Reviewer's report

Title: Levels of NPY in synovial fluid relate to pain in patients with knee osteoarthritis

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Reviewer: Nicole Cattano

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1. The question posed by the authors in a very interesting one, however, I do think that they authors can better define the foundational basis for their purpose. Some of the detailed information regarding NPY and its association with pain and inflammation that is included in the discussion could be used a little to bolster the initial purpose.

2. The methods seem appropriate, however, much more detailed information is required regarding inclusion/exclusion criteria, as well as stepwise information about what occurred during the office visit. This section is still poorly written and needs more information along. STILL NEEDS TO BE ADDRESSED from last revision: Another major concern is the lack of clarity surrounding the assigning of Hideo Watanabe’s pain related categorization. It is unclear as to how these assignments were made, whether there was a series of questions or a physician assigned a score based on a clinical history. I see the scoring system, however, there is no indication of previous literature using this (established validity/reliability) or how it is utilized. Similar concerns for the KOA radiographic scoring.

3. The data seems sound, but analysis is still very unclear. This section should be majorly revised.

4. The manuscript does NOT adhere to relevant standards for reporting. Demographics could be presented in a table format, and specifically could be provided for the Pain and Radiographic subgroups. The same information is presented in both the table and figures (table 3 and figure 1 as well as table 4 and figure 2). Pick which way best represents the data presentation and avoid redundancy.

5. Discussion and conclusions do not initially focus on the findings of this specific study. The 2nd paragraph of the discussion seems very introduction focused, and the authors finally get to their findings in the 3rd paragraph. Needs far more focus in this area, and how THIS STUDY supports or refutes previous literature or theories.

6. Limitations were not stated anywhere within this manuscript

7. The authors do not clearly acknowledge any work that they are building on.

8. The title and abstract to adequately convey what has been found. The abstract is confusing the way it is written, worded. NPY is listed as demonstrating a significant INCREASE which implicates multiple assays for NPY concentration.
This should be more appropriately state as significantly higher concentrations being found in KOA.

9. The writing is unacceptable as currently written. Needs substantial work in order to become acceptable for publication. Results are presented as if there is an INCREASE IN NPY concentrations as opposed to higher concentrations being found. Also, after NPY throughout the manuscript there needs to be a word such as concentrations or levels. The use of “upward trend” is confusing as well. Is it positive correlation or generally increasing NPY concentrations? The authors should try to write more in active voice. Furthermore, there are a significant number of typos and spacing issues throughout.

Major Compulsory Revisions:

Abstract:
1. Methods section in abstract is still very unclear. The subcategories should actually be in the results portion. Your methods appear to be (and should logically flow): Participant recruitment, Pain assessment, Radiographic assessment, Arthrocentesis.

2. Results: First sentence does not need Watanabe’s pain score lead in. Remove this and start with “NPY in synovial fluid was significantly higher in…”

3. Many spacing and capitalization issues throughout Results.

4. Results should be broken down into sub-analyse of pain score and stage.

5. Need spaces in between means and standard deviations

6. Results: unclear by what ‘upward trend’ is.

7. Conclusions: state that a correlation was found yet no correlational tests were run? Primary finding is that NPY concentrations were higher in KOA than in healthy controls.

8. Key Words: only 1 word is NOT in the title. Select words that are not represented in title (correct spelling error of synovie?)

Methods:
9. Still extremely unclear as written and substantial revisions are necessary.
10. No need for inpatients and outpatients to be stated…they are all patients and there is no further analysis nor mention of in vs. out-patient.
11. “One hundred patients were recruited from the department of…” No need for 100 joints.

12. Bilateral assessment is still not clear. In patients with bilateral KOA, it appears that the MORE SEVERE SIDE (?) was assessed. However, who determined which was more severe, was this by the physician or patient? And was this objective or subjective?

13. Exclusion criteria needs to be re-written. It is confusing as written and may need more explanation for certain areas. For example, history of knee joint trauma – is this EVER in their lives? Also, NSAID use…is this ANY use in the last
4 weeks? Lastly, other musculoskeletal condition…is this anything? Self-reported?

14. Control group consisted of 20 healthy participants…recruited from where???
How is the peak bone mass defined? No KOA or other diseases (All diseases???
Self-reported???)

