Author's response to reviews

Title: Relationship between CTX-II and patient characteristics, patient-reported outcome, muscle strength, and rehabilitation in patients with a focal cartilage lesion of the knee A prospective exploratory cohort study of 48 patients

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Author's response to reviews: see over
Authors’ response to reviews

Dear Editor,

We are pleased to submit our revised version of the manuscript entitled “Relationship between CTX-II and patient characteristics, patient-reported outcome, muscle strength, and rehabilitation in patients with a focal cartilage lesion of the knee. A prospective exploratory cohort study of 48 patients”.

We apologize for the delay with our revision of the manuscript. We are grateful for the reviewers’ constructive criticism which has helped us improving the quality of our manuscript.

Please see our point-to-point response to the reviewers comments below, all our comments are bulleted. In the uploaded revised manuscript we have used the “track changes” function on all changes made.

On behalf of the authors,

Sincerely,

Jan Harald Røtterud

Comments from the Associate Editor:
Good manuscript that addresses a void in the literature. There are a few minor edits/changes needed before publication can be considered.

Associate Editor’s Request:
We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.

• As requested by the Associate Editor we engaged a professional language editor to copyedit the manuscript and several corrections have been made.

Reviewer's report

Title: Relationship between CTX-II and patient characteristics, patient-reported outcome, muscle strength and rehabilitation in patients with a focal cartilage lesion of the knee A prospective exploratory cohort study of 48 patients
Reviewer's report:
This manuscript describes the study of a urinary biomarker, CTX-II, a breakdown product of type II collagen, in a population of patients who have undergone a 3 month exercise or rehabilitation programme, prior to being treated with autologous chondrocyte implantation. Results of this patient group were compared to a small group of ‘healthy’ adults.

It is an interesting study which appears to have been carefully performed; there are many studies of biomarkers in patient groups with other degenerative joint disorders but little has been done in this cartilage repair group. Hence there is certainly novelty value in the study and I would recommend its publication.

There are some relatively small points which might improve it a little.

1. How do the authors define osteoarthritis (page 4) for the purpose of excluding patients from the study? Is it the presence of any osteophytes, however, big and/or the loss of a certain measurement of joint space or some other way?
   - We agree that the definition used for OA is important information and have therefore added the following to the Method section: “The presence of OA was evaluated radiographically [13] according to the Kellgren-Lawrence (K-L) classification by the including orthopedic surgeon, [14] and OA was defined as K-L grade $\geq 2$."

2. Last line, page 5: presumably a ‘x’ is missing when describing the dilution required (ranging from 1-50)?
   - We agree, however, instead of using “x”, we rephrased the text as follows: “…, ranging from 1:1 to 1:50.”

3. 3. Page 7: Was any attempt made to record the level of activity of the control group, eg did they undertake regular sport or training or have a manual or sedentary job? This could be interesting given the results seen in the patient group in response to exercise. (Ideally this group would have undergone the exercise regime also!)
   - Unfortunately no data was collected regarding the activity level of the control group; therefore we have no data to add to the manuscript on this issue.

4. It would be interesting to know the relative values found in this patient group in comparison to other studies with osteoarthritic changes. Perhaps this could be included in the Discussion, since there are many studies of this marker,
particularly in OA.

- We agree with the reviewer that this information is of importance, and have therefore added the following to the Discussion section: “The mean CTX-II concentration found among the patients in the present study were 579 ng/mmol, which is on a similar or even higher level as CTX-II concentrations found in previous studies on patients with OA. Sowers et al. [7] found a mean CTX-II concentration of 345 ng/mmol in 20 patients with severe knee OA (K-L grade 3-4), and Jung et al. [25] reported a mean concentration of 429 ng/mmol in 37 patients with knee OA.”

The English would benefit from a little improvement but it does not hinder the interpretation of the science.

- Action taken, see our comments under Associate Editor’s Request.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being Published

- Action taken, see our comments under Associate Editor’s Request.

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.

**Reviewer's report**

**Title:** Relationship between CTX-II and patient characteristics, patient-reported outcome, muscle strength and rehabilitation in patients with a focal cartilage lesion of the knee A prospective exploratory cohort study of 48 patients

**Version:** 1  **Date:** 11 December 2013

**Reviewer:** Brian Pietrosimone

**Reviewer's report:**
I think the current study is interesting and timely. CTXII is a relevant marker of cartilage breakdown and potentially progression to OA following acute injury. The current study evaluated associations between CTXII and a variety of demographics and clinical impairments. Additionally, the authors attempted to evaluate differences in CTXII compared to a small control group. I think that there are a few issues that should be addressed.

**Major / minor essentials**
Abstract: The results in the abstract are ambiguous. There are points in the manuscripts when authors state that age was the only relationship while here and in the table quadriceps strength is associated with CTXII. Also, results of abstract say quad strength and CTXII correlate and later in that sentence muscle strength is said not to correlate- please address.

- The correlations between CTX-II and age and quadriceps strengths were the only statistically significant relationships. However, when the correlations were classified by strength ((correlation coefficient \([ r ] < 0.20\)), weak \((r = 0.20 – 0.39)\), moderate \((r = 0.40 – 0.59)\), strong \((r = 0.60 – 0.79)\) and very strong \((r > 0.80)\)), all correlations, except for age, were classified as weak or very weak. The relationship between age and CTX-II was therefore the only relationship considered as clinically relevant. The relationship between quadriceps strength and CTX-II was significant, but classified as weak/very weak, and therefore not considered clinically relevant. We have checked these results and statements thoroughly throughout the manuscript, including the abstract and tables, and we found no inconsistency. However, we agree that the classification of the correlations should be made more to clear, and have therefore added the following to the Methods section in the abstract: “Correlations were classified as very weak (correlation coefficient \([ r ] < 0.20\)), weak \((r = 0.20 – 0.39)\), moderate \((r = 0.40 – 0.59)\), strong \((r = 0.60 – 0.79)\), and very strong \((r > 0.80)\).”

