Peer Review File

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Reviewer A

This paper is a literature review on improving the properties of titanium alloys in biomedical engineering applications. It presents the most important problems associated with the use of titanium alloys for endoprosthesis components, as well as solutions that can improve the properties on their use in medicine. The purpose of undertaking the topic by the authors of this manuscript is most justified because of the great popularity of titanium alloys in biomedical applications, which makes these materials competitive with other metals and their alloys. However, the paper requires minor modifications to be made before publication in the Annals of Translational Medicine.

1. Line 38-44: The most important problems associated with the use of titanium and its alloys for implants are presented. However, it is worth noting that problems such as the osteogenic induction ability or high Young's modulus of titanium usually apply to solid materials produced by conventional methods.

Reply 1: The details were added as your demanded.

Changes in the text: Firstly, for the conventional titanium alloys, the osteogenic induction ability is weak, which may lead to the formation of fibrous connective tissue film on the bone-metal contact surface, affecting bone regeneration and integration.

2. Chapter 2: Alloy composition change. This chapter describes modifications in the chemical composition of titanium alloy. It would be useful to describe in more detail the effects of alloying additives on the properties of the titanium alloy, especially those shown in Figure 1. Alternatively, add those elements that appear in the text but are not shown in Figure 1.

Reply 2: Details of studies cited were added into the paragraph and the Figure 1 were modified as your advised.

Changes in the text: New sentence was added: Kopova et al. added small amount of Fe (0-2 wt.%) and Si (0-1 wt.%) to Ti-35Nb-7Zr-6Ta in order to regulating the Young's modulus and biological properties, thus developing a novel β type titanium alloy (Ti-35Nb-7Zr-6Ta-2Fe-0.5Si)[10].

Changes in the figure: Element Ni was replaced by Fe.

3. Chapter 2 appears twice: Alloy composition change and Surface and 3D structure transformation.

Reply 3: Thank you for pointing out this silly mistake for us. The sequence number have been corrected.

Changes in the text: The sequence numbers have been corrected.

4. The Chapter: Surface and 3D structure transformation presents the influence of the titanium implant surface on the possibility of better bone tissue overgrowth. The use of porous structures produced by incremental methods such as SLM or EMB is also mentioned. It is worth to complement the paper with the types of structures that can be used in the construction of endoprostheses. Currently, there are many researches which describe the influence of structure application on obtaining optimal properties of titanium alloys. Some of them are presented in the following publications

o Attar, H.; Löber, L.; Funk, A.; Calin, M.; Zhang, L.C.; Prashanth, K.G.; Scudino, S.; Zhang, Y.S.; Eckert, J. Mechanical behavior of porous commercially pure Ti and Ti–TiB composite materials manufactured by selective laser melting. Materials Science and Engineering: A 2015, 625, 350–356.

o Hedayati, R.; Ahmadia, S.M.; Lietaertc, K.; Pourana, B.; Lia, Y.; Weinansa, H.; Ranse, C.D.; Zadpoora, A.A. Isolated and modulated effects of topology and material type on the mechanical properties of additively manufactured porous biomaterials. Journal of Mechanical Behavior of Biomedical Materials 2018, 79, 254–263.

o Falkowska, A.; Seweryn, A.; Skrodzki, M. Strength properties of a porous titanium alloy Ti6Al4V with diamond structure obtained by Laser Power Bed Fusion (LPBF). Materials 2020, 13, 5138.

Reply 4: The recommended articles were carefully reading. And the contents were summarized in the text part. However, we think that the data of the second research were mostly processed on Co-Cr alloy, which could be slightly unsuitable for this review.

Changes in the text: Similarly, H. Attar et al. produced Ti and Ti-TiB alloy porous structures with different porosity levels. Then the properties test proved that 37% porous group showed elastic moduli close to that of human bone(42).

R. Hedayati et al. studied isolated and modulated effects of topological design and material type on the mechanical properties. Their result proved that the topological modification could significantly influent the properties of porous more than the material type(44).

Reviewer B

The title should be reconsidered.

