Tendon Structure's Lack of Relation to Clinical Outcome After Eccentric Exercises in Chronic Midportion Achilles Tendinopathy

Robert J. de Vos, Marinus P. Heijboer, Harrie Weinans, Jan A.N. Verhaar, and Hans T.M. van Schie

Context: Chronic midportion Achilles tendinopathy is a common and hard-to-treat disorder characterized by degenerative changes of the tendon matrix. Ultrasonographic tissue characterization (UTC) was successfully used to quantify structural Achilles tendon changes. This novel and reliable technique could be used in follow-up studies to relate tendon structure to symptoms. Objective: To quantify structural tendon changes and assess clinical change in patients with tendinopathy. Design: Prospective observational study. Setting: Orthopedic department in a university medical center. Patients: 23 patients with chronic midportion Achilles tendinopathy. Intervention: The patients performed a 16-wk home-based eccentric exercise program. An experienced researcher performed the ultrasonographic data collection with the UTC procedure. These data were assessed by a blinded observer. The severity of symptoms was established with the validated Victorian Institute of Sport Assessment–Achilles (VISA-A) questionnaire. Main Outcome Measures: UTC was performed to quantify tendon structure through measuring the proportion of 4 echo types. Echo types I and II represent more or less organized tendon bundles, and echo types III and IV represent disintegrated tendon structure. On the VISA-A, the total possible score is divided by 100 for a percentage score, with a perfect score of 100. Follow-up was at 2, 8, 16, and 24 wk. Results: The mean percentage of echo types I and II changed by 0.3% after 24 wk (P = .92, 95% CI –5.8 to 5.3). The mean VISA-A score increased slightly but significantly by 11.3 points after 24 wk (P = .01, 95% CI 2.6–20.0). An increased VISA-A score was not correlated with an increased percentage of echo types I and II (P = .94, r = –.02), and the baseline percentage of echo types I and II did not correlate with an increased VISA-A score (P = .74, r = .07). Conclusions: There is no short-term increase in organized tendon structure after eccentric exercises. Tendon structure is not related to symptom severity and cannot be used as a predictor of clinical outcome.

Keywords: ultrasonography, ultrasonographic tissue characterization, tendon degeneration

Chronic midportion Achilles tendinopathy is a common and hard-to-treat disorder. The diagnosis is based on the clinical triad of pain, swelling, and impaired performance, and on histology this condition can be characterized by degenerative changes of the tendon matrix. The role of conventional ultrasonography in tendon imaging is questionable, because it is influenced by machine settings and transducer handling by the observer, and structural changes can only be assessed qualitatively. Therefore, a novel method was recently introduced for human Achilles tendons. Ultrasonographic tissue characterization (UTC) was found to be a reliable method that was able to distinguish symptomatic from asymptomatic Achilles tendons using quantification of the 3-dimensional stability of the echo pattern. UTC is an established method in veterinary medicine, in which various stages of ultrastructural organization were related to the histomorphology of equine tendons as a reference test. Currently, a heavy-load eccentric calf-muscle exercise program is prescribed as usual care for patients with chronic midportion Achilles tendinopathy. Initially, several studies reported superior results with these exercises, but subsequent studies failed to achieve high patient satisfaction. Eccentric exercises are thought to enhance tendon collagen synthesis, but there is moderate correlation between clinical assessment and appearance on conventional ultrasonography. In a retrospective study in 33 patients with Achilles tendinopathy, ultrasonography was performed before the start of conservative treatment. Tendons with a normal ultrasonographic appearance had a significantly shorter recovery time than tendons with a hypoechoic area. In contrast, a prospective study in patients with symptomatic Achilles tendons showed that a reduced area of hypoechogeticity on conventional ultrasonography did not correlate with an

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improved clinical outcome using the validated Victorian Institute of Sports Assessment–Achilles (VISA-A) questionnaire to detect the clinical severity of symptoms.\textsuperscript{14}