Results section of abstract provides no correlations and that is the main outcome measure.

- In order to keep the abstract short and to the point, we have stated the most important results from the correlation analyses on an overall basis in the first paragraph in the Results section of the abstract: “Except for age and quadriceps strength, no significant correlations were found between CTX-II concentrations and baseline characteristics, KOOS or muscle strength. Except for age, all correlations were considered as weak or very weak.” To include the actual correlation coefficients would, in our opinion, not add crucial information to the abstract for the reader, but make it longer and more winding. However, all correlation coefficients are available for the readers in the tables.

Introduction: Add Chmielewski et al. ACL article to the introduction when you talk about CTX-II and its ability to predict progression to OA.

- We have added Chmielewski et al. as requested to the Background section with the following paragraph: “In addition, decreasing CTX-II concentrations after anterior cruciate ligament reconstruction have been associated with decreasing knee pain and improving function [11].”
Also the introduction does not explain why any of these associations should be evaluated or would be important for future treatment of post-traumatic OA.

- We believe this is stated in the Background section: “If CTX-II is to be used in monitoring treatment effects and natural history of cartilage lesions, there is a need for knowledge on the relationship between CTX-II concentrations and various patient-related clinical features and changes in CTX-II concentrations following rehabilitation in patients with cartilage lesions.”

Provide the timeframes in which you evaluated associations in the purpose statement as well as change scores.
- We have added “…undergoing a 3 month rehabilitation program” to the purpose statement in the Background section.

Methods

Did patients undergo traumatic injury? Were loose intra-articular bodies present
- We have added the following information to the Methods section: “24 patients related their debut of symptoms to a knee trauma and 13 patients had a history of osteochondritis dissecans.”

Did any patients have surgery in the past 3 months.
- There was a minimum of 6 weeks elapsed between the diagnostic arthroscopy and the baseline test session, so yes, some patients had surgery in the past 3 months. We have added this info to the Methods section: “All patients went through a diagnostic arthroscopy prior to inclusion. Baseline testing was performed at a minimum of 6 weeks after the diagnostic arthroscopy.”

Were the 4 patients lost to follow – up have different demographics than the mean of the rest of the sample.
- There were no differences in baseline characteristics between the patients lost to follow-up and the rest of the patients. Hence we have added the following information to the Methods section: “There were no differences in baseline characteristics between the patients lost to follow-up (n=4) and the rest of the patients (n=44) (data not shown).”

How was lesion size measured?
- We have added a description of this to the Methods section: “Lesion size was estimated using a standard 4-mm arthroscopic probe, measuring the longest anteroposterior distance and the width of the cartilage lesion.”

When were Urine samples taken? Second Void?
- Urine samples were collected at the same day as the physical testing was performed. Our priority was to collect the urine samples in advance of the
physical testing, in order to avoid any effects of the physical testing on the cartilage and CTX-II concentrations. Physical testing was done sequentially for each patient throughout the day from approximately 8 am to 3 pm. For the majority of the patients the urine samples were second void, however, we can not state this with certainty for all patients. We have therefore modified the statement as follows: “Urine samples were collected during daytime just prior to the physical testing”

Cite correction methods of CTXII concentrations.
- We have added “…as recommended by the producer,…” to the Methods section regarding this issue.

Controls did not due follow up testing…… is there data to suggest that Urine CTXII is a stable biomarker over time in healthy patients.
- Since we only analyzed CTX-II at one time-point (cross-sectional) for the controls, we have no data available regarding the putative stability of CTX-II over time in healthy individuals. Although, this would be of great interest.

Potentially term “CTX-II and baseline characteristics” as “CTX-II and baseline Demographics”
- We suggest in keeping the term “characteristics”, as we consider this a more adequate term in the case of describing the current variables. However, if “demographics” is the term preferred by the BMC, please let us know and we will of course change this terminology.

Why not make the history of previous knee surgery a dichotomous variable? Would this change if there is an association between CTX-II and this demographic.
- As suggested by the reviewer, we have now performed this supplementary analysis (correlation between previous knee surgery as a dichotomous variable and CTX-II), and it showed no significant correlation. Due to this outcome, we have refrained from adding the information to the manuscript.

Discussion: On page 10 there is no discussion about the relationship between CTX-II and quadriceps strength. Can you address this issue and explain what this association means at the initial presentation measure.
- We have added the following statement to the Discussion: “Even though a statistically significant correlation between CTX-II and quadriceps strength was found in the present study, the correlation was classified as weak and therefore not considered clinically relevant.”

The first paragraph on page 11 may be a bit strong suggesting that exercise is the reason for the change over time in CTX-II. There is no data to suggest that
exercise and not time or healing of the lesion could be the reasons for the
decrease in CTX-II over time.

- We agree with the reviewer, this study design could not conclude on any effect
  of rehabilitation. We have therefore added the following comment to the actual
  paragraph: “This trend could be related to a spontaneous healing of the lesion
  or just due to variations over time,…”.

**Level of interest:** An article of importance in its field

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

- Action taken, see our comments under Associate Editor’s Request.

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

- We consider that the statistical concerns from the reviewer are addressed in our
  previous comments.

**Declaration of competing interests:**
I have no competing interests