

Peer Review File

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The topic discussed is interesting; it is a somewhat debated topic and could be helpful in orthopedic clinical practice. Many concerns burden it with a major revision. Some suggested corrections have been listed below. Please answer point by point.

GENERAL SECTION

Comment 1: Generally, whether the manuscript is a literature review or a systematic review is unclear. Analyzing the whole text, it would seem to be more the second option. Therefore, one should try to conform with the manuscript type.

Reply 1: Thank you for this comment. We would like for this to be a literature review, so we have adjusted the text accordingly to match the style of a literature review and not a systematic review.

Changes in text: NA

Comment 2: Add the checklist as additional material (either the narrative review or the systematic review, depending on what direction you want to take the text).

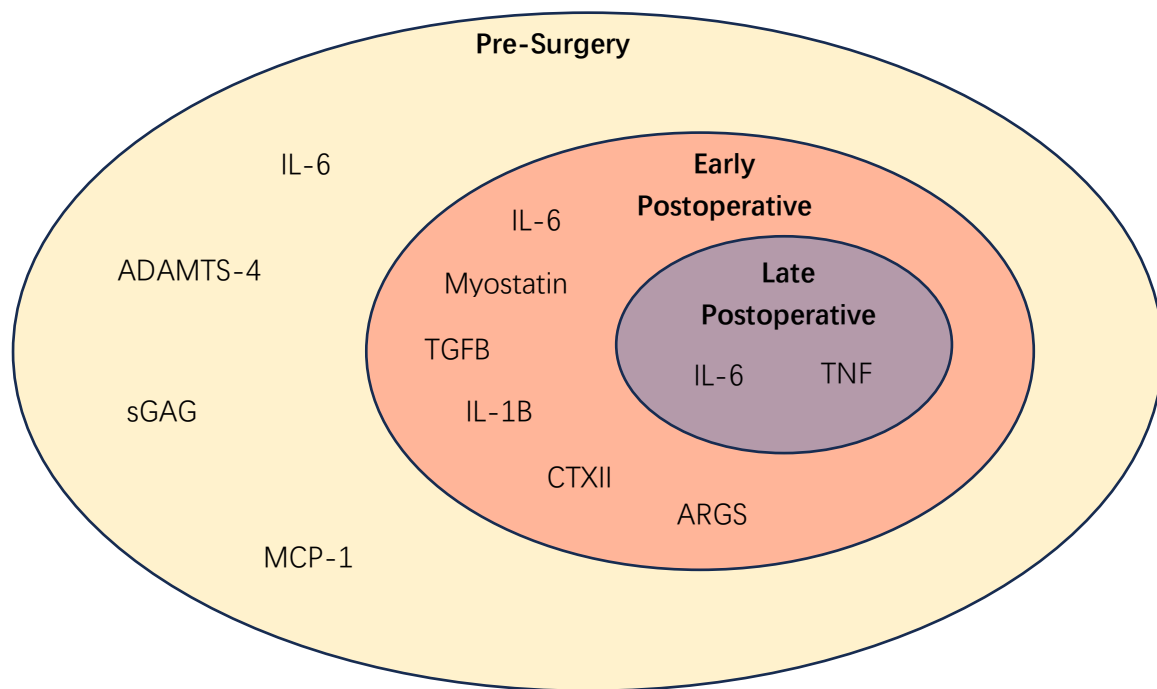
Reply 2: We have added in the checklist as additional material and have included the paragraph and the appropriate line numbers.

Changes in text: Updated narrative checklist is included in the supplemental portion of the submission.

Comment 3: I recommend adding figures in the manuscript.

Reply 3: Thank you for this suggestion. We have added in an additional figure on top of the one we included already.

Changes in text:



Comment 4: The manuscript is too long. Several general and well-known topics can be easily shortened without losing scientific information. The manuscript will improve with a reduction. It will be more straightforward, easier to read, and smoother. Remember that a manuscript should be as long as necessary but as short as possible.

Reply 4: Thank you for this comment. We have shortened the main manuscript from 4651 words to 3983 words.

Changes in text: Many areas of the text have been revised to make the overall manuscript more succinct.

