Author’s response to reviews

Title: Oral Symptoms and Oral Health-related Quality of Life of Individuals with X-linked Hypophosphatemia

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Author’s response to reviews:

Dear Professor Stamm,

We would like to thank you and the reviewers for revising our manuscript [HAFM-D-18-00092] entitled “Oral symptoms and oral health related quality of life in people with x-linked hypophosphatemia” and the constructive points discussed. The helpful comments and suggestions for improving the manuscript have been now incorporated into the revised version and manuscript changes can be tracked. In this letter, we provide a point-by-point response to each addressed comment. Therefore, we hope that the manuscript is now acceptable for publication in Head & Face Medicine.

Yours sincerely

Marcel Hanisch

Response to requests by the different reviewers

Editor Comments:

Thank you for your submission. While the outcomes are not unexpected, it is still of value publishing these findings.
Major suggestions:

Please consider adding a schematic/visual diagram outlining the pathogenesis of XLH, to supplement the text.

We included a diagram outlining the pathogenesis of x-linked hypophosphatemia as „Supplement 1“

Minor concerns:

Abstract:

“The average period elapsing between the first signs of her illness …”. Since your cohort includes both female and male patients, this should be changed

We changed the sentence to “For the combined genders, the mean period of time that elapsed between the first signs of the illness and the diagnosis was 5.52 years (range: 0–49 years)”.

(page 2, line 34-36).

“In total 77.50% described some oral symptoms”. Please list the 2-5 most common oral symptoms.

We changed the sentence to “In total, 77.50% of the participants described oral symptoms, such as tooth mineralisation defects (n=26), abscess or fistula formation (n=21), dysgnathia (n=9) and temporomandibular dysfunction (n=2)”.

(page 2, line 36-44).

Methods

Please explain how “all persons affected by the XLH in the Federal Republic of Germany from 16 years of age and older” were identified.
Please be more specific than “about” 90 individuals.

Is this data derived from German government records or from the support group?

We have substantially changed this confusing section “Participants” in the Methods section to “Anyone living in Germany, with a minimum age of 16 years old, who was affected by XLH was eligible to participate in this study. Because the questionnaires were only sent to the members of a self-help group, the range of participants was largely limited. According to the information provided by the self-help group, it included 90 members at the time of this study”.

(page 6, line 10-18).

Results

It is not sure what is meant by “Hard tissue mineralization” being a symptom. Do you mean “hypomineralization”; “defect of mineralization”, etc…?

We changed this to „tooth mineralisation defects“.

(page 7, line 65).

What is the significance of 80% having received orthodontic treatment?

The authors agree that this information is not relevant to this group of rare disease. The data was gathered because the questionnaire was developed to achieve different rare diseases. However, as this information do not provide any value result to this study, the authors decided to remove it.

Please explain “The OHIP values were statistically similar between male and female patients (p=0.944). p=0.944?

The statement was better explained as described below:
“The difference between the OHIP-14 scores of the male and female participants was not statistically significant (p=0.944)”.

(page 8, line 18-23).

Tables and Figures

Please do not use the term “milk tooth”

We changed this to „deciduous” as well in the manuscript (page 4, line 1) as in Figure 1 (page 19, line 23).

“Fig. 2. Panoramic image of a 5-year old patient with phosphate diabetes”. Do you mean with “XLH”?

We changed this to „Panoramic image of a 5-year old patient with x-linked hypophosphatemia with pronounced pulp horns”.

(page 19, line 28-30).

Please explain in the caption to all figures what the arrows point to

We included the meaning of the arrow in the caption of Figure 1 and 2.

(page 19, line 19-30).

Figure 3a (sex distribution) is not needed.

Figure 3a was removed.
Table 2. It is not clear what is meant by “satisfied with dentist”. Does it reference treatment outcomes; perceived quality of care; cost; access to care, etc… Please be more specific.

The perceived quality of care is meant. We changed this in Table 2 as well as in the manuscript.

(page 8, line 39).

Figure captions: please provide more detail. Sex of patient. Any other features evident besides the “pronounced pulp horns”

We included the gender (5-year old boy) and disease (x-linked hypophosphatemia) of the patient to the captions of Figures 1+2.

(page 19, line 19-30).

Reviewer #1:

This is a questionnaire of oral health related quality of life in people with X-linked hypophosphatemia (XLH).

