Author’s response to reviews

Title: Vastus medialis motor unit properties in knee osteoarthritis: a descriptive study

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Author’s response to reviews: see over
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Dear Dr. Ding,

We are pleased to submit a revised version of the manuscript, “Vastus medialis motor unit properties in knee osteoarthritis”.

We thank the reviewers for their thorough review and insightful comments. We feel that have adequately addressed the concerns of the reviewers and have strengthened the manuscript in the process. Each comment has been addressed in a point-by-point fashion (see below) and changes to the manuscript have been highlighted with the track changes tool in Microsoft Word.

Please let us know if there is anything else that you need. We look forward to hearing from you.

Sincerely,

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Reviewer 1

General Comments
The purpose of the present study was well defined. The method and results were appropriate and well documented, however some part of them was questionable. So, authors should modify or add some description. Discussion was well stated and supported by the results in the present study and previous studies. Small number of the subject would be limitation of this study. Moreover, there was large variability in severity of OA and weakness of force capacity for patient group. Consideration of interindvidual difference of them for patient group would need to fully understand the results of the present study.

Discretionary Revisions

1. “a descriptive study” may not be appropriate. Authors can omit subtitle.
   - “…a descriptive study”, has been omitted from the title. Please note that the “author guidelines” for BMC require a description of the study design in the title, but we as well would prefer to omit this if possible.

   [Abstract]
   -Background

   2. “… motor unit (MU) properties in a cohort of participants with ….” could be rephrased as “… motor unit (MU) properties in participants with ….”
   - this sentence has been altered accordingly

   [Background]

   3. “These results……(not greater) MU recruitment.” This description may be hard to understand for the readers. Authors need to rephrase or separate two or three sentences simply.
   - this sentence has been altered accordingly.

   [Second line in Discussion]

   4. “N-MUPs and S-MUP, provide…” could be rephrased as “N-MUPs and S-MUP provide…”
   - the comma has been removed.

   [Methods]
5. To show duration of knee OA (in years or month) can supply valuable information to understand characteristics of the subjects for OA group.
-We agree with the reviewer that symptom duration could have an impact on the observed MU differences, however we chose to define our population based on symptom severity according to Gossec et al. (2011). Furthermore, we suggest that symptom duration is difficult to measure as it is a subjective estimate based on patient recall, therefore we are reluctant to include duration of symptoms in the methods section. Assessing MU physiology in OA longitudinally would be a logical follow-up study to this one.

[Discussion]

6. Insertion of “number of Figure or table” after the sentences related with the results of the present study would lead to know whether authors are discussing for the result in the present study or not. For example,
-Third paragraph in Discussion “Alternatively, recruitment……observed in the OA group (Table 1).”
-“The significant of such small … control participants ( 1Hz) (Table 1) is questionable,”
-Fourth paragraph in Discussion “It is surprising … subjects was observed (Table 1)”
-references to Table 1 have been added throughout the discussion where appropriate for clarification.

[Fourth paragraph in Discussion]

7. “…was a non-significant ~22% difference …” could be rephrased as “…was a non-significant ~22% difference in maximal knee extension torque (or force capacity) …”
-this sentence has been altered accordingly

[Figure 1]

8. Please insert title into top of each panel group (MUP template; MUP stability; … ; Firing Graph) in Figure 1.
- The resolution of this figure has been improved. A title has been inserted at the top of each panel.

Major Compulsory Revisions

[Beginning of Back ground]

9. Because MVC test is the way to assess muscle weakness, assessment of muscle weakness in knee OA using MVC would be a matter of course. Thus, authors should state that there are little data about motor unit activation in knee OA patients during submaximal
contraction in this sentence if there are no studies to report about motor unit activation in knee OA patients during submaximal contraction.
- The first paragraph has been altered to reflect this idea. We suggest that the revised first paragraph provides clearer justification to undertake the present study.

[Methods, Motor unit properties, …about MU architecture and health.]

10. Mean of “health” is difficult to understand. Please rewrote in different word or add an explanation.
- The word “health” has been removed.

[Methods, Needle and surface EMG signalswere…]

11. Why did author select vastus medialis muscle within the four muscle components of quadriceps femoris muscle group. Please explain.
- Vastus medialis was selected for a numbers of reasons:
  1) DQEMG has been applied previously to the vastus medialis (see Doherty and Stashuk, 2003)
  2) Vastus medialis function is critically important of the biomechanics of OA (in particular the patellofemoral compartment, see Hinman and Crossley, 2007)
  3) Needle EMG is subjectively less painful in the vastus medialis than in the vastus lateralis
  4) Fink et al. 2007 showed muscle fibre morphological changes in the vastus medialis in patients with end-stage knee OA.
  5) Muscle atrophy as a clinical sign is usually noted in the distal vastus medialis.

