Author's response to reviews

Title: Dynamic contrast enhanced Magnetic Resonance Imaging in chronic Achilles tendinosis

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Author's response to reviews: see over
To the editor of BMC Medical imaging

Dear Editor
Thank you for considering our manuscript “Dynamic contrast enhanced MRI in chronic Achilles tendinosis”. We have now read and considered the comments from the reviewers. We have responded to those on a point-by-point basis, see below. We hope that you will now find the manuscript suitable for publication in BMC Medical Imaging.

Best regards,

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Reviewer 1 (Dr Jan D. Rompe)
1. The way how to perform dynamic MRI is described and understandable only to specialists in the field.
Answer: The following text has been added to the introduction (p2, §2);
At dynamic contrast-enhanced MR imaging (DEMRI) of the Achilles tendon several images are obtained at fixed time-points after the injection of an MRI contrast agent. By analyzing the changes in signal intensity it is possible to calculate the physiologic kinetics. This gives information about tissue vascularity, perfusion and capillary permeability [16-17].

2. No reasonable explanation was given on the discrepancy with the findings from Shalabi et al. [20].
Answer: We have now given a possible explanation to this discrepancy in the first § in the discussion section;
This finding is in disagreement with a previous study by Shalabi et al [23], and a study by Richards et al [20], where both these studies could show an increased AUC on the symptomatic tendon before treatment. This difference might be due to differences in duration of symptoms. The patients in Shalabi's study had a median symptom duration of 12 months compared to the 31 month median duration in our study. In Richards' study the duration was not reported. It might therefore be that the AUC had already returned to baseline due to the relatively long duration of the symptoms in our chronic tendinosis patients at the time of inclusion in our study.

3. With regard to "treatment":
How did you make sure, that only the symptomatic Achilles tendon did have heavy-load eccentric training, and not the asymptomatic as well?
Answer: The patients were instructed to exercise the injured tendon. It is possible that some patients might have also trained their uninjured tendon too. We have clarified this in the M&M section under the header "training" where it is now stated;
The eccentric loading was performed with all body weight on the symptomatic side.
and
The patients were instructed to train their symptomatic side, but it is possible that some patients might have also trained the non-symptomatic side.

4. How did you make sure, that there was reliable eccentric training as demanded from Alfredsson. How did you ensure compliance?
Answer: the patients were instructed by a physiotherapist. This has now been clarified in the manuscript;
To ensure compliance the patients saw a physiotherapist on two occasions and were contacted once on telephone.

5. A statistiscian should have a look at the "methods" section.
Answer: We consulted a professional statistician who conducted all statistical calculations.
Reviewer 2 (Dr Roland Syha)

Major Compulsory Revisions

1. Material and Method:
Patients: Concerning the previously published patient material the authors should point out in more detail whether data published in this study is concordant to the previous publication (e.g. are the evaluated pain/performance values identical to the data of the mentioned previous study?).

Answer: It is stated in the first line of the M&M section that the patients are a subgroup from a previously published study (Shalabi A, Kristoffersen-Wiberg M, Svensson L, Aspelín P, Movin T: Eccentric training of the gastrocnemius-soleus complex in chronic Achilles tendinopathy results in decreased tendon volume and intratendinous signal as evaluated by MRI. *Am J Sports Med* 2004, 32: 1286-1296.) Because median values are used in both studies the values appear to be identical, despite that there are 5 patients less in the current study than in the previously published study.

2. Evaluation of Dynamic MRI: “the most centred one was chosen”??? How did the authors reach that measurement in the follow-up examination was in the same location compared to baseline assessment.

Answer: All slices were placed by a skilled research radiographer who had received careful instructions by a musculoskeletal radiologist. These obtained slices were then reviewed by the researchers and the slice that was most centered was selected for further analysis. To enable correct placement of the ROI’s distance measurements were made. This has been clarified in the M&M section where it is now stated:

*From the two sagittal slices obtained from each Achilles tendon in every set, the most centered one was chosen by visual estimation.*

and

*The ROI’s distance from the upper posterior margin of the calcaneal bone was noted to ensure correct placement of the ROI at the follow up examination.*

3. If not, how does a change of location influence the reliability of measurement? Is data available concerning reproducibility of measurement?

