Author’s response to reviews

Title: Resistance and Resilience to Experimental Gingivitis: A Systematic Scoping Review

Authors:
Charifa Zemouri (c.zemouri@acta.nl)
Nicholas S Jakubovics (nick.jakubovics@newcastle.ac.uk)
Wim Crielaard (W.Crielaard@acta.nl)
Egija Zaura (e.zaura@acta.nl)
Michael Dodds (Michael.Dodds@effem.com)
Bettina Schelkle (publications@ilsieurope.be)
Bruno G Loos (b.g.loos@acta.nl)

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Author’s response to reviews:

Dear reviewer, dear Dr. Tatakis,

Thank you very much for your expert review of our paper. We note that almost all of the points in your letter were made in the review of the original submitted version of the manuscript. We addressed these in detail in the first revision (OHEA-D-18-00410 R1). It appears that there has been a miscommunication since we have received the same set of comments once again. We have reviewed our responses in detail and we feel that they are still appropriate. Therefore, we are returning the responses that we gave previously. In addition, we have answered the one comment that was new (Point 1 below).
1. "The one thing that I found curious about this one is the high number of studies that were excluded from analysis because of "full text not available", as reported in the supplementary material. In this day and age, I would think that this type of issue would be far more limited.

We have checked and 18 articles were excluded on the basis of a lack of access to the full text. Some of these articles were published in small dental journals such as the American Journal of Dentistry, which are subscription-only and industry focussed. There were a small number of articles published in more ‘mainstream’ journals such as the Journal of Periodontal Research that are not part of our institutions’ subscription portfolio. In future, we anticipate that the movement towards Open Access will make it easier for us to access papers like this, although even then the final, fully corrected versions may be difficult to obtain. For this manuscript, we decided to focus on articles where we were able to access the complete and finalised versions of the papers. We have added a comment to this effect on page 3, lines 127-129.

2. One could argue whether exclusion of split mouth studies is warranted, the author's explanation notwithstanding. The authors compare studies analyzing biomarkers (immunologic and biochemical) in GCF with studies analyzing biomarkers in saliva.

We have adjusted the abstract and more information on the immunological biomarkers is included. You were right that we originally only addressed only microbiology, this was narrow focused and not reflecting all results.

We added in the Abstract the following extra information (in Italics and underlined, page 1 lines 38-42):

“For immunological biomarkers, it was challenging to retrieve a robust pattern of changes across multiple studies. IL-1β and IL-6 in saliva and in gingival crevicular fluid increased during induction phase and returned in the resolution phase below baseline values. The biochemical parameters cystatin-SN, cystatin-S and lactoferrin in saliva were increased at the end of induction phase, however also here no clear pattern emerged based on all available studies.”

Given their rationale for exclusion of split mouth studies, the inclusion of saliva-based studies is questionable.
We have elaborated on our reasoning for excluding split mouth studies in the methods section and reiterated this in the discussion.

In the Methods section we added the following sentences (in Italics and underlined, page 3, lines 111-114):

“Studies on mouth rinses, placebo control groups, animals, surgical treatments, antibiotics, probiotics, those lacking a healthy control population, cross-sectional designs, any form of intervention during the induction phase, and split mouth experimental design were excluded. The latter type studies were excluded due to risk of transfer of fluids and biomarkers from one part of the oral cavity to another. Moreover, systemic responses are likely to be lower in a split mouth study design than in full-mouth EG due to the smaller gingival surface area of inflammation; this may then affect the inflammatory profile of plasma and GCF.

At the very least, I would suggest splitting these two groups (GCF vs saliva outcomes) and reporting separately on studies using GCF and ones using saliva. As someone who has pursued both types of studies (GCF and saliva biomarkers), I can say that the results can differ significantly between them.

With regards to your comment about splitting findings from GCF and saliva, we fully agree with you. We have now reported and rewrote the findings from blood/plasma/biopsies, GCF and saliva separately. The section 3 on ‘Immunological markers’ (from page 4 line 195 to page 6 line 277) and section 4 ‘Biochemical markers’ (from page 6 line 279 to page 7 line 330) were heavily reshaped according to reviewer’s suggestion.

3. When reviewing/reporting on studies involving smokers there is no comment on the ascertainment of smoking status (a biochemically based determination of smoking status is preferred over the more common self-reporting method).

We thank you for this relevant comment that we have addressed first in the Results and later in the Discussion section as follows:

In Results section (page 3 lines 134-136): “Five studies compared smokers to non-smokers in exposure to the EG trial (10, 12, 13, 23, 29); smoking status was always based on self-report and not biochemically assessed.”
In the Discussion section (page 7, lines 374-377): “However, this suggestion needs to be interpreted with care since it was found only in one study with a limited number of smokers (n=11) and non-smokers (n=14). Moreover, we acknowledge that when reviewing/reporting on studies involving smokers biochemical determination of smoking status would be ideal rather than the commonly applied self-reporting method.”

We hope we have addressed all comments satisfactory and we hope the paper is now suitable for publication.

Sincerely,

Charifa Zemouri and Bruno Loos, in name of all authors.