- The methods section has been altered to include justification for selecting the vastus medialis

[Methods]

12. It is suspected that detection of individual MUP is difficult in surface EMG at 20% of MVC because of superimposition of two or more MUP. Authors should demonstrate or explain validity of decomposition at this force level in detail.
- DQEMG uses the needle signal as a trigger to extract individual S-MUPs from the raw surface EMG signal. The DQEMG software is able to exclude *needle* MUPs that are the result of two superimposed motor unit action potentials at 20% MVC (see references by Boe et al. and McNeil et al. cited in the manuscript). Once an individual MUP is identified, it is used as trigger to extract an MUP from the surface signal. The average surface MUP is extracted through spike-triggered averaging, so that superimposition in the surface signal is not an issue.

We agree with the author that the surface EMG interference pattern is complex and that is why spike triggered averaging using the needle signal was used.
13. **Surface EMG signal** (shape of action potential) is strongly influenced by subcutaneous tissue thickness (Farina et al. 2004, JAP). Also, there is a strong correlation between subcutaneous tissue thickness and BMI (Ludescher et al. 2011, Clinical Endocrinol (Oxf.)). In this study OA group has high BMI, thus subcutaneous tissue thickness in OA group may be greater than control group. Authors should discuss the effect of subcutaneous tissue thickness on the results obtained in the present study.
- We agree with the reviewer that larger BMI in the OA group could affect interpretation of the study results as increased bio-electrical impedance from subcutaneous tissue can affect the surface signal. However, it is important to point out that increased adiposity in the OA group would be unlikely to manifest at the level of the distal vastus medialis (increased abdominal adiposity would be more likely). Furthermore, increased subcutaneous tissue would serve to reduce the amplitude of the S-MUPs observed in the OA group (we observed a tendency toward increased S-MUP amplitude in Figure 2). Therefore, we suggest that while this is a valid observation, its inclusion in the discussion would be tangential to discussion of the study results.

15. **There is large variability in WOMAC Score in OA group**, meaning that the individual subjects in OA group have different severity of OA. Moreover, large variability was demonstrated in weakness of MVC for OA group (approximately -45% ~ +1% to average value of control group). From these results, consideration of interindividual difference in severity of OA or MVC could lead to understand the results for OA group obtained in the present study. Thus, it would be needed analysis or discussion of the results related with interindividual difference in these characteristics for OA group.
- Unfortunately, we do not possess the necessary sample size in this study to undertake an analysis of the relationship between disease severity and MU changes. It is probable that the magnitude of MU change is related to the severity of symptoms. We have observed that other measures of quadriceps function (e.g. isometric torque, isotonic power, voluntary activation, muscle volume) are altered across a clinical spectrum of knee OA (papers under review with Journal of Applied Physiology and Arthritis Care & Research). It would be interesting in a follow-up study to measure changes cross-sectionally or longitudinally, however the purpose of this study was to measure MU parameters between a healthy versus and OA cohort. We have included this idea in the limitations paragraph.
Reviewer 2

Dear Editor,

The manuscript entitled ‘Vastis medialis motor unit properties in knee osteoarthritis: a descriptive study’ is a well-written manuscript and important in its field. Research investigating neuromuscular mechanisms of osteoarthritis is limited, especially at the motor unit level. This study utilizes needle electromyography to gain insight into potential alterations that may be occurring at the focal muscle level, with the advantage of also recording global muscle activity with the decomposition based electromyography system. The main limitation of this system is the inability to record muscle activity during maximal contractions. It would have been nice to see recordings from different percentages of maximum, not just 20% to see if motor unit recruitment strategies are also different at low-levels of MVC. The changes in motor unit recruitment and rate coding strategies observed in the OA group are findings that lead to a number of potential explanations, which helps advance the field in the direction that future studies can go. I have addressed a few grammatical errors and have made some discretionary/minor essential reviews in the following paragraphs.

Minor Essential Revisions:

1. Abstract. Last sentence of background, add ‘to’ after ‘The purpose of this study was’
   - Corrected

2. Abstract. In the results paragraph you need to clarify that the size-related changes and MUP firing changes were found during the submaximal contractions.
   - Corrected

3. Background: line 10. You state that ‘MU activity is altered in models of disuse, aging, pain and disease’. What are these alterations? Provide a sentence or two on what has been found.
   - The following sentences have been added: “For example, in healthy aging, collateral reinnervation leads to recruitment of larger MUs at reduced firing rates to maintain the same relative contractile intensity compared to younger subjects [1]. Also, experimentally induced joint pain leads to recruitment of different MUs and reduced firing rates compared to a non-painful muscle contraction [2].”

