Author’s response to reviews

Title: Three-Dimensional Finite Element Analysis of Silk Protein Rod Implantation after Core Decompression for Osteonecrosis of the Femoral Head

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Author’s response to reviews:

Dear Robin L. Cassady-Cain PhD,

Thank you very much for your time and effort with our manuscript. We are grateful to the reviewers for their constructive comments, and greatly appreciate the opportunity that you provided us to revise and improve our manuscript.

We have carefully addressed the reviewers’ constructive comments and revised our manuscript accordingly. The article has been revised by a native English speaker, and we hope that it is now much easier for the reader to understand.

We hope that you will agree with us that our revised manuscript has adequately addressed all the concerns and comments of the reviewers and is now suitable for publication in BMC Musculoskeletal Disorders.
Thank you for evaluation of our revised manuscript.

Sincerely yours,

Jun Xia

Reviewer reports:
Dewei Zhao (Reviewer 1):
By reading the paper, I know that you have done a lot of work on silk protein rod.
There are several questions that need your attention.
1."The three-point bending test was conducted using the Zwick 2500N machine (Figure 1)." Why is there no relevant result in this paper?
Response: The elastic modulus can be obtained by the compression test and three-point bending test. We finally chose the compression as the finite element calculation as the silk rod is not a standard part and the cross section has a greater influence on the elastic modulus in the three-point bending test.
2."The elastic moduli of the silk protein material sample 1, sample 2 and sample 3 were 1.15 GPa, 0.83 GPa and 0.50 GPa respectively. " Why are the results so different?
Response: Correction: Sample 1 should be 0.15 GPa. Sources of error: The asymmetry of the sample or the asymmetry produced by sample embedment and fixation during the mechanical test. Samples are not concentrically compressed or twisted during compression and torsion test, resulting in the error. (Results section, Line 193, page 6)
3."We compared the effectiveness of silk protein rod implantation on different areas of femoral head osteonecrosis, assuming three different cone angles of 60°, 90° and 120°. " Please explain how you define these angles.
Response: In ascending order, simulation and generalization of the actual ONFH in different positions and ranges are clinically expected.
4."Results from all 12 models were analyzed using single-factor ANOVA. " Please explain in detail how the 12 models are divided?
Response: The results are shown in Table 3 and Table 4.

The 12 models of three-dimensional finite element analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Osteonecrosis range</th>
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<tbody>
<tr>
<td></td>
<td>60°</td>
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<tr>
<td>Simple core decompression</td>
<td>Model 1</td>
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<tr>
<td>Silk protein rod implantation</td>
<td>Model 4</td>
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<tr>
<td>Fibula implantation</td>
<td>Model 7</td>
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<tr>
<td>Tantalum rod implantation</td>
<td>Model 10</td>
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Sujit Kumar Tripathy, M.S. (Ortho), MCH(UK) (Reviewer 2): This is a very good study and worth publication. However a major changes in the format is needed. Please try to make it simple so that it can be easily understood. A detailed review is as follows.

Introduction:
Osteonecrosis of the femoral head is a pathological process that can result from internal or external destruction of the blood supply to the femoral head, resulting in deformation and avascular necrosis of subchondral bone
I don't think it is destruction always? Deformation is a sequelae to avascularity and cell death with cartilage collapse. Deformation should not come first…Please rephrase it…

Response: Thanks very much for the suggestion. This part is not really appropriately expressed. The early stage of femoral head necrosis is caused by pathogenic factors that disrupt the blood circulation of the femoral head, resulting in cell degeneration and necrosis. The necrotic bone is absorbed and the articular cartilage sinks, the femoral head collapses and deforms, and ultimately the hip osteoarthritis is formed. (Background section, Line 61-64, page 2)

Conservative, non-operative treatment is only suitable in the early stages of osteonecrosis, and surgical intervention is often required as the disease progresses to prevent further damage to the femoral head, and to avoid or delay the potential need for an artificial joint replacement
There is no role of conservative treatment anymore….what do you mean by conservative treatment, elaborate and give evidence from recent reviews. CD is indicated in stage 1 and 2 and that is the early pre-collapsed stage….it has limited role once collapse is there…please rephrase the sentence

Response: "An evidence-based guide to the treatment of osteonecrosis of the femoral head." The Bone & Joint Journal Vol. 99-B, No. 10, 1 Oct 2017, pages 1270 mentioned "The outcome of the non-operative treatment of osteonecrosis therefore, remains uncertain, and further RCTs are needed", so the value of non-surgical treatment is still controversial. When the femoral head collapses, it is not suitable for CD, because CD is also difficult to prevent the femoral head necrosis from progression, and thus CD does have great limitations. But if the femoral head has not collapsed and only the necrotic area of the femoral head is degenerating, CD still has a great effect on the survival of the hip joint. (Background section, Line 66-69, page 2)

The classic surgical treatment of osteonecrosis of the femoral head is core decompression, which can effectively reduce the pressure on the femoral head, improve local blood circulation and relieve hip pain [3-5]; however, this can increase the risk of postoperative fracture and further collapse of the articular surface due to a lack of mechanical support.
Which method of CD the authors want to mention here? The classic 8mm/6 mm drill or recent 3mm/4mm mm drill bit. Be specific when the author expect collapse after CD?