The authors need to be clear about rare disease they compare the study to it. Does it have oral symptoms? The reference they depend on is written in German.

The reference which is compared (Hanisch M, Jung S, Kleinheinz J. Oral Health-Related Quality of Life in Rare Diseases with Oral Manifestations. Gesundheitswesen. 2018 Apr 13. doi: 10.1055/a-0592-7039), reports about the oral health reported quality of life in rare diseases with oral manifestations. The data were collected from Germanys first consultation hour for rare diseases with oral manifestations (page 9, line 42).

The study design section is quite incomprehensible and does not mention the required sample size, and if the authors validate the developed questionnaire.
The sample size was not specified due to the difficulties founded on trials investigating rare diseases. The questionnaire was distributed on self-help groups on which all participants (n = 90) were diagnosed with the disease, which hamper the calculation of the sample size based on the prevalence of the condition (Naing et al., 2006). The sample size was therefore considered appropriate based on previous studies investigating oral manifestations of 34 patients presenting the same disease condition (Duplan et al., 2017). Unfortunately, another limitation of the study design was the impossibility to validate the questionnaire, the reason why these details were not specified on the article. However, a paragraph describing the limitations of the study was added, as described below:

“ The main limitation of this study was that the study population was restricted to the participants of a self-help group in Germany, of which all 90 members were diagnosed with this rare condition. Thus, it is questionable whether the present findings may be extrapolated to the general population of people affected by XLH…”.

(page 11, line 50-57).

Why the author specifies ortho treatment? For example, Why endodontic therapy is not included in survey?

As cited above, the authors agree that this information is not relevant to this group of rare disease. The data was gathered because the questionnaire was developed to achieve different rare diseases. However, this information does not seem provide any value result to this study. In this sense, the statement below was removed:

“In total, 88.37% of respondents had received orthodontic treatment (n = 38). All 43 participants responded to this question.”

In the discussion, consider the limitations of the study and adjust the recommendations accordingly.

The limitations and recommendations were written as below:

“ The main limitation of this study was that the study population was restricted to the participants of a self-help group in Germany, of which all 90 members were diagnosed with this rare condition. Thus, it is questionable whether the present findings may be extrapolated to the general population of people affected by XLH. In addition, the chosen study design did not allow
for the authors’ clinical examination of the oral conditions. Further studies are required to investigate how specific oral manifestations, such as large pulp chambers and periodontal manifestations, can influence the OHRQoL of people affected by XLH”.

(page 11, line 50-65).

In discussion, How the XLH patients benefit from an early diagnosis compare to rare disease?

It could be assumed that oral manifestations, as existing in XLH, lead to an earlier diagnosis of the rare diseases. This was also ascertained in one of our other studies [Hanisch et al. 2018]. We included this in the discussion section (page 9, line 42).

What star and circle indicate in fig 4

The symbols indicate outliers of the study sample, and this was added on the figure legend as described below:

“Fig 4. Box-plot showing OHIP values (mean and interquartile range) for patients with and without oral manifestations. Symbols (star and circle) indicate outliers of the study sample.” (page 19, line 36-38).

Identify the abbreviation in table

We outlined the abbreviations in all tables and figures.

The quality of written English can be better. There are numerous grammatical issues.

We have now had the manuscript linguistically corrected by a professional agency.
Reviewer #2:

Critique From Reviewer & Recommendation and Comments for Manuscript Number HAFM-D-18-00092; Oral symptoms and oral health related quality of life in people with X-linked hypophosphatemia (XLH).

This is a very well written article, with relevance to the journal and the audience of Head and Neck Medicine. The following is a general critique of the write-up process:

1. The language limitations, and the influence of the foreign language on the paper body is very evident. Authors are encouraged to carefully review the manuscript & ensure that all the terminology adopted in this manuscript are familiar and used routinely. Past and present tense must be also corrected in a uniform way, throughout the manuscript.

We have now had the manuscript linguistically corrected by a professional agency.

2. In the abstract, lines 27 to 36, Authors referring to gender s "her" despite them having a mixed gender patient population. This needs to be corrected within the abstract as well as wherever applicable in the manuscript.

We changed the sentence to “For the combined genders, the mean period of time that elapsed between the first signs of the illness and the diagnosis was 5.52 years (range: 0–49 years)”.

(page 2, line 34-36).

3. Page 5, line 34, sentence should include bone and teeth mineralization rather than just bone.

We changed the sentence according to you recommendations (page 3, line 47).