The authors comment the issues with Ti alloy. Commenting on osteoinduction for Ti alloy is not relevant. The modulus is also something that many would look favourable on with respect to Ti alloys. The authors need to reconsider the direction and motivation for this work.

Reply 1: We think that there was a misunderstanding because of the words we used. The main idea of this article is trying to summarize and classify the methods that improve properties of Ti-based scaffold in bone tissue engineering. In our opinion,the physical properties and osteoinduction ability are both important applicating in bone void fillers manufacturing.

Changes in the text: Title is changed as your advice. Sorry we don't know if we need to change the title in our response letter.

L25-31 – This paragraph has sweeping statements that the literature does not support. If the purpose to provide a review of Ti alloy that is great. The authors do not need to write something to support this review as it is worthwhile.

Reply 2: Sorry for my poor English, we don't understand what you mean. We believe maybe you mean adding more citations?

Changes in the text: More citations were added into the reference.

L37 – Ti alloy is not artificial bone. The use of terminology should be correct throughout the paper.

Reply 3: We may have misused the description. What we intended is "a material for filling bone defect" thus the wording had been reconsidered as "artificial bone defect fillers".

Changes in the text: In the healthcare industry, titanium is non-toxic, biocompatible and corrosion resistant, making it a common material for the manufacture of artificial bone defect fillers and internal fixation screw system

L32-48 – The lack of citations in a review paper needs to be addressed. The authors have picked statements about Ti alloy that can be supported or refuted depending on the application.

Reply 4: The citations were added as you command.

Changes in the text: More citations were added into the reference.

The literature review does not provide an synthesis of the data but rather restates what is present in the papers.

The authors could consider what are the true shortcomings of Ti alloy in medicine and how improvements have been made? Ti and its alloys are successful implants worldwide.

Reply 5: Thanks for you comments. The discussion part has been revised.

Changes in the text: Discussion part.

Reviewer C

It is really insufficient that different kinds of surface modification are only divided into 4 types of titanium alloys in bone tissue engineering. More types and details can increase the readability for readers.

Reply 1: Thank you for pointing out the inadequacies of our article. More articles were referred and more details were added.

Changes in the text: The changes for more details are highlighted in red.

Reviewer D

The content of the paper is interesting, but insufficient for publication. The document also contains many misunderstandings that compromise the readability and the scientific soundness.

Many many many sentences in this document make no sense in English. Just one example: "the low strength of pure titanium in the human body caused by metal fatigue, by adding other metal or nonmetal elements to make up for the shortcomings became a popular direction in the research of material science"

Reply 1: We have modified our text as advised

Changes in the text: In the coming decade, the researchers found that the high young's modulus of pure titanium could result in the shade with bone stress and leaded to bone around implant dissolved, aseptic necrosis and fiber coated formation cause prosthesis loosening. And in the environment of body fluid, metal fatigue happened due to the low

strength of pure titanium. Adding other metal or nonmetal elements to make up for these shortcomings became a popular direction in the research of material science

Some of the biggest mistakes I could find:

Titanium is not used to produce artificial bone. Artificial bone refers to ceramic and polymer materials that mimick bone structures and are used as bone grafts.

Reply 2: We have modified our text as advised

Changes in the text: artificial bone defect fillers

Titanium can't cause "severe bone wear" around the prosthesis "because of the elastic modulus". It causes bone resorption. Wear is a specific surface fatigue process.

Reply 3: The words were revised as advised

Changes in the text: a degree of bone resorption

If the authors want to speak about the biological reactions caused by titanium wear debris in their review, they better bring scientific literature to support their statements.

Reply 4: More citations were added as advised

Changes in the text: More citations were added as advised

The authors seem to ignore that the specifications for Ti-6Al-4V and those for aerospace-grade alloys were different.

Reply 5: Sorry about our wrong predictions. We use these descriptions in order to describing the history of the development of the technology. To avoid misunderstanding, relevant words were deleted.

Changes in the text: Relevant words were deleted.

