ANSWERING REVIEWERS

October 27, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12766-review.doc).

Title: A systematic review: Is *Helicobacter pylori* associated with glycemic control in diabetics?

Author: Yi-Ning Dai, Wei-Lai Yu, Hua-Tuo Zhu, Jie-Xia Ding, Chao-Hui Yu, You-Ming Li

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12766

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer.
(1) You forgot the publication named "*Helicobacter pylori* infection and eradication are not related to glycosylated hemoglobin levels (HbA1c) in young patients with type 1 diabetes" by Khalil T *et al*. Therefore, you need to include this publication in your paper and in your tables.

RESPONSE: Dear reviewer, I'm sorry for the omission. This publication has been additionally included in our systematic review. The added study involved 100 *H. pylori* seropositive youth with T1DM, 49 of whom were confirmed infection by UBT. The study provided data regarding the HbA1c level before and after eradication treatment. The inclusion of this added study did not change the conclusion of our systematic review. Thank you very much.

(2) Another meta-analysis study did not find significant association between *H. pylori* and glycemic control in DM. Averaged overall study population was many more than current study. It is possible this factor affected the results. Further discussion is desirable.

RESPONSE: Dear reviewer, thanks for your advice! We have further discussed this issue in Paragraph 4 in the Discussion part of the revised manuscript. The limited population involved in the meta-analysis is a major limitation of our systematic review. Therefore, we urge to further large-scale studies to examine the association between *H. pylori* infection and glycemic control in diabetics. Compared to the other meta-analysis, we believe this study has evaluated the association between *H. pylori* and glycemic control in a more comprehensive perspective.

(3) In the selected articles, the smallest number of patients was 17. To include this is appropriate?

RESPONSE: Dear reviewer, the study (Candelli *et al*, 2012) with smallest number of patients included 69 subjects with T1DM, only 17 of whom were positive for *H. pylori*. In meta-analyses, the smaller the study sample, the lighter this study weigths on the overall effect. The pooling of the small-sample studies is one of the limitations of our study. Because most current studies only involved relatively small number of subjects, we combined all eligible studies to perform a meta-analysis, and to examine the overall effect. In this sense, it is reasonable to include small-sample studies, and we believe that our systematic review is meaningful. Thank you so much.

(4) The discussion about possible mechanisms that might explain an association of *H. pylori* and diabetes, if indeed, is perhaps too long, and the relationship is more than just an association. Perhaps the discussion would be better focussed on the strength and weakness of many of the analysed papers.

RESPONSE: Dear reviewer, the underlying mechanism regarding to the association between *H. pylori* and glycemic control is really complicated, and perhaps, is not the key point of our study. We have curtailed this part (Paragraph 6 in the Discussion part of the revised manuscript) according to your suggestion. Furthermore, the strength and weakness of the analysed papers have been discussed in Paragraph 5 in the Discussion part. Thanks for your advice!

(5) Inclusion criteria for selection of studies were wide and open. Different studies used different tools for diagnosing diabetes mellitus, glycemic control, and *H. pylori* diagnosis. Heterogeneity between the studies is unacceptable.

RESPONSE: Dear reviewer, due to the limited number of studies, we loosen the inclusion criteria and included studies using different tools to diagnose *H. pylori* infection (RUT, UBT and so on). On the other hand, although we included studies using various parameters to assess glycemic control, actually we combined and analysed them seperately, e.g HbA1c, FPG, insulin, C-peptide. The diagnosis of diabetes mellitus and measurement of parameters reflecting glycemic control in each study were checked in quality assessment. On account of the presence of heterogeneity, we adopted random effect model to maximally reduce the effect of this issue. Through subgroup analysis, only studies among T2DM showed significant heterogeneity, thus we did not conclude the association between *H. pylori* and poor glycemic control in T2DM. Furthermore, we tried our best to find the source of heterogeneity and have discussed it in Paragraph 1 in the Discussion part. Thank you!

(6) Only two studies are randomized controlled studies. In the meta-analysis, authors have pooled different studies with different methodology (mixture of observational studies and coupe of RCT). Qualities of the selected studies are doubtful.

RESPONSE: Dear reviewer, all studies evaluating glycemic control by *H. pylori* status were observational studies, and were combined to estimate the overall association of *H. Pylori* infection and glycemic control in diabetics. The two RCTs randomized the diabetic subjects with *H. Pylori* infection to different inventions, and evaluated the effect of eradication treatment on the decrease of HbA1c and FPG. We did not pool different studies with different methodology (mixture of observational studies and RCTs). As for the qualities of the selected studies, we have assessed the quality of each study using standards by reference to Quality Assessment Forms in observational studies, and Jadad Scale in RCTs. The former concerned the selection and representativeness of subjects, the diagnosis of diabetes mellitus and *H. pylori* infection, the comparability of cases and controls, the measurement of parameters, the loss of follow-up and other factors. Quality score was shown in Table 1. All observational studies scored $\geqslant$7, and Jadad scores of the two RCTs were both 3, which represented moderate to high quality. Thanks a lot!

(7) In the study by Toporowska-Kowalska E *et al*, HbA1c concentration was significantly higher in patients with *Helicobacter pylori* infection (7.87+/-1.51 vs. 7.17+/-1.46%; $p<0.05$). The given p value is wrong. In Figure 1, total mean HbA1c of five selected studies in the *H. pylori* positive patients are 44.3 and *H. pylori* negative patients are 42.43. It seems there was an error in plotting the forest plot.

RESPONSE: Dear reviewer, I have checked the figures and repeated the statistical analysis. The given p value you metioned here ($p=0.26$) represents homogeneity among studies on children and adolescents of T1DM ($I^2=25\%$), but not the statistical difference in the comparison in the study by Toporowska-Kowalska E *et al*. The outcome measure was presented as weighed mean difference

(WMD) with 95% confidence interval (CI). The meta-analysis was conducted by Review Manager 5.2. No error was detected in the forest plot. Thanks for your attention!

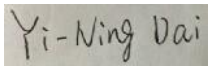
(8) In Figure 3, total number of pooled patients is very small. And both forest plots show high heterogeneity. 95% confidence interval of mean difference overlaps 0, but the big diamond favors *H. pylori* negative patients. What is the explanation?

RESPONSE: Dear reviewer, Figure 3 evaluated HbA1c decrease(A) and FPG decrease(B) in the comparison of *H. pylori* eradication group and non-eradication group. We have to admit that the total number is small. Cochran Q test showed significant homogeneity among studies (A: $p=0.76$, $I^2=0\%$; B: $p=0.52$, $I^2=0\%$). 95% CI overlaps 0, which demonstrated no significant difference in the comparison. But the diamond favors *H. pylori* negative, which showed that there might be a trend of better glycemic control after eradication. We further studied glycemic control before and after eradication to confirm the effect of eradication on glycemic control. Combining these two parts of results, the conclusion is that eradication does not improve glycemic control in a short-term follow-up. Thank you!

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



Yi-Ning Dai
Department of Gastroenterology
The First Affiliated Hospital
Zhejiang University School of Medicine
Hangzhou 310003, Zhejiang Province, China
Fax: +86-571-87236532
E-mail: daiyn@zju.edu.cn