or in part elsewhere. I am also willing to make any change to this manuscript as recommended by the reviewers. I have confidence in your judgment and recommendations. By submitting this manuscript for possible publication, I acknowledge that the copyright for the enclosed material is transferred to the journal.

The manuscript, as submitted or its essence in another version, is not under consideration for publication elsewhere, and will not be published elsewhere while under consideration by “BMC Cardiovascular Disorders”. All authors have made substantive contributions to the study, and that all authors have read and endorse the manuscript and conclusions.

Sincerely,

Fei-Shih Yang
On behalf of the authors
Author's response to reviews

Title: The Relation of Pre-diabetes and Region-specific Visceral Adipose Tissue: Quantified by Multi-Detector Computed Tomography

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Version: 2 Date: 09 August 2013
Author's response to reviews: see over
The Biomed Central Editorial Team

Object: MS: 3178418901047134 - The Relation of Pre-diabetes and Region-specific Visceral Adipose Tissue: Quantified by Multi-Detector Computed Tomography
Dr. Fei-Shih Yang et al.

The major revised portion in our previous version submitted will be summarized in the latter part of this letter. We are more than happy to make the modifications of the manuscript according to the journal requirements and reviewers’ comments.

Journal requirements:

1. Requesting ethics statement:
   Response: We thank for the kindly suggestion of the journal requirement. We have since then provided the full name and description of the Institutional Review Board based on ethics statement at the “Material and Method/Study population” part (page 5 in the revised version).

2. Competing interests
   Response: All authors have no financial or non-financial competing interests.

3. Authors' contributions
   Response: We thank for the kindly suggestion and add the author’s contribution as following:

   FY, CY, CH and BB have substantial contributions to conception and design.

   CH, TW, YH, CL, JK, YW have participated in acquisition of data, or analysis and interpretation of data.

   HB, CJH, HY, J JL, RC have been involved in drafting the manuscript and revising it.

4. Acknowledgements
   Response: We thank for the kindly suggestion and have added the “Acknowledgement” part in the main text.
Reviewers’ comments:

Reviewer #1:

a. Major points

1. The author’s working hypothesis and its conclusion in the current study remains unclear. Data of coronary artery calcium measurement are not required. The study defocused totally. The author should clearly re-write results based on the author’s working hypothesis.

   Response: yes, we deeply appreciate the reviewer’s comments on these. We have since then removed coronary artery calcification from the “result” and “discussion” part. In addition, we further focused on the relationship among blood sugar disorder, systemic inflammation and both VAT (PCF and TAT) in the modified manuscript accordingly.

2. Data of Table 1 and Table 2 should be sum up. Numbers of Gender (female) in Table 1 should be showed.

   Response: Yes, we thank the reviewer’s comment on this. We have summed up table 1, 2 and placed the number of female subjects on it.

3. In Table 3, the study subjects are subjects without established type 2 diabetes. We are difficult to understand what these data indicate the author’s working hypothesis. The author should delete Table 3 and these data in the manuscript.

   Response: Yes, we thank the reviewer’s comment on this. Diabetes status had been shown to be tightly associated with several clinical metabolic derangements and cardiovascular risks, with a key feature of essentially excessive visceral adiposity accumulation and activated systemic inflammation. However, data regarding the association between these cardiometabolic risks and visceral adipose tissue depots remained largely unknown in clinical pre-diabetes stage. The main issues in this study were two-fold; first, we examined whether there are significant differences and distribution of these VATs between subjects with pre-diabetes or diabetes. Second, we further aimed to examine whether visceral adipose tissue, either PCF or TAT, may still correlate several clinical cardiometabolic risks even in subjects without clinically overt diabetes (either in non-diabetic or pre-diabetic stage).

4. The author should sum up data of Figure 1 and Figure 2, and show data of VAT, TAT, PCF, but not CACS and hsCRP in Figure.

   Response: Yes, we thank the reviewer’s comment on this and have incorporated Figure 1, Figure 2 into the new Figure 1 and delete the CACs part.
b. Minor points
1. The author should change the title; (for example) High pericardial and peri-aortic adipose tissue burden in pre-diabetic and diabetic subjects
   Response: Yes, we thank the reviewer’s comment on this. We have changed the title of this manuscript as reviewer’s suggestion.

2. The author should correct the words; Table1; cholesterol to Total-cholesterol, HDL to HDL-cholesterol, LDL to LDL-cholesterol. Is “Hyperlididemia” included hypo-HDL-Cemia? to “Dyslipidemia”? 
   Response: Yes, we thank the reviewer’s comment on this and have done all corrections. And the definition of “hyperlipidemia” was based on known history for anti-lipid medicine as statin or fibrate usage. So hypo-HDL was not included.

Reviewer #2:
The authors are describing that the degree of pericardial and thoracic peri-aortic adipose tissue quantified using multi-detector computed tomography (MDCT), differs significantly in a normal, pre-diabetic, and overtly diabetic subjects. This retrospective study adds some information that is not very surprising since many studies have demonstrated the relationships between epicardial adipose tissue and insulin resistance. 

