Author's response to reviews

Title: Mechanical properties during healing of Achilles tendon ruptures to predict final outcome. A pilot Roentgen stereophotogrammetric analysis in 10 patients

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Author's response to reviews: see over
Dear Dr. Moylan,

A revised version of the manuscript ID 2856476761297146 has now been uploaded, and the reviewers’ critique has been addressed point by point (following this letter). The paper has two messages:

1. that this new method allows studies of tendon mechanics during healing
2. that mechanics during healing might predict the final result.

I believe this method might become useful for future studies, due to its relative simplicity, and therefore is of interest to publish. The second message is significant, based on sound statistics, but we agree that it might not be trusted anyways, due to the small sample.

The study has therefore been renamed as a pilot study, and the conclusion section starts with an acknowledgement of the need for a larger study to confirm the results.

We hope you will now find the paper acceptable.

Sincerely,

Thorsten Schepull
Authors reply to Dr. Leppilathi

Reviewer's report:

General
The aim of the study is interesting. The question “how mechanical properties could predict clinical results at AT rupture surgery” is also relevant and interesting.

However, this study consist only of ten patients, and two were annu excluded before one year, leaving 8 patients. My opinion is, that 8 patients is only a pilot of system, data is insufficient to give any recommendations and answers to the aim.
ANSWER: We agree that the small number of patients makes it suitable to describe this as a pilot study, and have changed the text accordingly. However, as you know, statistical methods do indeed correct for the number of data points, and we did use non-parametric methods.

At one year control repeat loadings were not measured and the pedal forces did not include 200N as in previous measures.
ANSWER: Due to the radiation dose, we had to limit the number of exposures. At the one year examination, we chose to use the limited number of exposures allowed to make a rough load-deformation curve, instead of repeat measurements. We agree that the approximation of the load-deformation curve as linear is a simplification that makes our estimates rough. However, in a future comparative study this will be a systemic error, and it will be the same for all patients.

So
1) The average of the strain per force values did not correlate with clinical outcome as heel rise index.
2) The modulus gave correlation, but the modulus of elasticity showed a great variation.
3) Specific stiffness did not correlate significantly with clinical outcome as heel rise.
Thus the power of the study is not sufficient and give any recommendations.
ANSWER: We admit these points. What the reviewer seems to suggest is that the significant correlation ($P = 0.02$) should be corrected for mass significance. However, the other mechanical variables are clearly dependent on each other, so that traditional correction would be too conservative, especially in consideration of the statistical trend for specific stiffness. Therefore the statistical significance of our modulus finding is strong. We have, however, moderated our statements and describe this as a pilot study.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Specific comments
Title of the study: This study do not show, that mechanical as strain/force and stiffness could predict the final outcome. Only modulus correlate.
ANSWER: We have changed the title to accord with this.

Abstract:
Background: There are clinical studies, where healing of human AT ruptures and specially tendon elongation have been monitored with titan markers. (Mortensen et al, Kangas et al).
ANSWER: We agree and now refer to both Mortensen et al. and Kangas et al. (which was unpublished when our manuscript was submitted) in the introduction. The abstract has been changed to highlight that we were interested specifically in the mechanics of healing.

Methods: 10 patients is insufficient number.
ANSWER: The statistical analysis is correct, and compensates for the number of patients. In spite of this, we now describe this as a pilot study.

Results: Included only the median strain per force, which however did not correlate significantly with clinical outcome.
Conclusion: Some of this belongs to results, for instance sentence: “Modulus of elasticity....
ANSWER: This has now been corrected, so that results are presented under the right subheading.

The centence “RSA has potential for comparing different treatments of AT ruptures” cannot be a conclusion, because this did not belong to a study protocol. The same concerns individual training and the influence of surgery on the outcome.
ANSWER: This has now been corrected, we only say that that the RSA method might have potential for comparing different treatments of Achilles tendon ruptures.

Background
First sentence is “ It is impossible to know when a patient with a healing tendon injury can first be recommended load-bearing, and how much load to start with.” There are studies concerning loading after AT rupture repair and the authors could refer to them.
ANSWER: None of these studies suggest a method for individual adjustment, but can only suggest general treatment regimes, i.e. “rules of thumb”.

“Postsurgical treatment has to rely on rules of thumb” There are a few randomized prospective studies concerning postsurgical treatment. See latest Cochrane from AT ruptures.
Does preinjury acticity (athlete, recreational athlete, nonathlete) play any role. Does previous tendon problems, tendinopathy play any role.
ANSWER: All patients were recreational athletes without previous tendon problems. This is now mentioned in the methods section.

Methods
Demographic data is insufficient. What is time from injury to treatment? What was preinjury activity of the patients (competitive athletes, recreational athletes, nonathletes). Did any has previous AT problems, and treatment of these?
ANSWER: All patients were operated on less than 2 days after injury, and all were seen on the day of injury. This is now mentioned. All patients were recreational athletes without previous tendon problems. This is now mentioned in the methods section.
Surgical technique: What was the thickness of Vigryl? Use of one or two Kessler loops? Use of circumferential sutures?
Answer: This is now described in the manuscript.

