Author’s response to reviews

Title: Minimizing risk of customized titanium mesh exposures – a retrospective analysis

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Author’s response to reviews:

Submission of manuscript
`Minimizing risk of customized titanium mesh exposures – a retrospective analysis`

Dear Prof. Mijiritsky,

On behalf of my coauthors, thank you for considering our research article ´Minimizing risk of customized titanium mesh exposures – a retrospective analysis´ for publication in your journal BMC oral health pending satisfactory revision in response to reviewer’s comments. The manuscript has been revised to address the reviewer’s comments, and a detailed point-by-point response to each reviewer/editorial point is attached. Amendments made to the manuscript are exactly described and are highlighted in yellow. We believe these changes have improved the manuscript, and reviewer’s comments are greatly appreciated.

Yours sincerely,

Dr. Amely Hartmann

Dear Editor/Reviewer,

Thank you for critically assessing our manuscript for publication in BMC oral health.

We wish to thank you for suggested improvements.
Suggestion 1:

Editor Comments:

dear authors, please revise your paper as per the reviewers' suggestions. in addition, please consider the possibility to resubmit your paper to the "digital dentistry" section, because you use here a digital method.

Response:

Thank you for this comment. We will resubmit our paper to the “digital dentistry” section.

Reviewer 2

Reviewer 2 - Suggestion 1:

Nihat Akbulut (Reviewer 2): Some grammatical fault should be revised. e.g. in "Data evaluation" section 17th line sentence that it should be considered for revising.

Response:

We apologize for this inaccuracy. We checked and double-checked the whole manuscript for any further grammatical fault. 17th line sentence in “Data evaluation” was reconsidered.

p.5, l.15-17:

Data presentation was performed by using JMP® 10.0 statistical software (SAS Institute, Cary, NC, USA). was used.
Reviewer 3 - Suggestion 1:

First, the title should indicate that this is a retrospective analysis/case series.

Response:

We corrected the title according to reviewer’s suggestion. The new title is

Title page:

Minimizing risk of customized titanium mesh exposures – a retrospective analysis

Reviewer 3 – Suggestion 2:

Abstract: Background: Please switch the first and second sentences.

Response:

We switched the first and second sentence in the Abstract: Background-section.

Title page/p.2, l.3-8:

The aim of this study was to evaluate a new protocol for customized bone augmentation in a digital workflow. Recommendations for soft tissue management associated with customized bone regeneration should be developed. The aim of this study was to evaluate a new protocol for customized bone augmentation in a digital workflow.

Reviewer 3 - Suggestion 3:

Results: Regarding the result p = 0.029, because the significance level applied was p < 0.05, this is no longer a trend.

Response:

We thank the reviewer for this comment, and we deleted this “trend”.

Title page/p.3,l.2-3:
A trend to reduce the exposure rate was found for Surgical splints were not evaluated to reduce the exposure rate (p=0.029).

Reviewer 3 - Suggestion 4:

Introduction

P 1 L 8: The sentence should end after the word "management."

Response:

The two sentences were split according to reviewer’s suggestion.

p.1,1.7-12:

Therefore, rebuilding such a complex defect also implicates a detailed focus on soft tissue management. and mMembrane and graft exposures are frequent complications associated with non-resorbable membranes [9-12].

Reviewer 3 - Suggestion 5:

M&amp;M

Study population

Please indicate the study's patient inclusion and exclusion criteria.

Response:

We specified the study’s patient inclusion and exclusion criteria.

Title page/p.2,1.11-24:

All three-dimensional grafting procedures were performed by the same trained surgeon (MS; Private Dental Practice, Filderstadt, Germany) by using a patient- specific titanium lattice structure (Yxoss CBR®, ReOss, Filderstadt, Germany).
Patients with three-dimensional bony defects were included. All three-dimensional grafting procedures had to be performed by the same trained surgeon (MS; Private Dental Practice, Filderstadt, Germany) by using a patient-specific titanium lattice structure (Yxoss CBR®, ReOss, Filderstadt, Germany). Female and male patients &gt; 18 years were included.

