Peer Review File

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Reviewer A

This narrative review summarizes some of the studies on cytokines and inflammation in the joint. While such a review could eventually be of value to the field, there are several similar reviews published already. There are several issues to be addressed.

Comment 1: The section introducing the basic science of cartilage is poorly referenced and inaccurate in several places. For example "There are four types of collagen, with the majority of the fibrillar collagen network of chondrocytes consisting of type II collagen (14)." There are several more types of collagen in cartilage. Lines 113-118 have statements that are not referenced, along with many others in the introduction.

Reply 1: Apologies for this inaccuracy. The sentence was meant to simply state that of the 5 main types, type 2 is the most prevalent in fibrillar collagen network. The sentence has been reworked to avoid this confusion.

Changes in Text: "Of the five main types of There are four types of collagen, with the majority of the fibrillar collagen network of chondrocytes consisting of type II collagen"

Comment 2: COMP has been used as a biomarker but like many others, its concentration is transiently changed following injury, so the concentration per se is not a good biomarker without knowing the time course. This is true for most biomarkers and has been reviewed previously.

Reply 2: We agree with this comment, as many biomarkers have a variable concentration, following injury, and without the associated time course, it's difficult to understand how these levels are fluctuating.

Changes in Text: We aren't sure how this comment could be addressed throughout the paper but we have added in a statement in the "Future Directions" section in order to stress the importance of time reporting relative to biomarker fluctuations.

Comment 3: IL-1B should be "beta". The abbreviations and terminology need to be cleaned up throughout the manuscript.

Reply 3: A review throughout the article has been performed, and these corrections have been made.

Changes in Text: examples include IL-1β and IFN-γ

Comment 4: The review has little depth or any take-home message, and it is just a listing of different cytokines with no direct interpretation of their value in PTOA.

Reply 4: Although we would like to have made more direct interpretations of bio marker influences in the post traumatic state, there doesn't seem to be any studies that have been controlled sufficiently to explicitly state the direct effect of each biomarker, and therefore, in order to avoid making statements that haven't been

officially proven, we have limited review to understand the various classes of bio markers that are associated with inflammation following injury.

Comment 5: The review is limited by use of the term "tibiofemoral" instead of also include "knee". Many papers are missed on this topic.
Reply 5: The term "tibiofemoral' was only used for an initial screening of relevant articles to include into the review, as we felt this was more specific to the articles of interest, but it was not a limiting factor for further collection of additional articles. Many other articles of the review were pulled from the original search of articles within the references and discussion sections, and these reviews also included search terms, including the word "knee".

Reviewer B

Overall, it is a very superficial review with a lack of clear focus. There is complete lack of proper citing of work related to PTOA and in general. Many sentences completely lack citations or do not refer to PTOA at all nor PTOA of the knee. The manuscript does not meet expectations – to create a readable synthesis of the best resources available in the literature. Several parts of the manuscript are poorly focused and the key Content and Findings [The chronic low-level inflammation that leads to osteoarthritis leads to the destruction of the cartilage extracellular matrix, which new and developing orthopedic research is still attempting to find resolve for. Some of this damage is attributed to the biomechanical alterations that occurs following injury, though with most procedures capable of joint biomechanical restoration, focus has rather been shifted toward the environment of inflammatory biomarkers] and Conclusions [Future studies will be aiming to improve the diagnostics of OA, focusing on a consistent correlation of inflammatory biomarkers with imaging. Additionally, biochemical treatments will need to focus on validating reproducible modulation of signaling molecules, in attempts to lessen the chronic elevations of destructive biomarkers] are not supported by the literature, which often focuses on OA and older studies rather than PTOA studies. These points and the following should be addressed prior to publication.

Comment 1: Many reviews have been published on this topic including [An Evidence-Based Systematic Review of Human Knee Post-Traumatic Osteoarthritis (PTOA): Timeline of Clinical Presentation and Disease Markers, Comparison of Knee Joint PTOA Models and Early Disease Implications (Khella et al 2021); Current status of catabolic, anabolic and inflammatory biomarkers associated with structural and symptomatic changes in the chronic phase of post-traumatic knee osteoarthritis– a systematic review (O'Sullivan et al. 2023); Improved Understanding of the Inflammatory Response in Synovial Fluid and Serum after Traumatic Knee Injury, Excluding Fractures of the Knee: A Systematic Review (Nieboer et al. 2023)]. Some of these articles provide a detailed clinical inflammatory timeline and sequence of events of inflammatory and other mediators present in the synovial fluid, serum,

plasma or urine following knee trauma. The authors need to cite these articles and describe how their article extends, complements or differs from those reviews.
Reply 1: Thank you for the suggestions, apologies that we weren't able to include them in our original submission. We have searched these articles and included important concepts from each, so that the review can be more thorough.