TITLE

Comment 5: Specify whether these are synovial biomarkers in the title as well.

Reply 5: This correction has been made and the title has been changed.

Changes in text: Lines 1-2: “Inflammatory Synovial Biomarkers and State of the Tibiofemoral Joint in the Post-Surgical Setting: A Narrative Review”.

ABSTRACT

Comment 6: Please better define whether it is a narrative review or a Systematic Review. In the first case, the abstract should be unstructured: 200~350 words, Keywords: 3~5 words; in the second case, the abstract should be divided as follows: Background, Methods, Results, and Conclusions.

Reply 6: Online at the AOJ Guidelines for Submission page it says the abstract should be structured with the following: Background and Objective, Methods, Key Content and Findings,

and Conclusions. We have made the abstract to follow these guidelines.

Changes in the text: Abstract section has been amended to best fit the style for a narrative review.

Comment 7: Add an aim in the abstract as well.

Reply 7: The aim of the study was added into the abstract.

Changes in text: Lines 43 to 45: The aim of this study is to analyze previous literature to determine which synovial fluid biomarkers contribute to knee tissue degradation and decrease patient outcomes in the post-surgical setting of the knee.

Comment 8: It is never clear if you are talking about synovial biomarkers, be more explanatory.

Reply 8: The contents of the abstract have been amended to ensure it is clear we are discussing synovial biomarkers.

Changes in text: All areas of confusion in the abstract section have been amended.

INTRODUCTION

Comment 9: Subparagraphs also go numerary, 1.1, 1.2, etc., etc.

Reply 9: Thank you for this reminder. The subparagraphs have now been given the proper numbering.

Changes in text: Line 77: 1.1 Background, Line 135: 1.2 Rational and Knowledge Gap, Line 145: 1.3 Objective

Comment 10: The entire introduction paragraph should be revised. The topic should be better introduced. The purpose is not clear.

Reply 10: The introduction has been revised to be clearer and introduce the topic with more clarity.

Changes in text: Lines 79-82: After acute injury to the structures of the knee, including ligamentous(1), meniscal(2), and cartilaginous(3) injury, surgical intervention is a common method to repair or reconstruct the damaged tissues to prevent knee tissue degradation and osteoarthritis. The initial injury and subsequent surgery can cause the joint to enter a proinflammatory state(1).

Lines 112-115: Synovial biomarkers typically appear earlier than OA symptoms, so determining the most important and relevant inflammatory biomarkers could be critical for developing improved post-surgical knee treatment options. To our knowledge, no other studies report on the various synovial fluid biomarkers of the knee in the post-surgical state of the knee.

Lines 146-153: 1.3 Objective:

The objective of this narrative review is to analyze the current literature relating to synovial fluid biomarkers of the knee relating to the post-surgical setting. By obtaining an improved understanding of the synovial fluid state of the knee after surgery, physicians and care providers can develop patient specific treatment options to improve short- and long-term patient

outcomes and decrease knee tissue degradation after knee surgery. Management strategies to decrease negative synovial biomarkers may help slow the progression of OA and inflammation of the knee joint, while preserving the beneficial biomarkers (18). Our hypothesis is that the post-surgical knee setting will have different concentrations of synovial fluid biomarkers than the pre-surgical setting.

Comment 11: Please provide the exact hypothesis in detail when explaining the purpose of the study. The reader must also understand why your study is clinically relevant. What makes your analysis more appropriate than others already published? What is new about it? What makes your study necessary?

Reply 11: The hypothesis describing the purpose of this study has been added to the introduction.

Changes in text: Lines 152 to 153: Our hypothesis is that the post-surgical knee setting will have different concentrations of synovial fluid biomarkers than the pre-surgical setting.

Comment 12: There are numerous abbreviations without ever having used the whole word before. This error is not only in the introduction but throughout the text. Please correct it. After mentioning an acronym for the first time, you can use only the abbreviation instead of writing the whole word. Correct the abbreviations in the text.

Reply 12: Thank you for this comment, the full names for all the abbreviations have now been mentioned in the text.

Changes in text: The various abbreviations used in the text now have full names spelled out the first time they are used.