Exclusion criteria were mentally disabled patients, pregnant women and patients &lt; 18 years. Local exclusion criteria were horizontal or vertical bony defects. Patients with three-dimensional defects treated with other bone augmentation procedures like distraction osteogenesis, block graft or onlay-technique were excluded as well. In general, patients with systemic or local diseases influencing the surgery were excluded before enrolment. Malignancies had to be excluded as well.

Reviewer 3 - Suggestion 6:

P 3 L 17 - 21: This information should not be part of the study population section. The outcome assessment section (primary and secondary) is missing. Please consider including this information (L 17-21) in the previously indicated missing section.

Response:

The reviewer is right; we added this section and included the information of L17-21.

p.4, l.1-19:

Outcome assessment

The primary aim of the study was to The population should be describe the population concerning the grafting success, a possible exposure rate and methods to reduce this exposure rate (Vacuum form splint, A-PRF® and flap design). Exposures of the titanium mesh were classified concerning their size. “A” was a punctual exposure, “B” an exposure like one premolar size and “C” a complete one whereas “D” was no exposure [24]. Outcomes and possible healing difficulties were assessed one week after surgery and during follow-up each month. Patients were instructed to contact the surgeon if any disturbances occurred. Success of the augmentation procedure was defined as the opportunity to place the implants in the planned position and achievement of an adequate primary stability until the re-entry and finalize with the individual prosthetic supraconstruction. Failure was defined as complete loss of the graft.
Secondary aim of the study was to assess possible risk factors (defect regions, defect and mesh sizes, smoking, tissue phenotype (thin and fragile phenotype, thick phenotype [25], diabetes) for developing an exposure. Mesh size was defined according to the missing teeth.

The exposures of the titanium mesh were classified concerning their size. “A” was a punctual exposure, “B” an exposure like one premolar size and “C” a complete one whereas “D” was no exposure.

Reviewer 3 - Suggestion 7:

No information is provided on the follow-up period.

Response:

We thank the reviewer for this comment. We do not know what the reviewer means exactly. This study reveals the possible healing difficulties during the healing process, not the prosthetic outcome afterwards or the bone level after e.g. 5 years. Our intention was to describe the time after insertion of the titanium lattice structure and the removal / implant placement. On page 6 timeline is described as followed:

p.6, l.4-9:

The Re-opening and removal of the titanium mesh was after approximately 4-8 months depending on size of the defect. Implant placement subgroups (Camlog Screw Line®, Camlog, Wimsheim, Germany) were well-balanced (implantation performed either simultaneously with mesh insertion (44.1%) or after a healing period of 4-8 months combined with the removal of the mesh (44.1%)).

Reviewer 3 - Suggestion 8:

At what time points the outcomes were assessed?

Response:

We apologize for this inaccuracy. This information was added in the outcome assessment section.

p.4, l.7-9:
Outcomes and possible healing difficulties were assessed one week after surgery and during follow-up each month. Patients were instructed to contact the surgeon if any disturbances occurred.

Reviewer 3 - Suggestion 9:

P 4 L 11-12: Here, please indicate what incisions were performed. The authors only indicated this in the results section.

Response:

The reviewer is right; we indicated the incisions performed during the surgery.

p.5, l.6-11:

Flap design was performed as appropriate in each case. The opening incision was carried out in accordance with the defect size and location of the neighboring anatomical structures of the region. Flap design was performed as appropriate in each case (full flap preparation, full flap and periosteal incision, periosteal incision, poncho/split flap or rotation flap). In some cases, a careful periosteal incision was performed.

Reviewer 3 - Suggestion 10:

P 4 L 19: Please indicate how many patients received autogenous bone grafts from the iliac crest and how many received grafts from intraoral sites.

