

Peer Review File

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Round 1

Reviewer A

This systematic review aimed to summarize the major proteins and peptides utilized to promote the success of dental implants. The topic is of interest and if the review is properly organized will be worth publishing. However, this manuscript has some concerns and comments should be addressed to strengthen the manuscript.

1. In the aim of the study, medical implants were also included? Please clarify and revise according to the whole manuscript.

Reply 1: Thank you very much for taking the time to provide feedback on this manuscript. Yes, medical implants were included in the study. The inclusion of medical implants were stated in line 114 and line 129-130.

Changes in text: “including those belonging to both medical and dental implants” added in Line 129-130.

2. Although PRISMA guideline was used, some methodology was not very solid. The checklists were not consistent and reported section/paragraph was not specified for many items.

Reply 2: Yes we left a few of the PRISMA checklist categories unanswered as some of the categories did not relate to our research study design. (e.g synthesis methods, certainty of evidence, etc). It has been recommended that this work be published as a narrative review rather than a systematic review, therefore the PRISMA checklist will not apply. The methodology of this review will be summarized using a table containing the search strategy summary according to the FOMM website rather than the PRISMA guidelines.

Changes in text: A search strategy summary table was created according to the FOMM guidelines for narrative reviews. **Write what table number it is.**

3. The table with included studies were poorly designed. At least the study design should be listed and categories into different level. Especially it does not support the synthesis of the results should be further evaluated. Eg. Quantitative results and analysis of different molecules, despite if it is preclinical.

Reply 3: Thank you for your comments. Would you be able to elaborate a bit further on this comment? From what we understood, you are saying that the study design of these

papers should be included (i.e in vivo/in vitro, molecular techniques, specific procedures, etc) and any studies similar in design should be categorized in the table accordingly? Also, what is meant by “studies not supporting the synthesis of the results should be evaluated”? We mentioned in the manuscript that certain studies did not find any differences, would you like us to elaborate on this further in the manuscript? We also did not understand the last sentence “e.g quantitative results and analysis of different molecules, despite if its preclinical.” What is meant by this?

4. All the results should also be discussed in terms of clinical significance and if such technology and advancement could help to resolve any clinical problem?

Reply 4: The molecules that we identified in our results were summarized by their mechanism of action, what is known in the literature and, if relevant, potential future perspectives if the molecule has controversial findings in the literature (i.e growth hormone, BMP-9). This manuscript summarizes the molecules and categorizes them accordingly, and we felt that it was more important to only discuss future implications if the molecule is controversial, or to discuss future implications of the molecules in a very broad sense since many of the molecules share many similarities.

5. The result section seems like a narrative review and not related to the extracted data for the table as a systematic review. Most of the content should belong to the discussion section.

Reply 5: The title of this review will be changed to a narrative review. Assuming this is now a narrative review, how does that change your view on the table and results section? Would the table and results section need revision?

Changes: changes pending response from reviewers.

6. There should be discussion on how those molecules were coated on the implants. Challenges and future perspectives....

Changes: A separate paragraph was dedicated to mechanisms of implant coatings in the beginning of the main text.

7. Figure 1 should at least reflects and highlights the molecules in this review.....

Changes: Caption of figure 1 will be modified to highlight molecules in review.

Reviewer B

In relation to the paper mentioned above, it is far away to accomplish the standards of a formal systematic review. Basically, it does not follow the minimum requirements for a systematic review

scientific manuscript. For all mentioning above, the unic option to recommend this article for publication, is to change to “narrative review”, but I encourage the authors to enhance the quality of this research, and indeed, the final manuscript. Even though, I would like to highline some points to help the authors to improve the research and the future incoming article:

1. Firstly, I would change the title to a narrative review instead that a systematic review. In this regard, authors can collect and update the most important information regarding the topic, but firstly defining very well the aims, primary and secondary, and the methodology to be employed.

Reply 1: Thank you very much for reading our manuscript and providing feedback. Yes, the title will be changed to a narrative review and primary/secondary outcomes along with an updated methodology fitting to a narrative review will be employed.

Changes: title updated to narrative review, methodology updated to fit narrative review with inclusion of narrative review table taken from FOMM website.

2. Extent the introduction, analyzing all the concepts involved, the state of the art of the issue, the current pros and contras of the topic, the inconvenient and potential benefits, as well as the potential future expectations.