Comment 2: Citations are very old and many focused on OA but not PTOA. Again, same comment as above, many papers have been published on this topic within the last few years. The authors need to consult the literature to include up-to-date citations on this topic. A a perfect example of this is citation (1) in paragraph one. The above reviews are better citations for these statements rather than citation (1).
Reply 2: Thank you again for the suggestions, these have been added to the paper.

Comment 3: Lines 71-73: citation not specific to PTOA. See Struglics et al paper on PTOA and complement measured clinically.
Reply: 3 Apologies, but not sure which citation is in question.

Comment 4: Lines 73-76: Provide the citation for the following sentence: Even in obese patients, who frequently endure OA as a result of increased joint forces and the subsequent amplified degradation of cartilage, synovial fluid has been shown to exhibit increased levels of interleukin (IL)-6 and soluble IL-6 receptor released from the infrapatellar fat pad.
Reply 4: Added the citation into the text.

Comment 5: Line 78: rational and knowledge gap. Based on the format (lack of structure and assessment of studies relevant to PTOA), it is hard for the authors to justify this. Lines 79-82: provide proof (citations) of for these comments.
Reply 5: Just for clarification, the line, "Furthermore, not all of the correlations found in differing levels of these inflammatory biomarkers between healthy and OA patients has been directly linked to cartilage destruction.", is meant to foreshadow what is mentioned also in the future directions section, of there being a lack of randomized controlled trials that directly link cartilage destruction with certain inflammatory markers. This is simply a general statement about there still having lack a specific marker for acute or chronic degeneration of cartilage. If desired, we can remove this statement.

Comment 6: Lines 157-158: While there are many inflammatory modulators involved in this process, the major players linked with OA are IL-1B and TNF (25). Again, provide better citations. The following citation has proven via a systematic study and clear evidence that TNF-α and IL-6 cytokines are causal factor of PTOA and that IL-1β and IL-17 are credible factors in inducing knee PTOA disease progresssion [An Evidence-Based Systematic Review of Human Knee Post-Traumatic Osteoarthritis (PTOA): Timeline of Clinical Presentation and Disease Markers, Comparison of Knee Joint PTOA Models and Early Disease Implications (Khella et al 2021).

Reply 6: Thank you for this suggestion, we have added this as a citation.

Comment 7. Lines 170-181: The following systematic review has focused on many of these markers and should be cited [An Evidence-Based Systematic Review of Human Knee Post-Traumatic Osteoarthritis (PTOA): Timeline of Clinical Presentation and Disease Markers, Comparison of Knee Joint PTOA Models and Early Disease Implications (Khella et al 2021).
Reply 7: Thank you citation has been added.

Comment 8: Lines 314-319: There are recent studies focusing on these aspects. Expand the paragraph and state was is being pursued as of present.
Reply 8: Additional citations have been added, from the suggested articles above, to this section to expand on the future directions to come in the field.

Comment 9: Lines 326-330: There are recent reviews covering these topics. Citations are needed on what is currently the focus and what is still missing (based on the conclusions of the reviews). Focus should be on PTOA reviews and include citations for a) Compounds that may be able to regulate the activity of cytokines, or by lessening their synthesis, may be achieved by increasing the level of inhibitory cytokines that antagonize the catabolic activities of OA developments (citations missing); advancing imaging (citations missing); drug delivery models (citations missing), so that we may better identify OA and understand its pathophysiology throughout the course of the disease.
Reply 9: Studies have been added to this section to expand on the future studies.

Comment 10: Overall, it is not clear what type of trauma this review focuses on. Add this in the inclusion section or elsewhere.
Reply 10: This has been added to the methods section.

Comment 11: The question should be asked (and answered/discussed): what does this study add to already published PTOA reviews?
Reply 11: A statement addressing this has been added o the conclusions.

Comment 12: Overall, the manuscript does not deliver what the abstract and title state. It is more of a selective simple review. Please revise both for accuracy.
Reply 12: The title has been modified to address this concern.

Comment 13: A table should be provided articles cited on inflammatory biomarkers of the post-traumatic knee that were included for review and which markers were measured and when.
Reply 13: A table was not able to be added as we are still compiling data from all articles, but this can be added in the future if desired.