Response:

The reviewer is right; we added this information.

p.5, l.15-17:

Autologous bone was harvested from the conventional intraoral donor sites (n=59, external oblique line (n=50) and operation site (n=9)) or from the iliac crest (n=8). In one patient, only bone substitute (Bio Oss®) was used.
Reviewer 3 - Suggestion 11:

Please also indicate where intraorally autogenous bone was taken.

Response:

According to reviewer’s suggestion, we added this information.

p.5, l.15-17:

Autologous bone was harvested from the conventional intraoral donor sites (n=59, external oblique line (n=50) and operation site (n=9)) or from the iliac crest (n=8). In one patient, only bone substitute (Bio Oss®) was used.

Reviewer 3 - Suggestion 12:

Were defect size and width assessed?

Response:

Defect width was described according to the missing teeth. Defect size was documented as three-dimensional and complex. We do not know the origin of any tooth loss in any case because of the referral character of the private practice which is specialised in bone augmentation procedures. We also added the missing information in the study’s limitation section (Discussion)

p.4, l.14-17:

Secondary aim of the study was to assess possible risk factors (defect regions, defect and mesh sizes, smoking, tissue phenotype (thin and fragile phenotype, thick phenotype [25]), diabetes) for developing an exposure. Mesh size was defined according to the missing teeth.

p.10, l.24-p.11, l.9:

In general, there are two major limitations in this study that could be addressed in future research. First, the study focused on augmentation procedures in three-dimensional defects. These defects were described by the surgeon. A more objective way to describe them clinically and radiographically by CBCT would be in mm³. This shortcoming is due to the retrospective character of the study and the next prospective study will define the three-dimensional defects in mm³ and according to a new classification.
Second, grafting outcome should be defined in mm3 after another CBCT and matching the two radiographs. According to our best knowledge, and lots of own tests, matching will not work exactly because of X-ray scattered radiation of the titanium lattice structure. Future research should aim to develop a new software excluding these effects.

Reviewer 3 - Suggestion 13:

P 5 L 7-10: This information should be moved one paragraph above.

Response:

We thank the reviewer for this comment. The information of P5 L7-10 was moved as suggested by the reviewer.

p.5, l.25-p.6,l.2:

Vacuum form splints were adjusted to enhance soft tissue healing in n=22 (figure 7). Patients received instructions concerning a proper oral hygiene. They had to avoid brushing at the grafting area and to wear removable dentures. All patients underwent an oral antibiotic therapy (Amoxicillin® 1000 mg 1-1-1 or Clindamycin® 600 mg 1-1-1) for 5-7 days starting at time of the surgery.

Reviewer 3 - Suggestion 14:

Data evaluation

Again, what were the primary and secondary outcomes, and according to which statistical tests were they assessed? This should be clearly indicated.

Response:

We clearly indicated the statistical tests used for primary and secondary outcome.
Statistical assessment was done using IBM SPSS® Statistics version 22.0 for Windows. T-test and Mann-Whitney-U-Test, Chi-square- or Fisher’s Exact test were used as appropriate. Level of significance was set to p<0.05. Data presentation was performed by using JMP® 10.0 statistical software (SAS Institute, Cary, NC, USA). was used. Grafting success, a possible exposure rate and methods to reduce this exposure rate (Vacuum form splint, A-PRF® and flap design) were defined as parameters showing the primary outcomes. For secondary outcome parameters possible risk factors (defect regions, defect and mesh sizes, smoking, tissue phenotype (thin and fragile phenotype, thick phenotype [25]), diabetes) for developing an exposure were defined. Statistical analyses were performed using Chi-Quadrat-Test and Fisher’s Exact-Test as appropriate for qualitative parameters, T-Test or Mann-Whitney-U-Test for quantitative parameters.

Reviewer 3 - Suggestion 15:

Results

How many cases failed?

Response:

Although exposures – and even severe ones - occurred, no cases failed. Success was defined as the possibility to place the planned implants. We added this information to the text.

No case failed. In total, 98 implants could be placed as planned.

A therapy according to the planned treatment protocol was possible in all the cases. No failure occurred.

