Author's response to reviews

Title: Erosive esophageal reflux vs. non erosive esophageal reflux: Oral findings in 71 patients

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Author's response to reviews: see over
Dear Professor Pietruska,

Thank you very much for all your endeavours. In the Revision, every effort has been made to address the concerns of the Reviewers. All revised parts of the manuscript are highlighted in red. Specifically, the following issues have been rectified:

Reviewer #1

The authors wish to thank this Reviewer for a very careful review and his comments.

1 The authors should define the term "acidic lesions". The term is used several times and only defined at the end of the manuscript (erythema and/or ulcer). I had no concept of what lesions were included in the definition of acidic lesions until the end of the manuscript.

Answer:
In the paragraph “Oral Mucosa” of the “Material and Methods” Section, the authors had stated that mucosal lesions were examined in the palatal, buccal, and tongue mucosa using the scoring system published by Yoshikawa 2012 et al. (score 0, no inflammation; 1, redness; and
2, ulceration). Moreover, this score may also be seen from Table 2. Accordingly, presence of erythema and/or ulcer was included in the definition of acidic lesions.

To clarify this issue, the paragraph “Oral Mucosa” was re-written as follows:

“Oral Mucosa. Acidic mucosal lesions were examined in the palatal, buccal, and tongue mucosa using the following scoring system: score 0, no inflammation; 1, redness; and 2, ulceration [13]. Accordingly, presence of erythema and/or ulcer was included in the definition of acidic mucosal lesions. Inspection was performed with use of a loup (Carl Zeiss, Jena, Germany, magnification x 2.3).”

2. The authors should state on line 75 that palatal lesions were demonstrated histologically in rats and then should discuss if this is a finding in humans or is it a model used in research that is applied to human subjects.

_Returned:_

To enhance clarity, this paragraph was re-written as follows:

“Recent literature has pointed out that other extraesophageal symptoms of GERD are acidic lesions of the oral mucosa. It has been demonstrated histologically in rats [5] that gastric acid reflux can cause acidic lesions of the palatal mucosa. These findings suggested that these pathological changes may reflect the relationship between laryngopharyngeal reflux and airway obstruction also in humans.”

Moreover, the following paragraph was incorporated in the “Discussion” Section:
“It has been demonstrated histopathologically in the rat model that reflux affects the soft palate, which suggests that these pathological changes may reflect the relationship between laryngopharyngeal reflux and airway obstruction [5].”

3. In my opinion it is patronizing to use the term "suffering from" when describing any medical condition (line 113). The authors should use a more objective term such as history of alcohol or illicit drug use (not use).

Answer:
The authors apologize. Accordingly, a more objective term was used in the revised manuscript. This paragraph reads now:

“Patients were excluded from the study if they had removable dentures, had undergone radiotherapy in the head and neck area, bisphosphonate therapy, or had a history of alcohol or illicit drug use.”

4. I am not sure why the authors failed to collect information on cigarette use such as quantity smoked daily and years patient has smoked. Additionally the authors did not collect information on other forms of tobacco such as spit tobacco, cigars? and pipes?.

Answer:
The authors are thankful for the opportunity to describe smoking habits more in detail. It was stated in the paragraph “Patients” of the “Material and Methods” Section of the manuscript that ethnicity, number of teeth and smoking habits (yes/no) were recorded during evaluation. However, the authors understand the concern of the Reviewer. To our knowledge, there is no consistent or mandatory mode of how to describe smoking habits in periodontal literature of the past decade:

In a recent study, “current smokers”, “former smokers” and “never smokers” were analyzed separately [please see Holtfreter B, Empen K, Gläser S, Lorbeer R, Völzke H, et al. (2013)


In other studies, smokers were completely excluded [please see Aspriello SD, Zizzi A, Tirabassi G, Buldrezghi E, Biscotti T, Faloia E, Stramazzotti D, Boscaro M, Piemontese M. Diabetes mellitus-associated periodontitis: differences between type 1 and type 2 diabetes mellitus. J Periodont Res 2011; 46: 164–169].

Accordingly, assessment of individual periodontal risks may focus on „smoking habits (yes/no)”, especially on „cigarette consumption“, which is well established in the literature [please see Eickholz P, Kaltschmitt J, Berbig J, Reitmeir P, Pretzl B: Tooth loss after active periodontal therapy. 1: patient-related factors for risk, prognosis, and quality of outcome. J Clin Periodontol 2008, 35(2):165-174 ]. In their study, Eickholz and coworkers combined “former and never smokers” and compared the results of this group with those of “current smokers”. Similarly, recent studies on periodontitis in type 2 diabetes mellitus patients also focussed on “smoking yes/no” [Pranckeviciene A, Siudikiene J, Ostrauskas R, Machiulskiene V: Severity of periodontal disease in adult patients with diabetes mellitus in relation to the type of diabetes. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2014, 158(1):117-123.].

Therefore, decision “smoking yes / no” without assessment of additional information such as quantity smoked daily and years patient seems to be justified from a scientific point of view.

