Author’s response to reviews

Title: Non-significant association between -330 T/G polymorphism in interleukin-2 gene and chronic periodontitis: findings from a meta-analysis

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Version: 1 Date: 15 Oct 2019

Author’s response to reviews:

Dear Editor Liam Messin,

Thank you for the e-mail.

We made the most changes suggested by the reviewers.

Reviewer #1 (Comments to the Author (Required)):

The submitted manuscript presents the results of meta-analysis study of -330 T/G polymorphism in IL-2 gene with predisposition towards chronic periodontitis. The authors choose IL-2 due to its possibility to suppress immune response and the correlation with -330 T/G polymorphism in IL-2 and periodontitis was not entirely determined jet. The authors summarized the results four studies in diverse ethnical groups totaling 1068 participial. This meta-analysis showed a non-significant association between -330 T/G polymorphism in IL-2 and chronic periodontitis.
Reply (#1): We are sincerely grateful to the reviewer’s comments for demonstrates scientific accuracy in reviewing our work. We hope that the changes we made in our manuscript may be positively considered by Reviewer.

Major comment

* I'm afraid that a meta-analysis carried out only from four studies including a total of 348 patients with chronic periodontitis and 720 control is insufficient for the publication in the journal BMC Oral Health.

Reply (#1). We understand the concern about the limited number of included studies in a systematic review or meta-analysis. However, our findings are accurated by a rigorous statistical methods and embased by our extended experience in meta-analysis. By means of a new literature search for the resubmission of the manuscript, we have found one other eligible article resulting in an increased number of included studies and participants in our meta-analysis. Besides we were encouraged by a previous meta-analysis that was published in BMC Oral Health that was composed by four articles (Zhang et al. IL-13 -1112 polymorphism and periodontitis susceptibility: a meta-analysis. 2018).

* Why authors stated that 5 studies were included in the meta-analysis? I think that study by Scarel-Caminaga et al., 2002 should not be considered as 2 works.

Reply (#1). As indicated by Cochran Handbook, we have solved this issue with a single pairwise comparison. We summed the values for the two interventions groups performed by Scarel-Caminaga et al., 2002 and we treated them as one single group.

* I suggest a change of the title, because there was no relationship between studied polymorphism and chronic periodontitis found.

Reply (#1). We have made this change.

* Results and Tables should be presented more clearly.

Reply (#1). We have reorganized the results and the grills from the table 1 for a better understanding.

Minor comments

*Gene should be written in italic.

Reply (#1): We have made this change.

*Numbering of tables in the text is confusing.
Reply (#1): We apologize for the mistake in the table description along the text, as you can see in Results, the correct sequence of tables was presented.

* I recommend English proofreading of the manuscript by the native speaker.

Reply (#1): We have followed this suggestion and the text was revised by an expert in English.

In the text there are several grammatically incorrect sentences or strange formulations, e.g.:

- Abstract - "... immune response molecules participants of periodontitis … ", "A retrieve in the literature … ", "... groups totaling 1,068 participants … "

Reply (#1): We have made this change.

- Background - p. 4 lines 6-9 sentence "Moreover, in Norway a total of 49.5% … ", p. 4 lines 10-14 sentence "The disease receives several … ", p. 4 line 23 "... to be an effective approach to autoimmune and inflammatory diseases … "

Reply (#1): We have made the change.

- Methods - Data collection process - p. 5 line 23 "...form that composed the table of…"

Reply (#1): We have made the change.

- Methods - p. 6 line 2 Incorrect form: diabetics disease

Reply (#1): We have made the change.

- Methods - Sensitive analysis and publication data - p. 6 line 41 "There was not publication bias was this meta-analysis which …"

Reply (#1): We have made the change.

- Discussion - p. 7 line 1 "The meta-analysis is a statistical tool in genetic studies …"

Reply (#1): We have made the change.

- Discussion - p. 7 line 23 Similar information: In addition, we consider that racial differences and ethnicity may influence the role of genetic variations in cytokines genes [41]. Therefore, this current meta-analysis attempted to considerate the influence of ethnicity in the results.

Reply (#1): We have made the change.
Reviewer #2. (Comments to the Author (Required)):

Reply (#2). Firstly the authors want thank the Reviewer by the comments that will guarantee the increasing scientific rigor of our work.

Page 4, Line 38.

In contrast to what is said in the manuscript, Scarel-Caminaga et al. conclude that there is an association between the -330 T/G polymorphism of IL2 and the severity of periodontitis. Still, Li et al. conclude that the results obtained after a logistic regression do not support the hypothesis of an association between this SNP and periodontitis.

Reply (#2). We have performed several changes in text with more details on the aforementioned articles and so, the elucidation of the described ideas in text.

Page 5, line 11.

"[(interleukin OR cytokine OR interleukin-2 OR IL-2) AND (genetic variation OR rs2069762 polymorphism OR -330 T/G polymorphism) AND (periodontitis OR periodontal disease OR chronic periodontitis)]" - Search in Pubmed n=567, publication dates: until March 2, 2019.

No reproducibility was obtained for the search strategy described in the manuscript. How did the authors obtain the total number of articles mentioned in figure 1 (n=389)? Were the terms and search strategies the same for all selected databases? Has any additional limit been used?

Reply (#2). The literature retrieve was performed by two experts in systematic search with the same search strategy for all used databases. This allows that the authors do not account articles that do not present relevant information for the search. It facilitates the literature search and consequently avoid a hard work during the collection of studies. Besides, everyday new studies are being available in the literature. As you can see in the resubmission a new search was performed which brought changes in the initial study collection number in figure 1. It also allowed the collection of a new eligible article that was included in the quantitative synthesis.

An article by Kobayashi et al. was not cited in this manuscript. This article can be found at: \<https://doi.org/10.1177%2F0022034509350037\>, and in Web of Science. Does this article meet the criteria to be selected for meta-analysis or a qualitative analysis?

Reply (#2): Unfortunately, this article did not bring the genotypic frequency for the selected polymorphism. The data from genotypic frequency is an inclusion criteria described in the Material and methods. We determinate this inclusion criteria due to the impossibility to obtain the exact genotypic frequency by means of allelic frequency and so, to unfeasible the genotypic comparisons.

Some MeSH terms can be simplified, because they are redundant in some MeSH trees (e.g Pubmed). This would facilitate the understanding and the rationality of the search.
Reply (#2): We have considered this suggestion and we are grateful for this information.

Table 1.

Information about Hardy-Weinberg equilibrium is not mentioned in this manuscript. Vahabi et al., for example, did not observe the presence of the G allele in their study. What would be the weight of these data in a meta-analysis of the magnitude of the polymorphism effect if you cannot measure the distributions of frequencies between cases/control?

Reply (#2): As suggested, we have included the information on HWE in table 1. The statistical program solve the issue questioned by the reviewer during the analyses and no single study significantly have changed the pooled OR values, as described in Sensitive analysis and publication bias.

Figure 2.

The authors of the manuscript used the same control group of Scarel-Caminaga et al. two times in the analysis. This double count may interfere with the estimation of the results. The Cochrane Handbook provides some recommendations for this situation: a simple recommendation to avoid this would be combine all the relevant intervention groups in the study into a single pair-wise comparison. Another strategy could be to select one of the intervention groups and exclude the other, although this will result in some loss of information. You can check more strategies to analyze multiple groups from one study in the Cochrane Handbook.

Reply (#2): We have solve this issue with a single pair-wise comparison. We summed the values for the two interventions groups performed by Scarel-Caminaga et al., 2002 and we treated them as one single group.