4. Page 5, line 46; the authors need to be specific regarding what do they mean by delayed dentition, is it delayed mineralization or delayed eruption or both?
It is meant „dentitio tarda (late secondary dentition)“. We corrected this (page 3, line 63).

5. Page 5 line 51; authors specifically and simply describe poorly mineralized dentin, avoiding terminology dentin dysplasia since dentin dysplasia is a recognized syndrome separates from hypophosphatemia, despite the fact that are they are not wrong.

We now included a revised paragraph explaining the structural defects more in detail (see „6.“). (page 4, line 21-63).

6. Page 6, line 12; Authors need to explain where his higher degree of endodontic therapy?? and how is what are they describing different from routine periapical pathology related to bacterial invasion of pulp canals?

We revised this paragraph: „Odontogenic abscesses in caries-free teeth are often observed in those affected by XLH [16, 17]. In general, XLH calls for a high degree of endodontic therapy due to apical periodontitis [18]. Such apical periodontitis (and the associated endodontic treatments) can be caused by multiple alterations in the dentin and enamel. Radiographically, large pulp chambers can be found, which reduce the thickness of the dentin and enamel. Histopathologically, the dentin shows various structural abnormalities caused the lack of calcospherite confluence, resulting in large interglobular spaces and unmineralized dentin. Conversely, the enamel is regularly formed with long cracks [9]. Because the teeth are constantly exposed to masticatory forces, the altered dentin can be exposed, resulting in the bacterial contamination of the dental tissues (Figures 1 and 2) [9, 19, 20]. The increased need for endodontic treatment is correlated with the increased age of the population affected by XLH, which implies a link between attrition/abrasion and occurrence of apical periodontitis [21]. When endodontic treatment is required, the risk of reinfection increases due to the altered dentin structure and large interglobular spaces [9]. The bacterial contamination due to the dental structure alterations differs from that due to decay in such a way that, when performing endodontic treatment, there is an increased risk of further contamination due to the structural defects [9]“.

(page 4, line 21-63).
7. Page 8, lines 7-12, sentence need to be revised, meaning of what authors are conveying is ambiguous!

The following sentence “For both sexes combined, the average period elapsing between the first signs of their illness to diagnosis, was 5.52 years (range: 0 to 49 years); for female patients alone, the average period was 5.06 years (range: 0 to 32 years), while the average period for males was 6.81 years (range: 0 to 49 years). There was no statistical difference between the age during diagnosis (p=0.862), such as for the time between the first symptom and the diagnosis (p=0.957) for female and male patients.” was replaced by:

“When considering the combined genders, the mean period of time between the first signs of illness and the diagnosis was 5.52 years (range: 0–49 years). For the female participants, the elapsed time was 5.06 years (range: 0–32 years), and for the male participants, the elapsed time was 6.81 years (range: 0–49 years). However, the difference between the genders was not statistically significant (p=0.957).”

(page 7, line 39-49).

8. Page 9 line 19, what do the authors mean by"the age during diagnosis" is it age at diagnosis? and how does this account for the major difference between female and male cohorts ages?? and the noticeable older age of females participated in the study?

Thank you for your observation, the authors meant “time at diagnosis” and this error was corrected. As the questionnaire was distributed according self-help groups, the authors believe that the difference between ages according to the gender is related to the fact that female participants tend to be more representative on these groups, and they may tend to participate in advanced ages. However, this difference should not interfere on the results of this study, since the main point was the age of participants at diagnosis.

9. Page 11 line 27, All of these patients to have completed the questionnaire, they must have been examined by their dentist who would verify or exclude the presence of clinically detectable fistulous tracts, accesses associated with vital teeth etc. etc.. Why the sentence "Although the symptoms described by the participants were not clinically verified??"
This sentence is confusing and therefore we rephrased this sentence to „…not clinically verified by the authors“.

(page 9, line 52).

10. Were the current findings from paired with any other studies of similar caliber and content??

To the best of our knowledge this is the first study which examines oral health related quality of life in people with XLH. Therefore no other studies with this content are known.

11. References need to follow journal format, uniformly.

The references were adjusted according to the journal´s guidelines.

12. Table 1, the P value for patients with oral manifestations of the syndrome is omitted!

The comparison was performed between participants with and without oral manifestations, and the p-value is related with the difference between groups. The table’s format was adjusted to avoid misunderstandings.