RESPONSES TO REVIEWER’S COMMENTS

First of all, I thank the editors of World Journal of Orthopedics for inviting me to submit a revised draft of my manuscript entitled, “Antibiotic-free antimicrobial poly(methyl methacrylate) bone cements: a state-of-the-art review”.

Second, I thank the reviewer for a detailed review of my original manuscript and for providing insightful feedback in the form of comments and requests for additional information.

In the Revised Manuscript, I have made several revisions that reflect my responses to the reviewer’s comments and requests for additional information.

To facilitate review of my Revised Manuscript, the following is a point-by-point response to the reviewer’s questions and requests for additional information.

**POINT 1**
The exact mechanism responsible for the antimicrobial activity of Ag has not been established but there is consensus on possible reasons, such as inactivation of the bacterial cell (cell membrane and enzymes) by the Ag ions interfering with enzymes that interact with sulfur in the protein chains and/or generating reactive oxygen species[54], which kill the cells. Please through light on the different theories of Ag antimicrobial effect.

**MY RESPONSE:**
I have thrown additional light on this issue by stating 2 more theories (uptake of free Ag ions and Ag ions causing separation of paired strands of DNA in the bacteria) and provided 2 new supporting references, [76] and [77]-----see Page 8 and List of References.

**POINT 2**
*Please mention the literature based possible antimicrobial effects of bioactive glass.*

**MY RESPONSE:**
I have added information on antimicrobial activity of a bioactive glass, including 2 new supporting references, [80] and [81]-----see Page 9 and List of References.
POINT 3

However, results of bacterial adhesion tests showed that each of the AFAMBCs significantly reduced biofilm formation relative to the plain cement\[58\]. These results suggest that while the AFAMBCs have no antimicrobial activity against planktonic bacteria, they have good potential for use in cases where prevention of bacterial adhesion is needed (for example, in primary TJAs)[58]. Please explain how is the biofilm phenomenon could represent a challenge for the antimicrobial effect.

MY RESPONSE:
I have added more information on biofilm, including 2 new supporting references [82] and [83]—see Page 11 and List of References.

POINT 4
Please combine the antimicrobial effects of each modality with its clinical relevance related to PJI In vitro cytotoxicity/cytocompatibility

POINT 5
Please explain importance and factors affecting biocompatibility of the cement and factors affecting bio adherence and more evidences regarding the negative effects of antibiotics on cellular adhesion.

MY RESPONSE TO POINT 4 AND POINT 5:
I have added more information on cytotoxicity/cytocompatibility/biocompatibility and bioadherence, including 2 new supporting references, [82] and [83]—see Page 17 and List of References.

POINT 6
Other cement properties The number of studies in which other cement properties were determined varied widely, from < 5 (example properties: tensile modulus, tensile strength, fracture toughness, and radiopacity) to ~20 (property: compressive strength) (Table 1). Among these results, some are clear evidence that for an AFAMBC, its maximum polymerization temperature is lower (which is desirable), setting time is longer (which is not desirable), compressive strength is comparable, flexural modulus is comparable, and cell viability is higher (please mention the clinical relevance for each character) After 7-28 days of immersion of specimens of bioactive glass powder-loaded cement in simulated body fluid, at 37 oC, there was evidence of agglomerates on the specimen surface that were rich in calcium and phosphorus (HAP) (Ca/P ratio = ~ 0.9 - ~4.0)[60,62,63].

MY RESPONSE:
I have added explanations of the clinical relevance of lower polymerization temperature, longer setting time, comparable compressive strength, comparable flexural modulus, and higher cell viability—see Pages 17 and 18.

POINT 7
Please clarify the added value of Calcium and phosphate in improving substance bioactivity

MY RESPONSE:
I have added explanations of the added value of Ca and P ions, and provided a new supporting reference, [88]—see Page 20 and List of References.

PLEASE NOTE THAT IN THE REVISED MANUSCRIPT, ALL REVISIONS I HAVE MADE IN THE TEXT AND IN THE LIST OF REFERENCES ARE SHOWN HIGHLIGHTED IN RED AND UNDERLINED.

I hope that the reviewer will find all the revisions I have made to be satisfactory and, as such, recommend that my Revised Manuscript be accepted.