Answer: We have not calculated the reproducibility of the measurements.

4. Why did the authors choose a ROI of 5mm in the fat ventrally of the tendon compared to a ROI of 2 mm in the other regions?

Answer: The largest possible ROI is desirable in order to avoid too much influence from noise. A ROI of 2 mm in the tendon was chosen in order to make sure that the ROI would fit inside all tendons, including thin tendons. In vessels a ROI of 2 mm was chosen in order not to include surrounding fat. In fat we used a ROI of 5 mm with the intention that a bigger ROI would give a more representative measurement.

Minor Essential Revisions

5. Introduction: One previous study concerning DEMRI is missing and should be added to introduction as well as discussion (Richards PJ et al, Longitudinal microvascularity in Achilles tendinopathy (power Doppler ultrasound, magnetic resonance imaging time-intensity curves and the Victorian Institute of Sport Assessment-Achilles questionnaire): a pilot study., *Skeletal Radiol.* 2010 Jun;39(6):509-21).
Answer: We appreciate being informed of this reference. The reference has now been mentioned in both the introduction and discussion section, in accordance with the wishes of the reviewer.

2. Material and Method:
Patient: Inclusion and exclusion criteria should be pointed out in more detail (e.g. what was the source of tendon pathology in those who were not mentioned as sports related? Did the authors exclude patients with systemic diseases or conditions which might influence tendinous tissue, e.g. gout, rheumatic diseases, drug intake…?).
Answer: In 11 patients the cause of the tendinosis was unknown. This has now been stated; The remaining 11 were regarded as idiopathic.

The exclusion criteria have now been written out in M&M;
Previous corticosteroid injections and systemic diseases such as rheumatic disease constituted exclusion criteria.

4. What did the authors mean by “technical problems” in detail?
Answer: The used protocol was not a standard clinical protocol. Unfortunately we experienced difficulties when starting the imaging protocol at the correct time in 3 of the patients and extravasation in one. To clarify we have now stated; Because of technical problems when performing the DEMRI (three cases of incorrect contrast injection timing, one with extravasation and in one case intolerance of the contrast agent) only 20 patients of the original 25 patients participated in this dynamic contrast study.

5. Concerning the practiced sport the study group is very heterogeneous. This should be mentioned in the limitations section of the discussion.
Answer; we have now mentioned the heterogeneity as a limitation;
In this study 20 patients with chronic achillestendinosis were studied. In nine of those the tendinosis was sports related, while 11 were idiopathic. Although most of the sports related were due to running (n=7) the heterogenous material in our study is a limitation. When our study was planned and conducted the questionnaire by Curwin and Stanish was used at our institution. That questionnaire is easier to use for the patients, but to enable comparisons with other studies it might have been better if the VISA-A questionnaire had been used.

6. Treatment: Did the patients perform the exercises with or without supervision? Please state on this!
Answer: The patients saw a physiotherapist at two occasions and were contacted once on telephone during the home exercise period. This has now been stated in the M&M.
To ensure compliance the patients saw a physiotherapist on two occasions and were contacted once on telephone.

7. Why did the authors choose the questionnaire of Curwin and Stanish. The used questionnaire should be compared to other established questionnaires (e.g. VISA-A).
Advantages and disadvantages as well as limitations should be pointed out in the discussion.
Answer: Please see above (point 5)

8. MRI acquisition: Figure 1 shows a T1 weighted imagewithout fat suppression. Did the authors use a fat suppressing technique for image acquisition? If not, could it be useful to apply a fat suppression?
Answer: We have now stated the image sequence (PD weighted image) in the figure legend. We agree with the author that fat saturation might theoretically have been beneficial, but we have no experience on fat sat at Achilles tendinosis imaging.

9. Discussion: The obtained results should be compared to other imaging approaches (e.g. Mailliaras P et al, Achilles and patellar tendinopathy loading programmes: a systematic review comparing clinical outcomes and identifying potential mechanisms for effectiveness, Sports Med. 2013 Apr;43(4):267-86). Concerning DEMRI the study mentioned above (Richards et al) should be included.