Reply 2: the introduction was extended as recommended. We believe relevant concepts are analyzed in the introduction. The state of the art of the issue in our study is that a comprehensive review of the major proteins/peptides used for implant surgery is lacking.

Changes: Changes were highlighted in red and included in the study were an update on the state of the art of the issue, potential future expectations and benefits.

3. Materials and methods are very general and short. It is highly recommended to highline the inclusion criteria referring to an objective criterion and clarify the exclusion criteria. In addition, it is highly recommended to describe the type of the studies included and excluded.

Reply 3: Materials and methods were updated to be of a narrative review. The types of studies in the inclusion and exclusion criteria were defined in the methodology section. We believe the included and excluded studies were described in a broad enough sense to not overload the reader with information.

4. I would recommend including in the objectives criteria, probably as a secondary objective, the description of the bioactive proteins and peptides. In this line, the description of those can be included in the results as it is at this moment.

Reply 4: Our objectives stated that we aim to review and summarize bioactive proteins and

peptides. This can be found in the introduction.

5. Results must be more concise and stricter to the point. Non relevant information must be removed from this section and think to include it in the introduction or discussion section.

Reply 5: results section eliminated now that the manuscript will be submitted as a narrative review. The manuscript will now take the approach of describing the molecules we reviewed and providing the evidence from the literature and giving a more critical evaluation of the molecules in the discussion section.

Changes: Results section removed from manuscript and is now represented in the “main body” of this narrative review.

7. Conclusions need to be completely reformed. No general information regarding the entire study must be mentioned, neither the aim nor methodology.

Reply 7: The beginning part of the conclusion was removed and now only provides the main ending points and does not contain the aim or methodology.

Changes: Beginning of conclusion removed.

8. Lastly bibliography must be corrected to improve homogeneity along all the references. Include year, volume, and page number in all the references.

Reply 8: No reply

Changes: Bibliography updated using Zotero reference manager to include year, volume, and page number in all references.

Reviewer C

This paper is a significant contribution to the literature regarding osseointegration of dental and orthopedic literature. There is much information included to direct further investigation into osseointegration. Several comments however: I would have preferred to see the perimplant group as a separate group and integrated with clinical factors to perhaps be more useful for clinicians. In your flow diagram, well done, you listed "biodynamics" as an inclusion factor. It would have been helpful for the authors to define their understanding of this criterion. Finally while you do provide a rationale for focusing on proteins and peptides, you have raised an interesting issue and perhaps a recommendation regarding this point could have been included in the discussion or conclusions

Reply: Thank you very much for your comments and reviewing. I agree with your preference of wanting to see a peri-implant group as a separate group for a more clinical approach. We did give mention to studies that were *in vivo* (canine, monkeys models, etc) but did not create a separate

group as the purpose of this review was to summarize the major proteins and peptides that have shown promising results in the literature, regardless of the study design, as long as it fit our inclusion criteria. The issue with this topic, which is elaborated further in the discussion and conclusion, is that there are little, if any, studies on this topic in humans (at the time of this study being conducted we could not find any studies in humans). Therefore, it would be difficult to integrate clinical factors into this manuscript as there is very little information in the literature that describes using these proteins/peptides in a clinical setting. Regarding the inclusion criteria and “biodynamics” as an inclusion criteria, because this review will be changed to a narrative review, the use of the PRISMA flow chart will longer be used. For the last point you mention, what sort of recommendation are you referring to? Would you elaborate a little further on this? Thank you.

Round 2

Review comments

This is a thorough review of much of the literature available regarding available proteins that can positively modulate integration of dental implants within the skeleton. This review has cited mechanisms and remarks from the literature regarding efficacy or lack of these proteins. While the authors propose that this review is directed to clinicians I would respectfully suggest that while the information is useful for the clinician, if this is the aim of the proposal, a more creative Discussion and Conclusion for proposed studies or applications of the information within the paper would be needed.

Reply 1: Thank you very much for your thorough review of our paper and your recommendations. In response to your comments “While the authors propose that this review is directed to clinicians I would respectfully suggest that while the information is useful for the clinician, if this is the aim of the proposal, a more creative Discussion and Conclusion for proposed studies or applications of the information within the paper would be needed,” we have made changes in red in the discussion section to further discuss our findings and its relation to clinical practice. We have also included more regarding future prospective and what is needed for advancement of this topic.

Changes in text: Changes made in red in discussion section