Reviewer 3 - Suggestion 16:

How was failure defined?
Response:

We specified failure and success as mentioned above.

p.4, l.9-13:

Success of the augmentation procedure was defined as the opportunity to place the implants in the planned position and achievement of an adequate primary stability until the re-entry and to finalize with the individual prosthetic supraconstruction. Failure was defined as complete loss of the graft.

Reviewer 3 - Suggestion 17:

Discussion

P 8 L 3: Please specify these benefits.

Response:

We specified these benefits according to reviewer’s suggestion.

p.10, l.2-6:

This study shows that treatment with customized titanium meshes offers the opportunity to provide high-quality work in large three-dimensional bony defects. The benefits like precise fit, shorter time of surgery, predictable outcome and good acceptance of the surgical procedure were already described in recent literature [24,27].

Reviewer 3 - Suggestion 18:

P 4 L 15: It is easier to write from 14.8% to 59% and add all references at the end of the sentence.

Response:

We think it is P8 L15? The reviewer is right; we added all references at the end of the sentence.
In customized bone regeneration, Sagheb et al. reported 33% exposures[16]. Other studies range from uneventful healing with no [31-33] and from 14.8 % to 59 % [28, 29, 34-37] of membrane exposure.

Reviewer 3 - Suggestion 19:

P 4 Ö 17: Regarding defect size and severity of exposure, please explain for the readers: do you mean that the bigger the defect is, the more severe the exposure?

Response:

We think it is P8, L17?

We are not sure what the reviewer means? This sentence refers to the exposure classification. We specified this and added a reference. We already mentioned that there is no relationship between size of the defect/mesh size and development of exposures?

p.10, l.17-21:

These different results may be caused by a lack in literature to precisely describe the exposures according to size. By distinguishing in severity of the exposure[24], we were able to show that most of them are only slight and only punctual. Another point is the various titanium mesh techniques, various surgical protocols and skills.

Reviewer 3 - Suggestion 20:

P 4 Ö 23: If this does not necessarily lead to failure, how many cases failed?

Response:

The reviewer is right; we clearly defined the “success” and “failure” and interpreted these results. No case failed. We also added this information to the M and M section and Results section. We think it is P8, L23?

p.4, l.9-13:

Success of the augmentation procedure was defined as the opportunity to place the implants in the planned position, achieve an adequate primary stability until the re-entry and finalize with the individual prosthetic supraconstruction. Failure was defined as complete loss of the graft.
No case failed. In total, 98 implants could be placed as planned.

A therapy according to the planned treatment protocol was possible in all the cases. No failure occurred.

Reviewer 3 - Suggestion 21:
How was failure defined? To make such a statement, you must clearly indicate the above.

Response:
We rewrote this section and indicated “Failure” and “Success” in the “Outcome assessment” section.

Success of the augmentation procedure was defined as the opportunity to place the implants in the planned position and achievement of an adequate primary stability until the re-entry and to finalize with the with the individual prosthetic supraconstruction. Failure was defined as complete loss of the graft.

Within the limitations of this study being retrospective without a control group it was possible to show that an exposure does not necessarily lead to grafting failure as defined above. A prospective study should compare different methods for bone augmentation in similar defect sizes in comparable study groups to present a superiority of one method.

Reviewer 3 - Suggestion 22:
However, it might be associated with the limited number of patient subgroups in this study.
Response:

We added this information to the text. Shortcomings of the study were also discussed in a separate section as suggested by the reviewer.

p.11, l.20-26:

The results may be due to a proper informed consent of the patients directly and their acceptance to reduce/avoid smoking after surgery. Additionally, the results may also be associated with the limited number of patient subgroups in this study.

The same can be applied for the findings concerning Diabetes. Diabetes as another risk factor in wound healing processes [39] was not proven to have an influence on developing exposures.

p.11, l.10-14:

Within the limitations of this study being retrospective without a control group it was possible to show that an exposure does not necessarily lead to grafting failure as defined above. A prospective study should compare different methods for bone augmentation in similar defect sizes in comparable study groups to present a superiority of one method.