Comment 13: Also, in the introduction, it is not clear whether you are talking about synovial or serum biomarkers. Please specify better.

Reply 13: We are discussing synovial biomarkers; this has been specified in the introduction and the rest of the manuscript.

Changes in text: Any areas of confusion have been amended.

Comment 14: Line 72: "surgery creates ..." what does it mean? Introduce it better because this way, it sounds like a sentence inserted in a context that was totally about something else.

Reply 14: Thank you for this comment. This sentence has been reworded to provide more clarity.

Changes in text: Lines 108-110: After the initial traumatic response to an injury, the secondary trauma caused by surgery can lead to persistent and long-term inflammatory biomarkers that may be different from the initial biomarker composition that occurs initially after injury(19, 25)

Comment 15: Line 97: "We present...reporting checklist," this sentence should be reported in the methods. Also, no Checklist was attached. Please see to it.

Reply 15: Thank you. This sentence has been added into the methods section. The reporting checklist was added as well.

Changes in text: Line 201: We present this article in accordance with the narrative review reporting checklist.

MATERIALS AND METHODS

Comment 16: Should clarify in more detail the patients who met the inclusion criteria. The inclusion and exclusion criteria should be addressed in more detail.

Reply 16: No specific patients or patient population analysis was performed in this review. However, we did specify with more clarity which publication and manuscripts met our inclusion criteria for this manuscript.

Changes in text: The methods section has been reworked to offer more clarity. Lines 156-202: A narrative review was conducted of the literature reporting on synovial fluid biomolecular markers associated with the post-surgical knee. The literature review was performed using sources from PubMed and Medline. All studies were cross referenced to find additional sources. Studies were initially screened by analysis of the abstract and then further analyzed if the abstract was relevant to the topic of choice. Studies were included that contained information for synovial fluid biomarkers in the post-surgical knee including studies discussing ways to manage these biomarkers. There was no exclusion based on date of publication. We present this article in accordance with the narrative review reporting checklist. The summary of the search methods can be found in Table 2.

Comment 17: The MESH terms are necessary for systematic review, not narrative review. Decide what type of study is yours and modify accordingly.

Reply 17: This has been modified for the narrative review.

Changes in text: Line 997

Table 2. The search strategy summary

Items	Specification
Date of Search (specified to date, month, and year)	7/10/23
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters) Note: please use an independent supplement table to present detailed search strategy of one database as an example	(inflammatory biomarkers OR knee biomarkers OR inflammatory markers OR inflammatory biomarker inhibition) AND (Knee surgery OR knee osteoarthritis OR ACL reconstruction OR anterior cruciate ligament reconstruction)
Timeframe	2006-2023
Inclusion and exclusion criteria (study type, language restrictions etc.)	Full text peer reviewed articles, English, single case reports were excluded.

<p>Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)</p>	<p>Article selection was performed by determining relevance from title and abstract and was performed independently by two co-authors (LT and MK). Consensus was obtained by analyzing the full text.</p>
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Comment 18: If it is a systematic review as it would seem, several important paragraphs are missing in the methods, each to be added and analyzed in detail: Data selection (with the number of articles evaluated, duplicated, included, excluded, by title and abstract, and finally analyzed in the final evaluation), Data extraction (data collected and analyzed), Qualitative evaluation of included studies, and statistical analysis performed (descriptive, analytical, tests used).

Reply 18: Thank you for this comment. We are attempting to write a narrative review, so the format of the manuscript has been made to match what is listed online in the AOJ Guidelines for Authors.

Changes in text: Structure of the manuscript has been written to match the format for a narrative review.

3. Post-Surgical Inflammatory State

Comment 19: This part would seem to be the "Discussion" section of the text. Please divide the text into numbered sub-sections and give a title to the first part.

Reply 19: This section is the “main body” of the narrative review. A discussion section and a conclusion section have now been added at the end of the manuscript.

Comment 20: Start the "Discussion" section by affirming the study's main finding, to be added at the beginning of the section.

Reply 20: The new Discussion section mentions the main study findings at the beginning of each paragraph.

Changes in text: Updated discussion section.