Due to the fact that none of the study participants consumed other forms of tobacco such as spit tobacco, cigars or pipes, the authors focussed on “cigarette smoking”. Spit tobacco is not used in germany to any significant extent. Moreover, it may be mentioned that smokeless (spit) tobacco use increases the risk of localized recession but its effect on periodontitis seems to be unclear (http://www1.umn.edu/perio/tobacco/tobperio.html).
However, to meet the concern of the Reviewer, the following paragraph was added to the paragraph “Patients” of the “Results” Section:

“All smokers in this study used to smoke cigarettes. No other forms of tobacco such as spit tobacco, cigars and pipes were consumed.”

Moreover, the following paragraph was added to the “Discussion” Section:

“Due to the fact that the smokers among the study participants did not consume other forms of tobacco such as spit tobacco, cigars or pipes, the study focussed on „cigarette smoking“.”

5. I am not sure how the information on smoking is relative to anything if we don't know form of tobacco used, frequency and chronicity of use of tobacco.

**Answer:**

As it was stated in Answer 4, additional information on smoking habits is provided now in the revised manuscript. All smokers among the study participants used to smoke cigarettes. This information was incorporated in the “Results” and “Discussion” Section of the revised manuscript.

Nevertheless, the authors have to confess that they did not record frequency and chronicity of use of tobacco. Indeed, it can not be excluded that frequency and chronicity of use of tobacco differed significantly between the two groups (ERD, NERD). However, due to the fact that percentages of smokers in both groups were relatively small and did not differ significantly, it may be assumed, that the results yielded may be regarded as reliable. In Addition, none of the conclusions is based on smoking habits. Percentage of “smoking yes/no” was only described to demonstrate that smoking habits were similar in both groups (ERD and NERD patients), please see Table 1.

However, to meet the concern of the Reviewer, the following paragraph was added to the “Limitations” Section:

“Third, frequency and chronicity of use of tobacco were not recorded. Accordingly, it can not be excluded that frequency and chronicity of use of tobacco differed significantly between the two groups (ERD, NERD).”
6. I am surprised that the authors did not collect information on last dental visit or whether the patients routinely assess preventative dental care (such as dental prophylaxis). Perhaps the finding of periodontal disease in this population studies are not representative of the general population. Perhaps the findings of the study participants may be attributed to lack of accessing routine dental care including dental prophylaxis. This seems to be a major flaw and significantly weakens the stated association of periodontal destruction.

Answer:
The authors apologize, again. Indeed, in the “Material and Methods” Section, information on data collection is scarce with respect to medical and dental care. In the paragraph “Medical History”, it was stated that “details of the health status were assessed”. Moreover, only limited information was provided in the “Results” Section of the manuscript. Again, the authors thank for the opportunity to provide more information.

During assessment of health status, all study patricipants had provided name and address of their family doctors and family dentists and had confirmed to see them regularly. Nevertheless, in accordance with the Reviewer, it cannot be excluded that patients are not representative for the whole population because they were recruited from an outpatient setting of a medical department of a university hospital (this fact had already been stated in the “Limitations” Section of the former manuscript). In contrast, it seems unlikely that there was a lack of accessing routine dental care including dental prophylaxis. Munich, Germany, is very well provided for dentists and german insurances cover most of costs.

To meet the concern of the Reviewer, the following paragraph was added to the „Medical History“ paragraph of the „Results“ Section:

“With respect to medical care, all study patricipants had provided name and address of their family doctors and family dentists and had confirmed to see them regularly.“

Accordingly, the following paragraph was incorporated in the „Medical History“ paragraph of the „Discussion“ Section and reads now:
“Due to the fact that all study participants had confirmed to attend regularly medical and dental care, it seems unlikely that periodontal findings in this study may be attributed to lack of accessing routine dental care including dental prophylaxis.”

7. Line 147 Planamesa Inc address is incorrect. There is no town in California named Anytown. The correct location for Planamesa Software is in Sunnyvale, California, USA (http://www.aboutus.org/Planamesa.com).

**Answer:**
The authors apologize. The revised manuscript reads as follows:

“Statistical analysis was performed using a commercial computer program (NeoOffice 3.1.1, Planamesa Inc., 123 Main St. Sunnyvale, California, USA and StatXact-program, version 5.0.3, Cytel Inc., Cambridge, Massachusetts, USA). Statistical significance was tested by the Chi-square test and Student’s t test. A p-value less than 0.05 was considered to indicate statistical significance.”

8. Line 160
Define conservative prosthetic dental reconstructions. I am not familiar with the term. What does it include? Operative dentistry, fixed full and partial coverage restorations?

**Answer:**
It is assumed that there might be a misunderstanding due to the little word “or” which was most probably overlooked by the Reviewer. In the former manuscript, it was stated that there was no significant difference between the two groups of patients with respect to conservative or fixed prosthetic dental reconstructions. Conservative dentistry covers reconstructive dental therapy except prosthetics (please see http://www.efcd.eu).

To prevent further misunderstanding, this paragraph reads now in the revised manuscript:
“With respect to conservative dental restorations (fillings, endodontic treatment) or fixed prosthetic dental reconstructions, there was no significant difference between the ERD and NERD patients.”