Reviewer 3 - Suggestion 23:

The same goes for P9 L 8 - 12.

Response:

We added this information to the text. Shortcomings of the study were also discussed in a separate section as suggested by the reviewer.

p.11, l.20-p.12, l.2:

The results may be due to a proper informed consent of the patients directly and their acceptance to reduce/avoid smoking after surgery. Additionally, the results may also be associated with the limited number of patient subgroups in this study.

The same can be applied for the findings concerning Diabetes. Diabetes as another risk factor in wound healing processes [39] was not proven to have an influence on developing exposures. It is tempting to speculate that all the included patients suffering from diabetes are well-controlled type 2 diabetic patients and Erdogan et al. [40] have found GBR technique in such cases being a proper treatment opportunity.
Reviewer 3 - Suggestion 24:
P 9 L 13: Here, you should write 'One might' because a letter is missing."

Response:
We apologize for this inaccuracy and changed it according to reviewer´s suggestion.

p.12, l.3-4:

One might assume that a thin tissue phenotype [25, 41] is much more difficult to handle, to receive aesthetic outcomes and that it might lead to an earlier mucosal rupture.

Reviewer 3 - Suggestion 25:
P9 L 13 - How were the thin and thick phenotypes defined? Please add a reference.

Response:
We apologize for this inaccuracy. We defined the phenotypes and added a reference.

p.12, l.3-13:

On might assume that a thin tissue phenotype [25,41] is much more difficult to handle than a thick one; also, to receive aesthetic outcomes and that it might lead to an earlier mucosal rupture. This is in accordance with previous studies [42]. They describe thick gingival phenotypes associated with additional blood support during wound healing because of the missing periodontal ligament support in implant therapies. These findings are contrary to the results at hand. A possible reason for this may be in the patient group itself. Large three-dimensional defects like described in this study, are the result of numerous preceding surgeries like teeth extraction, inflammation processes or others. According to authors opinion, scar tissue as a result of these former interventions – in thin and thick tissue phenotype – might be the real reason for developing an exposure.

Reviewer 3 - Suggestion 26:

In addition, an explanation should be added to the M&M section.
Response:

We added this information to the M and M section.

p.4, l.14-17:

Secondary aim of the study was to assess possible risk factors (defect regions, defect and mesh sizes, smoking, tissue phenotype (thin and fragile phenotype, thick phenotype[25]), diabetes) for developing an exposure. Mesh size was defined according to the missing teeth.

Reviewer 3 - Suggestion 27:

P9 L 15: Regarding reference 27, how did this author define thin and thick phenotypes? Different definitions lead to different results, so please clarify this.

Response:

We thank the reviewer for this comment. We changed this section to clarify the objective.

p.12, l.3-13:

On might assume that a thin tissue phenotype [25,41] is much more difficult to handle than a thick one; also, to receive aesthetic outcomes and that it might lead to an earlier mucosal rupture. This is in accordance with previous studies [42]. They describe thick gingival phenotypes associated with additional blood support during wound healing because of the missing periodontal ligament support in implant therapies. These findings are contrary to the results at hand. A possible reason for this may be in the patient group itself. Large three-dimensional defects like described in this study, are the result of numerous preceding surgeries like teeth extraction, inflammation processes or others. According to authors opinion, scar tissue as a result of these former interventions – in thin and thick tissue phenotype – might be the real reason for developing an exposure.

Reviewer 3 - Suggestion 28:

P 9 L 22 - P 10 L 9: Please present the discussion on gender in a more readable manner.

