Author's response to reviews

Title: Periodontitis and COPD - Epidemiological or Causal Association

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Title: Periodontitis and COPD - Epidemiological or Causal Association

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Author's response to reviews: see over
Cover letter for revision of review article: Chronic Periodontitis and COPD – Epidemiological or Causal Association.
Dr. Adam Usher, Prof. Rob Stockley

Reviewer: David Scott

Many thanks for your feedback. I have addressed the points raised as outlined below. The location of the edited text refers to the word document when viewed without “tracking changes” markup visible.

1. There is no search strategy noted. How did the authors select which literature to include – or exclude - in the review?

(Page 4, Paragraph 3, Lines 5-9: A search strategy has been included)

2. Please provide the epidemiological evidence of an association between COPD and periodontitis in a table. It seems rather premature to be writing a review of mechanisms that may underlie a phenomenon that has not been established. In other words, please “sell” the concept much more strongly and upfront. “respiratory conditions” do not correlate with COPD. Worse oral health does not correlate with periodontitis, etc (Ref 28, 29). Obviously, some referenced studies are more robust. Please discuss the strength of the epidemiological evidence using language similar to most evidence-based reviews. This reviewer finds it difficult to come to a conclusion on any epidemiological association, as written. What evidence is lacking to allow a more definitive conclusion to be made?

(A recently published meta-analysis referenced in the paper (Ref 50) has a detailed tabulated form of the studies included in my review article. I think that a table of epidemiological studies is best suited to a meta-analysis paper, and I have not reproduced it in this manuscript. Page 8, Paragraph 1: This deals with the poor quality of most of the epidemiological studies. The association is suggested, but better quality studies are needed before a definite link can be established. This may seem a premature position in which to write a review article, however, review articles serve two purposes, to consolidate what is known and to question what is believed).

3. The negative studies receive less attention in the text. Please expand.

(Page 8, Paragraph 1: Expansion of commentary on neutral and negative studies)

4. Figure 1. Oxidants and particulates, as well as systemic smoke-derived insults, are key inducers and/or exacerbators of inflammatory periodontal diseases. The Figure implies this is only true for COPD. Also, while there may be similarities in the mechanisms of disease progression in COPD and periodontitis, it is difficult to accept that the processes are “identical”, as claimed.

(Figure 1: Adapted to show the role of smoking/particulates on periodontitis pathogenesis. Figure 1 Legend: Stated that this is merely a hypothesis that the process may have features and predisposition in common. We make no claims that the processes are identical. Explanation that this only represents the “principal” triggers of inflammation.)

5. Please define what is meant by “periodontitis”. It is assumed the authors refer to chronic periodontitis rather than aggressive, etc?
6. Please check terminology throughout (periodontitis is a group of diseases/C-reactive protein induces cytokines but is it a cytokine itself? / interchangeable use of COPD and emphysema).

(Page 3, Paragraph 1, Line 9: Added that emphysema is a pathological subtype of COPD to emphasise the relationship between the two. In many studies, the generic “COPD” term has been used rather than the specific pathological type. Page 3, Paragraph 2, Line 3: Expanded information on cytokines. Page 15, Paragraph 2, Line 1: Emphysema changed to COPD. Chronic periodontitis and periodontitis are used interchangeably to some extent, though the emphasis on chronic disease is emphasised early in the review. The distinctions between all the different types are not used consistently in much of the literature.)

7. There are a number of extensive reviews on the role of neutrophils in periodontitis and COPD; and smoke-immune/disease interactions that are not referenced.

(Page 8, Paragraph 2: Added section on other cell and immune interactions with references to many reviews on this and the role of neutrophils).

8. The authors support the hypothesis that abnormal neutrophil function is associated with COPD and perio. Please discuss the alternate, that normal neutrophils whose prolonged recruitment and activation to and by inflammatory stimuli (e.g. smoke / bacteria) lead to tissue destruction over long periods of time.

(The alternative is possible despite lack of evidence that this is specific in either disease, whereas neutrophil function has been shown to be abnormal in COPD and periodontitis)

9. The authors tell us that “periodontitis” occurs in half of adults. What is the equivalent for (a) COPD and (b) both diseases simultaneously?

(Page 3, Paragraph 1, Line 8: Prevalence data on COPD inserted. Odds ratios vary considerably in the studies though some have been included in the paper (Page 6, Paragraph 2). This remains a contentious issue in need of further research).

10. The Abstract should include a statement on whether the authors conclude that the association is epidemiological or causal.

(Page 2, Paragraph 1, Line 10: Author conclusion added, emphasising the need for future research to answer this question).