The number of alloys cited by the authors is just the tip of the iceberg. There are so many other interesting Ti-based biomedical alloys that were not mentioned in this review.

Reply 6: Sorry for our ignorance. It is so hard to cover all research progress. We try to add more related studies to increase readability.

Changes in the text: The changes for more details are highlighted in red.

The authors speak about Nb alloys and beta alloys as technological advancements, but both did not find a real industrial application so far, so they cannot be considered a real innovation. The reasons should also be stated in this review.

Reply 7: The advised content was added.

Changes in the text: However, the complexity of manufacturing process and high production price limit its mass production and clinical application. More cost-efficient and convenient production methods need to be explored.

Authors discuss only Vanadium toxicity, but Aluminum toxicity has also been one of the major concerns about Ti-6Al-4V.

Reply 8: Thank for your advice. The missing part was added.

Changes in the text: First, niobium (Nb) becomes a substitute metal element of vanadium (V) and aluminium (Al) in many studies due to its lower inherently cytotoxicity (11-15)

The discussion about titanium alloys microstructure doesn't really go into the details of the different structures. Ti-6Al-4V can also form α' martensite, for example. Most of the microstructural properties of these alloys are strongly related to the thermal treatments.

Reply 9: Related studies were summarized and added into the suitable place.

Changes in the text: Traditionally, effect of thermal effect on alloy phase had been researched for decades. Malinov, S et al. (19) found that the alloy phase was changing from α to β in a under-control temperature and proper chemical environment.

PEO is basically a coating technology, it doesn't produce different microstructures, it produces titanium oxide and should be discussed in a different chapter.

Reply 10: Thanks for your criticism. We cite it here wanted to emphasized the importance of research into relevant methodologies. Details were added to avoid misunderstanding.

Changes in the text: Due to the different element composition of three types of titanium alloy, their manufacturing as well as casting processes are also very different. It is important to study the treatment mechanism and method of β type titanium alloy. For example, Plasma Electrolytic Oxidation (PEO) is a traditional surface microstructure treatment technology. In a recent study, Tanase, et al……

I can't figure out what "dissipation of metal components" means. Based on the cited research, I guess it might be "release of metal ions" or "biological response of metallic components", but it's hard to tell. Stil, the research is on a ceramic bioglass, totally unrelated to the topic of this review.

Reply 11: The words were changed as advised. In this study, we mentioned that the original words are "Ti-based BMG (Ti40Zr10Cu34Pd14Sn2) alloy". And the this material is a kind of metallic glass which was based on metal. So we want to demonstrate a novel material to avoid release of metal ions thus avoiding cell toxicity.

Changes in the text: Kokubun, et al. (25) conducted animal experiments with titania-based biological glass alloy (Ti40Zr10Cu34Pd14Sn2), and found that it could effectively reduce the release of metal ions thus avoiding related cell damaging while reducing Young's modulus.

EBM and SLM are drastically different in their output because of the different size of the energy beam, different temperature and different working atmosphere. The resolution that can be achieved by SLM is not comparable to that of EBM.

Reply 12: The mentioned part was revised as advised.

Changes in the text: There are differences between the two methods. For example, SLM have higher resolution ratio and cost more than EBM. Although the operational approaches of technologies are different, some scientists found no significant difference in the construction of titanium alloy scaffold (45)

I never heard of "bionic deposition" and a research in literature suggest that it is was wrongly translated.

Reply 13: The related words were changed.

Changes in the text: chemical deposition

Carbon graphene is NOT an apatite-like material.

Reply 14: The related words were changed

Changes in the text: Some compounds containing carbon and phosphorus

The number of coating and functionalization technologies discussed in this paper is just a minimum fraction of the relevant ones.

Reply 15: More articles were referred and more details were added.

Changes in the text: The changes for more details are highlighted in red.

As a final comment, this document is poorly designed and the contents are not discussed with a critical attitude by the authors, that just listed data results without even trying to find a common thread.

Reply 16: Thanks so much for your criticism. We have tried our best to achieve your demands. Because of your careful comments, we have learnt a lot during the revision.