Answer: The study by Richards and Malliaras have been added to the discussion section; In a recent review of loading treatment programmes the majority of studies did not find any association between improved imaging parameters and clinical outcome in Achilles tendinosis [24]. A pilot study evaluating longitudinal microvascularisation of Achilles tendinosis showed that pain is not invariably associated with microvascularity. [20]. This may explain the lack of correlation with symptoms in our study.

10. The conclusion is quite short and not very informative. What are consequences for the future? What are possible next steps?

Answer: Reviewer 1 appreciated the short conclusion. We have therefore decided to make a "midway" between those two opinions, so that the two last paragraphs now read; The lack of correlation with symptoms indicates that dynamic enhanced MRI is currently not a useful method to evaluate chronic Achilles tendinosis compared to MRI without contrast media. Further development of imaging methods to visualize the pathology at chronic Achilles tendinosis is necessary. For example, the use of ultra short echo time (UTE) at MRI makes it possible to demonstrate features that are not apparent with conventional MRI sequences [25] which may make it possible to quantify the subtle signal changes at Achilles tendinosis and its treatment.

In conclusion there was an increased contrast-media enhancement in the fat ventrally of the tendon in Achilles tendinosis that disappeared after three months of training, but otherwise dynamic contrast enhanced MRI did not show any additional value.

11. Figure: Patient gender and age as well as clinical setting should be mentioned. Image type (T1 weighted without fat suppression) as well as sequence type should be added.

Answer: Imaging details have been added;

Proton density weighted turbo spin-echo image of the right Achilles tendon prior to eccentric training in a 45-year-old man with chronic Achilles tendinosis. There is a fusiform thickening of the mid-portion of the Achilles tendon with increased intratendinous signal. The measurement regions of interest were placed in: A = the tendon, B = the fat ventrally of the tendon and C = a vessel.

Discretionary Revisions
12. Introduction: The pathologic background is described shortly, but adequate. Maybe different imaging approaches to tendinosis should be explained in more detail and advantage/disadvantages should be pointed out (ultrasound,
non-enhanced, contrast enhanced MRI).

Answer: The following text has been added to the introduction section; *By using ultrasound tendon thickening, hypoechoic areas and neovascularisation can be visualized and quantified [4,10,11]. Unfortunately ultrasound is user dependent and reproducibility is limited [12]. MRI techniques focus on measuring tendon thickening and on quantifying areas of intratendinous high signal [10,11,13]. By also administering intravenous gadolinium contrast media the intratendinous signal changes have been shown to be more pronounced [11].*

13. Furthermore new approaches in MRI (UTE) could be mentioned at the end of the first section as they underline the theory of change of intratendinous water content.

Answer: The second last § has been modified so that UTE is now mentioned; *Further development of imaging methods to visualize the pathology at chronic Achilles tendinosis is necessary. For example, the use of ultra short echo time (UTE) at MRI makes it possible to demonstrate features that are not apparent with conventional MRI sequences [25] which may make it possible to quantify the subtle signal changes at Achilles tendinosis and its treatment.*

13. Was a post-processing of MR images concerning motion artifacts performed?

Answer: No post-processing was performed

14. For quantification of vascularity signal intensity and area under the curve were chosen as surrogate parameters. Other common used parameters are blood flow, blood volume or k-trans for assessment of permeability. The authors should point out the advantages and disadvantages of the different parameters in the discussion.

Answer: The more classic parameters of dynamic contrast enhanced MRI such as blood flow, blood volume and K-trans are useful in more vascularised tissues such as brain. In tendinosis the vascularisation is probably too low to enable such measurements. However, we do not have any experience of such measurements in tendons so we have therefore chosen not to speculate on this matter.

15. Furthermore the usefulness of application of i.v. contrast medium is not really underlined by this study. Maybe a comparison to other parameters (non-enhanced MR images, Diameter, Volume) could be helpful to highlight the additional information gained by the use of i.v. contrast medium.

Answer: In our study we could not see any additional value of contrast media in patients with chronic Achilles tendinosis. However, a previous study has shown such a value. To better point out the previous research we have reformulated a sentence in the introduction section, which now reads; *By also administering intravenous gadolinium contrast media the intratendinous signal changes have been shown to be more pronounced [11].*

16. **Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

Answer: We consulted a professional statistician who conducted all statistical calculations.