- Minor Essential Revisions

11. Were the MMP studies discussed controlled for smoking status?

(Page 7, Paragraph 2, Line 3. The study this refers to does not control for smoking – there were significantly more former smokers in the COPD group. This has not been expanded on as it was a negative study in terms of saliva MMP levels and only aims to highlight the research or scarcity of
research in this area. Page 10, Paragraph 3, Line 4: Reference has been changed to a better early study of MMP and emphysema. Smoking history is given, but they are not matched (Ref 46).

12. It is unclear why the authors argue that socio-economics are not related to periodontitis risk (e.g. Am J Public Health. 2006; 96: 332–339 / Contemp Clin Dent. 2010; 1: 23–26)?

(Page 5, Paragraph 2, Line 8: Added information on socio-economic status and a positive study relating to periodontitis risk)

13. The authors tell us that, presumably systemic, cytokine levels are raised in both perio and COPD. Can they provide some data? Are the increases similar in both diseases? Is there any evidence of disease synergy wrt cytokine levels.

(Page 4, Paragraph 1, Line 2: Reference for cytokine level and disease severity synergy added).

14. The importance of bacteria in periodontitis is clearly established. The importance of bacteria in COPD has not and is contentious. The manuscript, however, is attempting to equate the two.

(The evidence in COPD is only contentious if viewed superficially. Bacterial colonisation, load and increase in load, or prevalence in exacerbations all relate to the degree of neutrophilic inflammation. Many reviews fail to account for the key factor of load.)


(There is no good evidence currently linking AATD and periodontitis. I have included a study looking at the clinical measures of periodontitis in relation to AATD – Page 11, Paragraph 3. I would only expand this if there were more recent papers with larger numbers of patients.)

16. Considering that deep periodontal pockets are anoxic or microaerophilic, how important is ROS production likely to be? Are non-oxygen dependent killing mechanisms likely to be more prominent? Please delineate cell and soluble anti-oxidants. Also, discuss smoke and anti-protease inactivation.

(I believe that the local oxygen concentration does not limit the ability of cells to generate ROS. In fact hypoxia can increase ROS production and low oxygen environments increases inflammatory gene expression and cytokine production J Clin Periodont. 2010;37:1039-48).

17. It is unclear why NETs are discussed (a) in the context of periodontal destruction (rather than bacterial control) without specific evidence of their potentially destructive nature and (b) why they are discussed if there is no evidence of them as common mechanisms in perio and COPD.

(Page 15, Paragraph 4: I have inserted some evidence of NETs as factors in propagating inflammation and tissue destruction. They are discussed as a possible mechanism.)
Many thanks for your feedback. I have addressed the points raised as outlined below. The location of the edited text refers to the word document when viewed without “tracking changes” markup visible.

1. Neutrophils are not the only players in COPD and not the only source of oxidants.
   (Page 8, Paragraph 2: A section has been added detailing the roles of other inflammatory cells. Figure 1: Modified so that it explicitly mentions cigarette smoke as a source of oxidants in COPD and periodontitis).

2. Do imply that periodontitis cause COPD or visa versa, or both have same causative mechanism(s). This must be clear in the text.
   (Page 8, Paragraph 1: I have explicitly stated that causation e.g. one condition leading to the development of the other is entirely speculative and that more research is needed here. The review then focusses on similarities in the proposed pathophysiology of the two conditions).

3. Since smoking causes COPD and is a significant risk factor for periodontitis why only a fraction of COPD patients showed periodontitis?
   (Smoking is only a significant risk factor for some patients with COPD and many smokers do not develop the condition indicating a susceptibility as with periodontitis. When controlled for smoking and other risk factors, there is still an increased co-prevalence of COPD and periodontitis implying a common susceptibility modifier, or that further independent factor/s may be responsible.)

4. Although stated, the treatment effect is very weak!! Are there any evidences if treating COPD (antibiotics) could affect periodontitis?
   (Very few studies on the treatment effects exist and are included Page 16, Paragraph 1. There is, to our knowledge, no evidence on the effect of treating COPD on periodontitis as it has not been considered in publications on COPD management. Specific research is needed in this area).

Finally, the text is too long and should be shortening.

(Excluding references, the paper is around 4,300 words. Reviewer 1 described it as “a good introduction to the topic, although it is by no means exhaustive”. We have kept the paper a similar length after the revisions).

Figure 1 should be modified to include the other sources of oxidants.

(Figure 1 – Modified so that it explicitly mentions cigarette smoke as a source of oxidants in COPD and periodontitis).

Figure 4 should be omitted does not add relevant information.

(Figure 4 legend – I have expanded this to include how they may be relevant in disease pathogenesis. Compared to the effect of ROS and proteolytic enzymes, NETs are a relatively novel
component of disease pathogenesis and we feel this needs to be included in the text with accompanying figure).