Major points:
1. The flow of the manuscript was hard to read. Although the authors focused on visceral adipose tissue and region-specific adipose tissue, no data was shown regarding the target adipose quantification in the table 1, 2. And then they jumped to the table 3 which mentioned the relevant adipose tissue quantification.
   Response: Yes, we thank the reviewer’s comment on this and we have since then modified the introduction part and added these information in table 1 accordingly as well as re-do the statistic analyses for new table 2 and table 3.

2. In table 3, they only described data on PCF and VAT while omitting TAT.
   Response: Yes, we thank the reviewer’s comment on this and have corrected the error from VAT to TAT.

3. The statistical analyses need to be done again. The authors are doing a univariable
analysis (table 3) but they are not mentioning if the important metabolic parameters without significance in this analysis found were tested in the multivariate analysis (no data table but description in result session). Or they should mention how they selected the risk factors for both uni- and multivariate analysis.

Response: Yes, we thank the reviewer’s comment on this and have since then added another new table 2, addressing the uni-variate associations between both VAT (PCF and TAT) and continuous or dichotomous clinical variables. We have similar findings as previous study published in circulation regarding these VAT and several metabolic risks and adopted similar way in including these clinical confounders as our multivariable models. For these clinical variables included in models, they have stronger associations with these VAT and thus were included. We have since then added a new table 2 as well as revised table 3, and further revised the contents in the results section (page 9) accordingly. Based on your comments, we have re-do the statistic analyses and generated new table 2 illustrating how these clinical variables may correlate with these adipose tissue data and further examined the multivariable relationships between HOMA-IR or hs-CRP with these visceral adiposity in table 3 for clarify our working hypothesis. For the variables enrolled in multivariable models, we chose those variables with strong correlations with both visceral adiposity from data in Table 2, which is actually very close to the findings from previous research (Circulation, 2008, reference number 13) published. These parts were further described in the statistical section.

4. It would be great to have this uni- and multivariate analysis separated for men and women. Moreover, gender (female) data was lost in table 1. I would also suggest to mention that this multivariate analysis was not significant for coronary calcium score. Again, do it for each sex separately. respectively).

Response: Yes, we thank the reviewer’s comment on this. We have removed coronary calcification from the “result” and “discussion” accordingly. Due to we included fewer women than men (male/female: 401/161), which may limit its generalizability and hardly performing the subsequent analyses for men and women separately. We added this issue as one of our limitations in the last paragraph of “discussion”. However, this is a great point for our project and we will definitely incorporate it into our future follow up study.

5. There is lacking scientific data and logical approach: In our study, we also found that an interaction between visceral adipose tissue and systemic inflammation in subjects without established diabetes, with TAT having a pronounced effect on
HOMA-IR and hs-CRP, whereas PCF exhibited only a borderline relationship with coronary artery calcification through multivariate regression analysis.

Response: Yes, we thank the reviewer’s comment on this. We have modified this paragraph and add “region-specific” to describe our finding precisely.

6. Did the authors have the IRB approval for data mining and analysis.
Response: We thank the reviewer’s comment on this. We have since then provided the full name and description of the Institutional Review Board based on ethics statement at the “Material and Method/Study population” part (page 5 in the revised version).

Reviewer #3:
This study showed the association of pericardial and periaortic fat burden with the patients with prediabetic and diabetic patients and the relations between visceral fat and systemic inflammation. Five-hundred sixty two subjects including 357 healthy person, 155 pre-diabetic and 50 diabetic patients who underwent annual health surveys. The amount of pericardial fat and periaortic fat were measured by 16-slice MDCT and various clinical variables including hsCRP and HOMA-IR were assessed. As a result, the pericardial and periaortic fat burden were increased significantly in patients with pre-diabetes and type-2-diabetes than in healthy person. Also, the periaortic fat burden correlated well with insulin resistance and systemic inflammation in multivariate analysis. The manuscript is well written and the authors revealed the significant association of periaortic fat with systemic effect. Especially, the authors showed the accumulation of regional visceral fat even in prediabetes.

Major point
1. The main point that I have to discuss is the comparator. The authors enrolled healthy (or normal) as a comparator. They defined the normal as no hypertension, no Type2-Diabetes, and no hyperlipidemia in their ‘Materials and Methods’. The authors emphasize the importance of pre-Diabetes in this manuscript. So, the comparator might be selected in normoglycemia, not healthy (or normal). I think the propensity-matching technique might be taken into consideration.

Response: Yes, we thank the reviewer’s comment on this. This is a great point of detailed evaluation of VAT among preDM and normoglycemia with/without hypertension and dyslipidemia. However, the number of our cohort is limited. And the separation of the current group may lose the power of statistic analyses. We deeply
appreciate this comment and pledge to accomplish it in the future larger cohort and/or follow up studies.

2. The data about gender was omitted in Table 1.

Response: Yes, we thank the reviewer’s comment on this and we have since then added these information in table 1 accordingly.

Sincerely,

Fei-Shih Yang
On behalf of the authors