Response:

We fundamentally changed the discussion concerning this issue.
In this study, neither age nor periodontitis were evaluated to influence the exposure rate. These findings are according to Sagheb et al. [16]. In their study, they evaluated no relationship between gender and the risk to develop an exposure. This goes along with other studies [43] but is not in accordance with findings of this study where we were able to find a significant relationship between male and the development of exposures. On the one hand one might assume that especially steroid hormones in female patients appear capable of influencing the normal bacterial flora and the subgingival ecology [44,45]. Consecutively, healing difficulties may arise. On the other hand, male patients were already described to suffer from an increased infection rate after implant placement by Figueiredo et al. [46]. This is in accordance with Kim et al. [44] who evaluated male gender to have the highest risk of wound dehiscence in guided bone regeneration. These results are in line with our findings. The same observation was also described in dermatology. Dao et al. [47] reported about gender differences in skin regeneration. They described modified immunological processes in elderly men caused by an increasing testosterone level. Male-specific instructions on postoperative care may help to overcome these healing difficulties. Further gender-specific studies in intraoral healing processes are needed.

Reviewer 3 - Suggestion 29:

P 11 L 6: At the end of the sentence, please add a reference.

Response:

At the end of the sentence, we added a reference.

PRF as a biodegradable scaffold consisting of stem cells, fibrin, platelets and leucocytes boosts microvascularization and epithelial cell migration [54,55].

Reviewer 3 - Suggestion 30:

P 11 L 8: At the end of the sentence, please add a reference.

Response:

We thank the reviewer for this comment, we added the reference but we also refer to this reference at the end of the next sentence.
In a recent systematic review, there was limited evidence on the effects of PRGF in intraoral bone grafting procedures [54]. They concluded the need for further studies with special emphasis on the standardized surgical procedures [54].

Reviewer 3 - Suggestion 31:
The study’s limitations must be discussed.

Response:
The reviewer is right; we added a section discussing study’s limitations.

Sumida et al. evaluated less exposure rates for customized meshes compared to the conventional titanium mesh technique [17]. Evaluating the grafting protocol without a control group is a shortcoming of this study due to its retrospective character. In general, there are two major limitations in this study that could be addressed in future research. First, the study focused on augmentation procedures in three-dimensional defects. These defects were described by the surgeon. A more objective way to describe them clinically and radiographically by CBCT would be in mm³. This shortcoming is due to the retrospective character of the study and the next prospective study will define the three-dimensional defects in mm³ and according to a new classification.

Second, grafting outcome should be defined in mm³ after another CBCT and matching the two radiographs. According to our best knowledge, and lots of own tests, matching will not work exactly because of X-ray scattered radiation of the titanium lattice structure. Future research should aim to develop a new software excluding these effects.

Within the limitations of this study being retrospective without a control group it was possible to show that an exposure does not necessarily lead to grafting failure. A prospective study should compare different methods for bone augmentation in similar defect sizes in comparable study groups to present a superiority of one method.
Reviewer 3 - Suggestion 32:

Conclusions:

P 12 L 4: The authors claim that this does not affect the outcome. Firstly, what was that outcome? The conclusions must be based only on the findings.

Response:

The reviewer is right. We defined our outcome / treatment success in “Outcome assessment” – M and M section. Then rewrote the “Conclusion” section.

p.15, l.2-11:

In complex bone reconstruction, the new surgical protocol in customized bone regeneration was proven to be a promising technique.

Interpreting the primary outcome of this study, exposures are proven to be complications that did not affect the defined outcome and success of the grafting procedure. To improve soft tissue healing, especially A®- PRF should be recommended. A tension-free wound closure seems to be more important than a specific flap design. There were no special potential risk factors associated with this protocol. Concerning the secondary aim of the study, future prospective research should aim to evaluate the gender specific risk of developing exposures and in general for developing healing difficulties in augmentation procedures.

Reviewer 3 - Suggestion 33:

The authors found a significant association between gender and exposure, so how can you make the statement in P 12 L 7?

Response:

We thank the reviewer for this comment and apologize for this inaccuracy. We changed this statement according to your suggestion.

p.15, l.8-11:

There were no special potential risk factors associated with this protocol. Concerning the secondary aim of the study, future prospective research should aim to evaluate the gender specific risk of developing exposures and in general for developing healing difficulties in augmentation procedures.