Author's response to reviews

Title: Different associations between obesity and impaired fasting glucose depending on serum gamma-glutamyltransferase levels within normal range: a cross-sectional study

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Version: 3
Date: 20 June 2014

Author's response to reviews: see over
To the Editor:

Thank you for considering our manuscript. We appreciate the careful review and valuable comments by the reviewers. The reviewers’ comments have been addressed below, and our manuscript has been revised accordingly. In addition, the language has been reviewed by a native English speaker from a professional English editing service. As such, revisions have been made to the manuscript, but the results and interpretation of our data remain consistent with the original manuscript.

We believe that these changes have improved our manuscript and hope that the current version is acceptable for publication in your journal.

Best regards,

Duk-Hee Lee, MD, PhD

Reviewer's report

Title: Different associations between obesity and impaired fasting glucose depending on serum gamma-glutamyltransferase levels within normal range: a cross-sectional study

Version: 2 Date: 10 May 2014

Reviewer: Danxia Yu

Reviewer's report:
The authors examined whether the association between obesity and impaired fasting glucose was modified by liver enzyme GGT. They analyzed data from a cross-sectional survey of middle-aged Korean men and women and found that BMI was positively associated with risk of IFG only in subjects with elevated GGT, not in those with low GGT. Overall, the authors appropriately defined the question and described the methods and results, although redundant. I have some comments regarding their discussion, conclusion, and further data analyses.

Major Compulsory Revisions:

Comment 1: The authors cited several papers that reported an interaction between
obesity and GGT on the risk of type 2 diabetes, but the present study failed to observe such an interaction. Comparison with previous studies is needed in the discussion. What about the association for newly diagnosed diabetes (participants with no history of diabetes but fasting glucose >126 mg/dl)?

Response 1: When newly diagnosed diabetes was used as the outcome, the patterns were similar to the previous findings on type 2 diabetes. However, P values for interactions failed to reach to statistical significance, and some ORs were unstable due to the small number of cases. We added these results as Supplementary Table 3 and included discussion on these findings.

Comment 2: Can the authors find an interaction between BMI and GGT that influences fasting glucose concentration as a continuous variable?

Response 2: Generally, the patterns were similar when FBS was used as the dependent variable. As most of the current study subjects had normal FBS levels (< 100 mg/dL), we think that the original approach comparing subjects with IFG to subjects with normal FBS would be more reasonable and interpretable for readers.

Comment 3: The authors may not want to conclude “obesity itself may not be a sufficient cause of T2D”, because BMI is not a good marker of obesity/adiposity, the present findings on T2D are not significant, and there is still a trend of positive association between BMI and IFG in the lowest tertile of GGT. What about using waist or waist-to-hip ratio?

Response 3: We revised the interpretation to "obesity itself may be only weakly associated with IFG and T2D when GGT levels are very low." When we used waist circumference as an index of obesity, the strength of the association between waist circumference and IFG tended to become stronger as serum GGT levels increased, especially among women. However, the overall patterns of waist circumference were weaker than those of BMI. Unfortunately, as hip circumference was not measured in KNHANES, the information on WHR is not available. We added the results of the waist circumference analyses as Supplementary Table 1.

Comment 4: Because of the cross-sectional design, it is possible that IFG happens before elevation of GGT or obese adults with low GGT are in an early stage and will eventually develop IFG. So the authors should fully acknowledge their limitations and not overstate the “important clinical implication”.

Response 4: As we already mentioned in the limitations of the study, any causal relationship is not clear because this was a cross-sectional study. However, our conclusion was based on
the current and previous findings of the same study topic. In fact, some prospective studies of T2D also tended to show no or weak relationships between obesity and T2D in persons with very low GGT levels. Therefore, when evaluating all findings on this issue, we think that “these findings have an important clinical implication” is not an overstatement.

Minor Essential Revisions:

Comment 1: The current model was adjusted for frequency of alcohol drinking. It is better to consider the amount of alcohol consumption, as well as pack-years of cigarette smoking.

Response 1: In the revised version, we included daily alcohol intake for alcohol consumption and the status of cigarette smoking (current, former, or never) and pack-years of cigarette smoking as covariates.

Comment 2: In the 1st paragraph of methods, can the authors provide the numbers of excluded participants due to different reasons?