Arthrocentesis:
15. As listed….it appears that arthrocentesis was done prior to pain assessment and radiographs.
16. This section should not have a 1 sentence paragraph about positioning on stretcher. Fold into the 2nd paragraph
17. Unclear as to the location of the aspiration… “directly behind the patella” was their a superior/inferior or medial/lateral approach?
18. Sentence starting with “Upon insertion…” there are spacing issues and it is unclear with the “and after 20sthe synovial” Only 1 to 3 mL was aspirated? Was this as much as could be aspirated? Was it the same for each person? How did you decide on the 1-3 if you put 3 mL of saline in???
19. Same sentence as comment 18, change centrifugal to centrifuged. And “until needed” to “until analyzed”

KOA Pain assessment:
20. Pain was assessed according to Hideo….
21. I am still unclear as to WHO categorized patients…did patients select this, did physicians assign based on a history?

KOA radiographic assessment:
22. Eliminate first sentence (unless a decision was made AFTER radiograph was taken).
23. Radiographs were weight-bearing, please include in 2nd sentence.
24. You have a capital The…consider having this a stand alone sentence instead of a compound sentence
25. This Grading seems like a modification of Kellgren Lawrence (which is fine), and it seems that the grades come from Koshino, however, who decided on the defining of the Stages?
26. Unclear as to WHO assessed, was it one physician? Radiologist? Study investigator?

Statistical Analysis:
27. This section needs to be re-written with drastic revisions.
28. STILL did not address what statistical package was utilized for analyses.
29. First sentence seems like a fragment…is there a table that you want to reference with this?
30. ANOVA is not typically done for homogeneity of variances
31. State that group t-test was used to compare the means of KOA group with healthy control group….but OF WHAT DEPENDENT VARIABLES?

32. Still question whether analyses were correct. ANOVA, Pearson’s correlation, and t-tests are definitely appropriate. But perhaps a linear regression for the pain scale sub-analysis?

Results:

33. KOA pain and NPY: subdivisions no pain group (n = 12)….use parentheses and maybe put an n.

34. Page 7 under figure 1: how is there a positive correlation with no correlations ran in the analysis section? This is possibly where a linear regression will be more appropriate.

35. Same page/paragraph, 2nd sentence starting with “NPY concentrations demonstrated…” reword to NPY concentrations were significantly higher in KOA patients than in healthy participants” Take out or SUBSET the subcategories into the final sentence of that paragraph.

36. KOA radiographic grade and NPY: 1st sentence…revise to 100 KOS patients were divided into 3 stage groups according to Tomihisa scoring system: Early, middle, and advanced.

37. Page 8 under figure 2…spacing issues in 1st sentence. Also, same issues as comment #35.

Discussion:

38. First 2 sentences unnecessary. Eliminate.

39. Sentence starting with “Due to the important role” NPY has already been previously defined.

40. 2nd paragraph, Primary finding is that MPY concentrations were significantly higher in KOA patients compared to healthy controls. Eliminate according to watanbe’s pain score until the next sentence.

41. Consider new paragraph starting with “As pain increased we found significantly higher NPY concentrations…..”

42. Bottom of page 8 “which matched the reported clinical observations where…” this sentence is a run on and extremely confusing…rewrite.

43. Page 9: Sentence that starts with Moreover… You already dated this is a primary finding. I would start this paragraph with “NPY concentrations in synovial fluid of middle and advanced KOA stages were significantly higher than early KOA stage.”

44. “We further demonstrated a positive correlation” Still no evidence of a correlation being run.

45. Sentence starting with “But NPY in synovial fluid of adavanced stage KOA..” this sentence is very confusing. Re-write or eliminate.

46. I like the notion of lack of agreement between objective x-rays and subjective
pain reporting by patients. This is a strength of your study that you highlight other research finding as well. BUT did they use any of the same subscales of classifications as you did?

47. Last Paragraph that goes into pro-inflammatory mediators is unnecessary and I would eliminate altogether.

Conclusion:

48. Study demonstrated a positive correlation? Still no evidence of this anywhere. What you found was biochemical distinction of NPY concentrations in KOA vs. healthy patients.

49. This paragraph should be re-written as I do not think it articulates the summary of your findings. Therapeutic interventions would not USE NPY, but would perhaps target NPY.

50. The last sentence of the conclusion should be what the paragraph is built around, perhaps move this to your 2nd sentence.

Minor Essential Revisions

1. Background: correction spacing issues in last sentence.
2. Background: consider changing “concentration of NPY” to “NPY concentrations” throughout document
3. Patients: “change control groups were twenty” to control group was 20 healthy participants
4. Results: space after 56 before the sd.
5. Results: 2nd sentence, which was not significantly different (Drop the e typo at the end of the word)
6. Results same sentence, P = should be lower case p that is italicized

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.