9. In regards to defining periodontal disease, there are more parameters than CAL. The authors, in my opinion, need to discuss these parameters and state why they are choosing to only use one of the criteria for defining periodontal disease. Attachment loss is representative of a chronic condition, use of PPI in this study population was of a limited duration. I do not make the implied connection of periodontal disease possibility and association with use of PPI.

Answer:
The Reviewer stated that the authors had only used one of the criteria for defining periodontal disease (CAL). Honestly speaking, this is unclear to the authors: In this study, also the Plaque Index and a modified Bleeding On Probing Index (BOP) were recorded, not only the CAL (please see the paragraph “Periodontal Parameters” of the “Material and Methods” Section. All four indices (PI, BOP, CAL, CAL $\geq$ 5 mm) were described in detail. However, severity of periodontitis was defined indeed only with the parameter “CAL $\geq$ 5 mm” which was taken from the literature [Hintao 2007]. This was also clearly pointed out in the paragraph “Periodontal Parameters”.

Unfortunately, to our knowledge, there is no similar study in the literature available on periodontitis in ERD and NERD patients. Therefore, the authors are unable to revise the manuscript with respect to the other indices according to the concern of the Reviewer.

Furthermore, the authors agree with the Reviewer that mucosal and periodontal changes are quite common and not pathognomonic and specific of GERD patients, which is in accordance with the literature cited in the manuscript [Ranjitkar 2012, Petruzzi 2012]. However, recent literature [Song 2014] has stated that GERD was independently associated with an increased incidence of chronic periodontitis, although the two phenotypes of GERD were not evaluated separately. Therefore, the purpose of this study was to determine if ERD patients show different oral soft tissue findings and periodontal conditions as compared to NERD patients, both with ongoing PPI therapy.
Therefore, the authors had the following hypothesis: As PPI medication is suspected to reduce salivary gland activity, reduction of salivary gland activity is expected to occur equally in both ERD and NERD patients. Accordingly, severity of periodontal destruction (CAL ≥ 5 mm) was also expected to be equal in both groups (but was more severe in ERD patients). Therefore, it was concluded that other parameters such as more aggressive acidic reflux must contribute to the more severe periodontal destruction in ERD patients. In addition, it was assumed that PPI medication had no adverse effect on periodontal health in ERD and NERD patients (which could have resulted from a reduced salivary gland activity). Accordingly, the authors had not stated that the more severe periodontal destruction (.CAL ≥ 5 mm) was connected to PPI medication.

We hope that this explanation might have helped to clear this misunderstanding.

10. A major flaw of this study is there is no objective assessment of the "acidic lesions". Erythema and ulceration of the oral mucosa is a very common finding with multiple confounding etiologies. How can the authors assure us that a finding of erythema or oral ulceration in a NERD or ERD patient is related to their diagnosis?

**Answer:**

Similarly to Answer 9, the authors agree with the Reviewer that mucosal changes are quite common and not pathognomonic and specific of GERD patients, which is in accordance with the literature cited in the manuscript [Ranjitkar 2012, Petruzzi 2012]. In another study, histologic examination of palatal mucosa – not of ulcers - found a greater prevalence of epithelial atrophy, deepening of epithelial crests in connective tissue and a higher prevalence of fibroblasts in 31 GERD patients compared with 14 control subjects [Silva 2001]. However, biopsies were not performed in this study, in accordance with the huge majority of studies on GERD patients. From a clinical point of view, it seems unlikely that acidic lesions in GERD Patients are caused by other acids and not by reflux acid. Due the fact that the huge majority of 85.7% - 95.2% of all study participants demonstrated a clinical score 0 (Table 2), there were only ca. 5 – 15 % of patients who had shown score 1 and 2 lesions. Again, it seems unlikely that these “few“ lesions in GERD patients may be attributable to other acidic origins.
However, to meet the concern of this Reviewer, the following paragraph was incorporated in the “Limitations” Section:

“Four, erythema and ulceration of the oral mucosa is a very common finding with multiple confounding etiologies. It can not be excluded that some lesions in this group of GERD patients are caused by other origin and not by reflux acid.”

**Reviewer #2**

The authors wish to thank this Reviewer for the comments.

1. These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential. I think this article needs figures, photographs and graphs showing their results.

*Answer:*

The authors wish to thank the Reviewer for this proposal. According to the comments of Reviewer 1, several clarifications were provided in the revised manuscript (please see answers 1 – 10).

To prevent overloading of the manuscript, photographs were not incorporated because they are textbook knowledge and it is assumed that other Reviewers might propose omission. Provision of graphs is difficult because patients were not controlled over the long term.

The authors hope that their answer is satisfactory for this Reviewer.

**Comments to the Editor**
The authors appreciate all efforts of the Reviewers. Again, to you and the Reviewers, the authors would like to express their appreciation for all of your endeavours. In its revised form, we hope you will find the manuscript suitable for publication.

Sincerely yours

Prof. Dr. Herbert Deppe