Response 2: We have added this information.

Discretionary Revisions

Comment 1: Redundancy. For example, the abstract background is exactly the same as the 2nd sentence of introduction, which are also similar to the 1st sentence of introduction.

Response 1: We modified these parts of the abstract and introduction to prevent redundancy.

Reviewer's report 2

Title: Different associations between obesity and impaired fasting glucose depending on serum gamma-glutamyltransferase levels within normal range: a cross-sectional study

Version: 2

Date: 19 May 2014

Reviewer: Kavita Venkataraman

Reviewer's report:

The manuscript overall is well-written and clear, with a coherent and logical flow from introduction to discussion and conclusions.
Comment 1: The authors have chosen to use both BMI and GGT as categorical variables in their analysis, and the reasons for this are not very clear in the methods section. As these are inherently continuous variables, it may be preferable to analyse them as such, in the absence of specific compelling reasons.

Response 1: Even though both BMI and GGT are inherently continuous variables, we think that the interpretation of analytic results based on the categorization of these variables (if the categorization was not done arbitrarily) is more sensible and much easier for readers to comprehend. In addition, our approach was identical to what other researchers used for the same topic. Therefore, comparison among results from different studies is easier. We have mentioned this justification in the Methods section.

Comment 2: In the results section (page 6 lines 130-136), the authors conclude on the basis of table 3 that BMI has no effect on risk of IFG at lower levels of GGT. However, the table can also be interpreted as GGT having no effect on risk of IFG at lower BMI (<23). Such an interpretation is in fact more consistent with the risk of DM described in supplementary table 1. This aspect has also not been explored in the discussion section.

Response 2: In the revised version, we changed the sentence “BMI has no effect on the risk of IFG as lower levels of GGT” to “BMI was only weakly associated with IFG at lower levels of GGT.” It is also correct to describe the association between GGT and IFG at lower BMI (< 23) as a weak association rather than no association.

This study was performed to evaluate whether the well-established association between obesity and IFG differed depending on serum GGT levels within the normal range. Therefore, the primary focus of the findings and interpretations was the association between BMI and IFG, rather than GGT and IFG.

In this study, both BMI and serum GGT showed weak associations with IFG in the lowest category of the other variable. However, previous studies (Lim JS, 2007 (ref #7), Lee DH, 2003 (ref #5), Lee DH 2004 (ref #3), etc.) showed that, even within the low BMI group, the risk of T2D increased as GGT levels increased, while BMI was not associated with T2D in the lowest GGT group. Therefore, the best summary of the previous findings may be that serum GGT is more critical than obesity in the development of T2D. We thought that this alternative interpretation required substantial discussion. Furthermore, this issue would require a more detailed discussion of persistent organic pollutants, which was briefly mentioned in the current manuscript. Therefore, considering all these aspects, we did not include this alternative interpretation.

Reviewer's report 3
The authors reported that the associations between obesity and impaired fasting glucose (IFG) depended on serum gamma-glutamyltransferase (GGT) levels among Korean adults aged 40 years and over in a cross-sectional survey: those with highest level of GGT and BMI $\geq 25$ kg/m² had an unproportionally higher risk for IFG than their counterparts with other levels of GGT and BMI. These findings are interesting and novel for few relevant data are available. The major limitation is the cross-sectional design.

Major revisions: None.

Minor revisions:

Comment 1: There are also some grammar errors in the Method and Result sections.

Response 1: A native English speaker from a professional language editing service edited and proofread the revised manuscript.

Comment 2: In the statistical analysis section, how interaction terms were constructed was not mentioned.

Response 2: We added a sentence on how interaction terms were included in the model in the Methods section.

Comment 3: Two same figures were uploaded.

Response 3: This was corrected.

Discretionary Revisions:

Comment 1: What were the associations among the three liver enzymes (GGT, ALT and AST)? Why GGT, but not ALT and AST had significant interactions with obesity on IFG?

Response 1: Many recent studies on serum GGT have shown consistently that the biological and clinical meanings of serum GGT within the normal range are different from those of
other common liver enzymes. As we mentioned in the Background, serum GGT within the normal range is suggested as a marker of oxidative stress or a biomarker of exposure to some environmental pollutants. Therefore, it is not surprising that ALT or AST did not show interactions with obesity.