Postoperative treatment with 6 weeks of immobilization is today quite conservative postoperative treatment. Today the trend is early motion. Why early motion was not used allowing free plantar flexion but restricting dorsiflexion to neutral?
ANSWER: We used the most common treatment, but agree that the trend is going towards early motion.

“In this study weight bearing was allowed as tolerated.” What does this mean? How it was tolerated?
ANSWER: They were allowed full weight-bearing. “as tolerated” has been removed from the text.

“Postoperatively the patients started training program.” What kind of program? Was it standardized program? How long a time?
ANSWER: All patients were seen by the same physiotherapist. This is now described in the text.

The elongation was measured first time after six weeks. This is problem, because elongation occurs in every repaired Achilles tendon already within six weeks. (See Kangas et al 2007, Mortensen).
ANSWER: Our main interest was to estimate the mechanical properties of the callus tissue at different times. Measuring the elongation from one examination to the next was a secondary objective. We agree that it would be of interest to study elongation during immobilization and intend to do that in a new study. The discussion of this has been rephrased.

At one year examination there were 2 major problems: Why repeat loadings were not measured? Why the pedal forces did not include 200N as in previous measures?
ANSWER: Due to the radiation dose, we had to limit the number of exposures. At the one year examination, we chose to use the limited number of exposures allowed, to make a rough load-deformation curve, instead of repeat measurements. We agree that the approximation of the load-deformation curve as linear is a simplification that makes our estimates rough. However, in a future comparative study this will be a systemic error, and it will be the same for all patients.

US was use to measure the transverse area. What was the level? Was it the thickest level?
ANSWER: For reasons of standardization, this was done mid-between the distal and proximal markers.

The measure error?
ANSWER: We did not determine this.

Functional outcomes.
Functional results were not as good as usually reported in the literature. 50% of the results were unsuccessful (3 fair results, 2 poor results). The
analysis of unsuccessful results are lacking. There was only one excellent result.

**ANSWER:** This is probably how the results normally are in an orthopaedic department without special dedication to athletes. These patients were all treated according to every-day routines.

Strain per force values had a considerable variation, but did not correlate significantly with outcome. Also the modulus of elasticity showed a great variation. There was also variation in stiffness, but also this did not correlate significantly with outcome.

**ANSWER:** The high variation is one of the important findings of this study. As motivated in the discussion, this variation most probably reflects true biological variation (not measuring error).

Why the elongation was not measured within the first 6 weeks. Previous studies of Mortensen et al, Kangas et al) have shown, that elongation is significant already during the first 6 weeks. 4 of eight AT shortened between 18 weeks and 1 year but have no correlation with mechanical property.

**ANSWER:** Our main interest was to estimate the mechanical properties at different times, in order to follow healing. Measuring elongation was a secondary objective. We agree that it would be of interest to study elongation during immobilization and intend to do that in a new study. The discussion of this has been rephrased. (see above)

Discussion
Discussion is also too long and not compact. Measurement of hysteresis is not perhaps possible with RSA.
This is however discussed.

Conclusion:
My conclusion is, that RSA can be used in this kind of study, but methods have so serious weaknesses that his study is insufficient to be published in this journal.

**ANSWER:** It is an entirely new concept to use RSA in this context. The method is simple and fast. We believe that there is interest in the possibilities that the method might enable in future studies. Therefore, we have now rewritten it as a pilot study.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Authors reply to Dr. Narici

Reviewer's report:

General

This is an interesting and innovative paper, however minor revisions is required. Specific comments and recommendations on the paper are given below:

The use of RSA for measuring tendon deformation in vivo is a very interesting and practical application. However, I think that more information is required about how exactly elongations were obtained. For example, it seems as though single scans were taken at different points in time as the tendon was loaded - between the scans the tendon will need to be re-loaded and the experimental set-up changed. What is the reference frame that they use to standardise limb position, because potentially there is quite a lot of room for error here if the limb is not positioned in exactly the same position as the previous scans(s). ANSWER: The foot was held in a frame with about 8 degrees plantiflexion. However, the RSA method also uses a reference "cage" with markers in space. This enables determination of distances in any direction, and the distance between the markers is therefore independent of changes is foot and ankle joint position. We regret that this was unclear, and have now rectified this by adding a short description and a reference regarding the RSA method.

- There's only two data points 25N and 200N for the first three measurements (6, 12 and 18 weeks), I wonder why the Authors haven't included more data point as they did after one year. In this way they assume the tendon force-elongation relation is linear, which it is clearly is not. The problem is that following injury the shape of this curve may change markedly (as we saw from our data with SCI patients) and with this approach they won't see this. So any estimate of tendon stiffness must be considered as a very gross estimate. ANSWER: Due to the radiation dose, we had to limit the number of exposures. At the one-year examination, we chose to use the limited number of exposures allowed to make a rough load-deformation curve, instead of repeat measurements. We agree that the approximation of the load-deformation curve as linear is a simplification that makes our estimates rough. However, in a future comparative study this will be a systemic error, and it will be the same for all patients.