Response: It’s 8mm/6 mm drill. After CD, the femoral head necrotic area lacks mechanical support, and implants are usually added into the channel to increase the mechanical strength. (Background section, Line 70-72, page 3)

core decompression combined with bone impaction grafting or implantation is the main operative approach used, and can increase the strength of the femoral head and reduce the risk of articular surface collapse
The problem in understanding the article is because the author have not mentioned any severity grading system...please mention when CD and bone grafting or metallic rod implantation is needed, steinberg classification/ficat arlet or ARCO

Response: CD or CD combined with bone grafting/implantation generally used in Steinberg stage II. (Background section, Line 74-77, page 3)

Implantation options include porous tantalum rods and vascularized fibular grafting,
There are many other procedures for implantation, for examp: nonvascularised fibular graft…please use etc.

Response: Corrected as suggested. (Background section, Line 78, page 3)

Methodology:
The study design and experiment was not described in a simple language. It is incoherent and the flow of the study is bit confusion. How biomechanical testing was done? Why it was not tested for tantalum rod? How the machine could read the deformation/ what is meshing and how meshing helps in deformation calculation…should be explained. How the computer can read the different properties of the material in femoral bone model in terms of deformation? Please elaborate to make it easy. It is very good to see biomechanical testing and 3d model analysis have been mentioned separately. I still don't understand why six fibula were needed? Model 1,2, 3,4 only mentioned..

How biomechanical testing was done? Why it was not tested for tantalum rod?
Response : Biomechanical testing step: According to the three-view design drawn on the engineering drawing, the denture acrylic and denture liquid were mixed at 3.5:1, and the silk protein rod and the tibia were embedded. The silk rod and tibia were subjected to compression test and torsion test on a MTS 370.02 BIONIX test machine, and a three-point bending test was performed on a Zwick 2500N test machine. The compressive force displacement map, the torsional force displacement map and the three-point bending force displacement map are obtained respectively. The data are processed by the formula to obtain the elastic modulus and the shear modulus. (Methods section, Line124-127, page 4)

How the machine could read the deformation/ what is meshing and how meshing helps in deformation calculation ?How the computer can read the different properties of the material in femoral bone model in terms of deformation?

Response : Grids are objects that are used for discrete analysis. The grid is used to break the femoral head into tens of thousands of sections meshes. Grids come in different shapes, with tetrahedral grids and hexahedral grids. Take the tetrahedral grid as an example it has four angles which are also call nodes. The finite element simulation first calculates the displacement of the nodes, and the stress of each position on the grid can be calculated using the mechanical principle. So in the end we can collect the displacement of the node, and in the meantime the strain and stress of the entire femoral head can also be calculated.

Why it was not tested for tantalum rod?
Response: Since the elastic modulus of the tantalum metal rod is known, no further biomechanical
testing is required.

Why six fibula were needed?
Response: Because in the compression test, torsion test and three-point bending test, two tibias are applied for each test. The elastic modulus results of the compression test are finally selected for the next stage of the three-dimensional finite element study.

Discussion section:
'relatively common'….please provide incidence, to which comparison it is said relatively common, is it relatively common compared to world average ????

Response: There is no epidemiological statistics on the incidence of femoral head necrosis in China. It can only be evaluated based on clinical experience, and the incidence of femoral head necrosis in China is relatively high compared to other hip joint diseases. (Discussion section, Line280-281, page 8)

"While conservative management is appropriate in the early stages of the disease, implantation following surgical core decompression is the preferred treatment option in more advanced osteonecrosis"…I don't agree with this sentence, there is no role of conservative treatment. Early diagnosis and treatment is the key to success. Core decompression is a treatment in early stage. What is implantation meaning here? Is it fibular graft/tantalum rod or anything else? Give reference that it is the preferred treatment?

Response : Because there is no obvious symptom in the early stage of femoral head necrosis, early diagnosis is difficult. We agree with the reviewer's opinion that early diagnosis and treatment are the most critical parts. There are many studies pointing out that treatment like pharmacological treatment, hyperbaric oxygen, and extracorporeal shockwave therapy, etc. can also improve the survival of femoral head for patients with Steinberg Stage I-II/ARCO I-II, but more RCT studies are needed to identify the efficacy of non-surgical treatment. However, when the femoral head necrosis progresses to Steinberg Stage II, it is recommended to use CD to completely decompress the femoral head necrosis area. After decompression, the decompression area of the femoral head is hollow, requiring material implantation to strengthen the mechanical strength of the femoral head. Current methods of implantation include non-vascularized bone grafting, vascularized bone grafting, and tantalum rods, etc. (Discussion section, Line284-290, page 8)

Our results should be considered with some caution as some results were based on reported known values and error in the software and calculations used. The elastic modulus, Poisson's ratio and yield stress of silk protein rods and fibulas were acquired from previous biomechanical studies; some inherent error resulted from manual operations during 3D finite element studies, such as finite element mesh size and loading sites; and the stress results were obtained using a difference method, and may have accumulated some error. The above para need to be put in limitation section before conclusion.
Response : Corrected as suggested. (Limitation section, Line271-278, page 8)