4. Background: At the very end of your background section state what your hypothesis is
   - “We hypothesize that MU recruitment and rate coding strategies will be altered in the presence of chronic knee pain associated with OA.”
5. Methods: in the ‘Motor unit properties’ paragraph, first sentence, change to: “…..from both an intramuscular concentric needle electrode and surface recording electrodes.”
- corrected

6. Methods: in the ‘Motor unit properties’ paragraph, your first use of S-MUPs is introduced with spelt out in long form, therefore that should read “The MUP train further serves as a time-locked trigger to extract individual surface motor unit potentials (S-MUPs) from the…..”
- corrected

7. Methods: in the ‘Motor unit properties’ paragraph, when discussing how the needle and surface EMG signals were acquired….when you state the active electrode was applied to the belly of the vastus medialis, and tell the reader your means to determine its location, you need to also clarify here that you placed the active electrode over the motor point of this muscle as it is a monopolar recording.
- changed to: “The active electrode was applied over the motor point of the vastus medialis (3 fingerbreadths superiomedial to the base of the patella).”

8. Figure 1. This figure is not at all clear in the print out, so make sure it passes the quality check.
- Please see response to comment 8 for Reviewer 1.

9. Results section: did you compare the males/females within each group to make sure no differences in MUPs? If so, should state that you compared the males and females within each group and found no differences. If not, this should be addressed.
- We did not compare males and females as we did not possess the necessary study power to do so. While sex differences in MU recruitment in an OA cohort are possible and require investigation, we suggest that because this was not a primary purpose of the study and because groups were matched for sex in this study, that this comparison be omitted.

10. Results section: second paragraph, 7th line. “The area-to-amplitude ratio (ARR)” needs to be changed to (AAR).
- corrected

11. Discussion: Need to address the fact that the knee OA group may not actually be doing an MVC (or getting as close to an MVC) compared to the healthy group due to pain.
- We agree with the reviewer that reductions in voluntary activation have been observed between a control group (or limb) and OA group, however it has recently been established that this observation is not uniform throughout the literature (Pietrosimone BG, Hertel J, Ingersoll CD, Hart JM, Saliba SA: "Voluntary quadriceps activation deficits in patients with tibiofemoral osteoarthritis: a meta-analysis. PM R, 3:153-162.") and differences may be due to
methodological issues associated with measurement of voluntary activation. We also have recently submitted a study showing that with proper warm-up and motivation, even participants with severe knee OA can achieve levels of activation similar to healthy controls (submitted to Journal of Applied Physiology, June 2011). Furthermore, as we did not measure voluntary activation in this study, it would be speculative to suggest that participants in the OA group would not be able to achieve a “true” MVC due to joint pain.

12. Discussion: It is mentioned that duration and AAR are not as affected by electrode position, but you should also address the point that needle-MUP duration is not a reliable measure.
- In the discussion, we reference a review by Stalberg highlighting the reasons why duration and AAR are more valid and reliable than N-MUP amplitude in providing information about MU morphology. It has also been shown by our group that N-MUP duration is a reliable measure in a test-retest situation (see, Boe SG, Stashuk DW, Doherty TJ: Motor unit number estimation by decomposition-enhanced spike-triggered averaging: control data, test-retest reliability, and contractile level effects. Muscle Nerve 2004, 29:693-699 and Boe SG, Antonowicz NM, Leung VW, Shea SM, Zimmerman TC, Doherty TJ: High inter-rater reliability in analyzing results of decomposition-based quantitative electromyography in subjects with or without neuromuscular disorder. J Neurosci Methods, 192:138-145).

13. Discussion: paragraph that starts with: “Alternatively, the recruitment of larger MUs ……” The third sentence in this paragraph, “as a result, the discharge rate…..” is very awkward/confusing, can you reword this.
- altered to, “In this scenario, a larger MU would be required to maintain a given contractile intensity in the setting of reduced firing rates (i.e. a matching of rate coding to recruitment to maintain a given contractile intensity).”

14. Discussion: The second sentence following the above mentioned (12), “it has been shown in experimental pain models that MU firing rate……” Needs a reference.
-reference added

15. Acknowledgment at funding section. “MB is supported by….needs to be changed to “MJB”
- corrected

16. Reference section: reference 5 is missing information about journal page numbers and volume
-corrected
17. Reference section: reference 16 is missing information about journal page numbers and volume
   - corrected

18. Table 1. It would look nicer/read easier if you lined up all the +/- in the control and OA columns
   - corrected

19. Figure Legend. Figure 2. What you state is represented as your control (open bars) and OA (solid bars) is different than what is in your actual figure.
   - corrected