Comment 21: Lines 123-130 and 132-134: It is not clear whether you are talking about serum or synovial markers. There is excessive confusion in the text. Please reshape this part by making the whole discussion clear and straightforward.

Reply 21: This part has been reworked to make it clearer. Additionally, this confusion has been corrected throughout the entire manuscript.

Changes in text: Lines 218 to 256: Preoperative synovial biomarkers can help determine the state of the knee prior to surgery and determine if any predictive inflammatory biomarkers are already present from the initial injury. Certain synovial biomarkers have already been reported to be associated with cartilage breakdown and OA progression, like macrophages and cytokines. The presence, or absence, of certain synovial biomarkers related to the breakdown

of cartilage and inflammatory signals could offer insights into determination of surgery, preoperative planning, and postoperative rehabilitation and guidelines.

Some knee cartilage treatments, like autologous chondrocyte implantation (ACI), attempt to treat full thickness articular cartilage defects by using patient specific lab grown chondrocytes. A study by Wright et al(12) measured preoperative synovial biomarkers before ACI surgery and reported that **a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4)**, which is an aggrecanase that plays a key role in early cartilage destruction, had elevated activity in the synovial fluid of patients who had decreased clinical outcomes(11).

Comment 22: Bibliographic references are missing and should be added in many parts of the text. I have attached examples:

- Line 150: one reference is missing.
- Lines 171-173: missing references
- Line 181: missing references
- Line 216: missing references
- Line 233: missing references
- Line 242: missing references
- Lines 255-263: missing references
- Line 298: missing references

Reply 22: References that are missing have been added to these sections. Additionally, some of these sections may have been deleted while shortening the paper to make it more succinct.

Changes in text: Line 150: Section deleted.

Lines 171-173: Section deleted.

Line 181: 2 references added.

Line 216: 1 reference added.

Line 233: Section deleted.

Line 242: Sentence reworked, and reference added.

Lines 255-268: 4 references added.

Line 298: 1 reference added.

Comment 23: Require discussion on strengths and limitations of the review at the end of the "Discussion" section and before the "Conclusion" section.

Reply 23: Strengths and limitations section at the end of the discussion has been added.

Changes in text: Lines 696 to 702: Current limitations to understanding the effects of postoperative synovial fluid inflammatory biomarkers include the inability to specifically differentiate post-injury and post-surgery biomarkers. Many of the inflammatory and cartilage degeneration biomarkers are similar between post-injury and post-surgery, more should be done to determine differences in concentration and if there are biomarkers present after surgery that are not present at any other points. Additionally, altered knee biomechanics, even after reconstruction and patient rehabilitation, need to be studied in more depth to determine the true cause of decreased patient outcomes.

RESULTS

Comment 24: Missing this section in the text

Reply 24: Since this is a narrative review, this section is not required due to what is says online at the AOJ Guidelines for Authors page. We have included a “main body” section but not a results section.

DISCUSSION

Comment 25: Missing this section in the text

Reply 25: A Discussion section has now been added.

CONCLUSION

Comment 26: The conclusion must leave the fundamental concept of the study to the reader. It should be made more interesting by focusing on the key points of the study. Get to the point. Write what you found important without being repetitive and your research's importance.

Reply 26: Thank you for these suggestions. The conclusion section has been amended to match these points.

Changes in text: Lines 713 to 741: Synovial fluid biomarkers in the post-surgical knee setting may contribute to decreased patient outcomes and the progression of knee tissue degradation. There is no current consensus on which of these biomarkers are the most detrimental or associated with decreased patient outcomes. With an improved understanding of the individual biomarkers, potential personalized therapeutic treatment could be used by physicians in the future to improve patient outcomes after surgery.

Comment 27: Lines 402-411: This part represents the "Future Directions" of the study and should be inserted before the conclusions at the end of the discussion.

Reply 27: The Future Directions part has been moved to the Discussion section of the paper.
Changes in text: Future direction paragraph has been moved to the proper location in the manuscript.

REFERENCES

Comment 28: Add missing references in the text as suggested above.

Reply 28: References have been added.

Changes in text: Reference section has been amended.