

October 3, 2014

Prof Lian-Sheng Ma,
President and Editor-in-Chief.
World Journal of Cardiology
Sir,

Please find enclosed the revised manuscript (Review article) No. WJC/2014/12163, entitled "**Role of *Helicobacter pylori* infection in pathogenesis of atherosclerosis.**" The manuscript has been improved according to the suggestions of reviewers. The modified sentences are in red font in the manuscript. The point wise clarification of the reviewers written in blue font is as follows:-

Reviewer 1:-

The review by Dr. R. Vijayvergiya from Advanced Cardiac Center in Chandigarh entitled "Role of *Helicobacter pylori* infection in pathogenesis of atherosclerosis" is focused on the potential role of *H.pylori* in the pathogenesis of atherosclerosis. *H.pylori* as the most prevalent infection worldwide induces chronic gastritis that represents the low-grade inflammatory state leading through the release of pro-inflammatory cytokines and acute phase proteins to the acceleration of atherosclerosis. Author presents a review on this topic. Points of criticism: 1.The title is misleading because the author mainly concentrates on the role of *H.pylori* and the pathogenesis of coronary artery disease. In my opinion, Dr. Vijayvergiya should include also more data on the role of *H.pylori* in ischemic stroke and peripheral artery disease. **An additional para on both the aspects has been added in the manuscript.** 2. The evidence that *H.pylori* is involved in the pathogenesis is still very controversial and speculative, the number of positive and negative studies is almost equal. It is not enough to list the publication. The author should present this topic more critical. **Critical analysis and representation has been done regarding the relationship between *H.pylori* and atherosclerosis. Few more pertinent references have been added in the mansucript.** 3. The metabolic consequences of *H.pylori* should be presented more in detail. However, concerning this point, there is still a need for large interventional trials in order to prove a causal association between *H.pylori* and changes in lipid profiles. ***H pylori* related metabolic consequences has been elaborated especially that of perturbations in lipid**

metabolism, insulin resistance and glucose metabolism. As of now there is no concrete evidence to prove the causal association between *H.pylori* and metabolic perturbations.

4.H.pylori in the manuscript should be written *Helicobacter pylori* or *H.pylori* in italic and not H.Pylori! **Needful correction has been done in the manuscript.** 5.The Table 2 should be presented as a figure. The authors should show the different pathogenic links between *H.pylori* and the development of atherosclerosis. **Figure 1 explains the mechanisms of *H pylori* mediated atherosclerosis (Figure form of table 2).**

Reviewer 2:-

In this manuscript, the authors review on mechanisms of *Helicobacter pylori*-related atherosclerosis and its association with coronary artery disease, and conclude the association is not strong and causal role is not yet known. The article is well written and the results are very interesting. Therefore, the reviewer considers it can be accepted with minor changes: All nonstandard abbreviations should be defined, i.e., CAD, and correct misspelled words, i.e., Epstein-Barr virus. **Needful correction has been done.**

Reviewer 3:-

The topic is interesting, but the reading of this enormous amount of data is made difficult by the lack of summary tables. From the methodological point of view it has been not presented how was performed the analysis of the literature. Even in the case of a not systematic review, to more fully understand the strength of the items, the paper require a summary (table) for each section indicating synthetic data for each study and a synthetic judgment (example: +++, ++ -, + --, ----). At the end of the introduction it should be better explained the significance of the division into two large chapters. **A section on methodology has been added in the abstract. Abstract has been divided into 3 sections (background, methods and conclusions).**

Methodology : We performed the literature search on MEDLINE electronic database using keywords like *H. pylori*, infection, atherosclerosis, mechanisms, coronary artery disease, myocardial infarction, stroke, cerebrovascular disease, peripheral arterial disease and inflammation from the MESH index with all possible and relevant combinations of the above keywords. All possible studies like meta-analysis, case controlled studies, prospective and retrospective studies, review articles, abstracts, editorials and commentaries have been

studied and analysed. Both the authors independently performed the literature search, selected studies and analysed them. Relevance of dividing the review into two sections has been explained at the end of introduction.

Reviewer 4:-

This manuscript provides quite impartial but critical review of the literature on the possible relationship between Hp infection and atherosclerosis. Tough manuscript is well written and quite informative as reflected by the long list of references, there are several omissions which require additional attention. Firstly, to the readership of the Journal the abbreviation "CAD" is not obvious and should be defined in the introduction. The other, more serious issue, is the fact that the role of Hp major endotoxin, LPS, in the proinflammatory events is totally ignored. Hence, the section Ib on "chronic inflammation" should be expanded to include the proinflammatory mechanism of Hp LPS action, and include some pertinent references,i.e., Am. J. Molecular Biology,vol.2(2012)113-1123; OA Inflammation 2013 April 01;(1):1-8; Inflammopharmacology vol. 21(2013)67-78; and Inflammopharmacology vol. 21 (2013)241-251. **Coronary artery disease (CAD) is defined in the introduction. The role of *H. pylori* cell wall LPS mediated inflammatory cascade and relevant references are included in appropriate sections. All 4 mentioned references are added.**

I hope the answers to reviewer query are satisfactory. If any further clarification is required, please feel free to contact me.

With kind regards,

Yours sincerely,

Dr. Rajesh Vijayvergiya, MD, DM, FACC, FSCAI, FISES

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