Further, there's no description of how stiffness, modulus, or CSA have been measured in the methods, but from the discussion I see that the Authors have expressed stiffness as N/strain, which is an inappropriate mix of variables. ANSWER: We apologize for the unclarity and have now added a short description of these calculations in "methods". The term "specific stiffness" is used for the inversion of strain per force, i.e. N/strain. Ordinary stiffness is described as N/mm.

- The influence of antagonistic coactivation and joint rotation have been neglected. Joint rotation is perhaps less important, but more importantly this is related to what I mention above about how they ensure exactly the
same limb position relative to the scanner for the acquisition of repeated static scans. Coactivation is perhaps more important as this could be potentially altered following a period of immobilization. **ANSWER:** We have now mentioned the problem of the unmeasured coactivation in the discussion: “A major weakness with our study is that we did not control for co-activation of the extensor muscles, which might explain some of this variation.”

-For the first three measurement time points (6, 12 and 18 weeks) the Authors state that each load (25 and 200N) was tested twice and that this was to establish reproducibility and to precondition the tendon, which seems a good approach, but this was not done during measurements taken after 1 year, so there was no preconditioning. This seems particularly relevant because on page 13 they discuss the persistence of an elongation after loading. **ANSWER:** This had to do with the limited number of x-ray exposures possible (see above).

-The Authors state they have positioned beads at two locations -1) at the rupture site and 2) above the injury site within a "healthy" portion of the tendon. There should be a clearer distinction between the elongation in both locations, it's not always clear which site they are referring to. A detailed comparison of the mechanical properties at these two different location would be very interesting. **ANSWER:** Two beads were located distal, and two proximal to the lesion.

-Why were two beads used in each location and not just one? **ANSWER:** The reason two beads were used for each location was to allow for checking bead stability; that they both gave similar results implied that they were fixed in the tendon tissue. Moreover, the computer program for the RSA requires at least 3 beads.

-CSA seems to increase up until 18 weeks and then decrease after 1 year, is this due to some inflammation? -this is not discussed in the results or discussion **ANSWER:** We don’t know, but suppose that the callus continues to grow for such a long time. The inverse relationship between increase in material properties and increase in dimensions is briefly discussed.

-They use kg in the results (e.g., p. 11), but N in the methods -need to be consistent for clarity. **ANSWER:** We agree and have changed to N throughout the article.

-It seems strange how they report median strain, in the abstract for example. **ANSWER:** The values refer to the median value of all patients at the respective time point.
Authors reply to Dr. Zwipp

This paper tries to answer the interesting question: how are the biomechanical properties changing during Achilles tendon healing. The authors implanted tantalum beads in conjunction with the surgical repair. The operation technique was one Vicryl suture (which thickness? ANSWER: Size 1) and fibrin glue. The postoperative treatment was 3 weeks cast in equinus and 3 weeks in neutral position. Tendon healing was studied with Roentgen stereophotogrammetric analysis in 10 patients.

The authors stated: There are presently no methods described for in vivo monitoring of the healing of human tendon ruptures. However, it is well known, that ultrasound is a good method to control the course of tendon healing without radiation exposure. If a defect or dehiscence is seen within the tendon, the clinical outcome can be predicted reliably and helps the indication to repeat surgery.

ANSWER: We have rephrased the sentence to clarify that we are interested in the mechanics, which ultrasound can not measure: "There are presently no methods described for in vivo monitoring of the mechanics of healing of human tendon ruptures,..."

The question arises, why the position of the markers was determined by CT scanning rather than with ultrasound, because this exposes the patients to larger doses of radiation.

ANSWER: We believe CT is more certain and less investigator dependent, as we did not do the US ourselves.

As has been shown previously, tendon elongation develops after a biphasic course (appr. 1 cm after 7 weeks) [Mortensen et al., 1992]. In the technique used by the authors (Vicryl suture and fibrin glue) a correction of the foot position to neutral after 3 weeks presumably will determine most of the elongation by that time. When starting with the measurement of elongation after 6 weeks, it is impossible to measure the real tendon elongation.

ANSWER: We agree. However, our main interest was to estimate the mechanical properties of the callus tissue at different times. Measuring the elongation from one examination to the next was a secondary objective. We agree that it would be of interest to study elongation during immobilization and intend to do that in a new study. The discussion of this has been rephrased.

The authors should discuss the existing literature dealing with implantation of metal markers.

ANSWER: We agree and now refer to both Mortensen et al. and Kangas et al. (which was unpublished when our manuscript was submitted).

It is felt that this study has no clinical consequences. The results are nevertheless interesting (large variation of the strain/force and stiffness, changes between 18 weeks and 1 year). It is hard to draw any valid conclusions from the small patient sample with high individual variation.

ANSWER: Due to the small number of patients, we have now described this as a pilot study.