It appears that eccentric exercises can result in improvement of symptoms over time, but there is a discrepancy in the direct relationship between tendon-structure organization and symptoms. This may be because conventional ultrasound might not reliably quantify the structural changes after these exercises.\textsuperscript{3,4} Therefore, the effects of eccentric exercises on tendon structure are difficult to determine over time. This is the first study to assess quantified tendon structure and symptoms after eccentric exercises over several time points. Thus, the first aim of this study was to evaluate whether an improvement in tendon structure could be observed after an eccentric exercise program, and the second aim was to evaluate the relationship between the change in severity of symptoms, using the VISA-A score, and tendon structure as quantified by means of UTC.

Methods

Study Design

The study design was an observational prospective clinical trial performed at an orthopedic outpatient department in a university medical center. Ultrasonographic data were collected using the novel UTC method, and patients’ symptom severity was measured using the VISA-A score during a 16-week home-based eccentric exercise program with follow-up at 2, 8, 16, and 24 weeks. After a mean of 2.2 years follow-up, patients were asked to complete the VISA-A questionnaire by e-mail.

Patients

Suitability for inclusion was evaluated by an experienced orthopedic surgeon. Inclusion criteria were age above 18 years and presence of symptoms for more than 3 months. The diagnosis was made clinically, based on history and physical examination. All patients had a painful thickened tendon with diminished activity. The tendon thickening was located approximately 2 to 7 cm proximal from the calcaneal insertion. Exclusion criteria were having participated in an intensive program of heavy-load eccentric calf-muscle exercises and being unable to perform heavy-load exercises. Patients with insertional disorders, an abnormal Thompson test, and systemic disease were also excluded. None of the patients received injection therapy or had undergone surgical treatment before.

Twenty-six patients visited the university medical center to participate in the study between April 2007 and January 2008. One patient was excluded because of an insertional disorder, and 25 patients were included in the study. To determine the level of sports activity in relation to the load capacity of the Achilles tendon, the Ankle Activity Score was obtained at baseline. The instrument (score 0–10) has been validated, but not specifically for Achilles tendon injury. It objectively quantifies ankle-related activity and was only evaluated at baseline to evaluate the activity level of the study population.\textsuperscript{15} Patient characteristics are presented in Table 1. The patients did not receive other interventions during the first 24 weeks. After a mean of 2.2 years, 15 patients had not received other treatment options, 1 patient had received a platelet-rich plasma injection, and 5 patients had undergone a surgical procedure (debridement of degenerative tissue) for their Achilles tendinopathy within a median of 5 months (interquartile range 2–11) after the 24-week follow-up time point. The progress of the patients in the study is shown in Figure 1.

The study protocol was approved by the regional medical ethics committee of the hospital (Rotterdam, The Netherlands). All patients provided written informed consent.

Interventions

Patients who were interested in participating in this study contacted the researcher by phone or e-mail. The researcher informed the patients about the study if they seemed suitable for inclusion. Subsequently, an appointment was made at the orthopedic outpatient department.

After inclusion, all patients were instructed on how to perform the eccentric exercises. The exercises were performed with straight knees and with bent knees as described by Alfredson et al.\textsuperscript{6} The researcher supervised the exercise program as patients were asked to make a

<table>
<thead>
<tr>
<th>Table 1 Patient Characteristics and Outcome Variables at Baseline</th>
<th>Patients (N = 25)</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>46 ± 9.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>female, n (%)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>male, n (%)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Body-mass index, kg/m²</td>
<td>25.9 ± 4.7</td>
</tr>
<tr>
<td>Duration of symptoms, wk, median (IQR)</td>
<td>36 (20–84)</td>
</tr>
<tr>
<td>Active in sports, n (%)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Ankle Activity Score</td>
<td>4.8 ± 1.5</td>
</tr>
<tr>
<td>VISA-A score</td>
<td>47.3 ± 16.4</td>
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<tr>
<td>Echo type I</td>
<td>46.8 ± 12.9</td>
</tr>
<tr>
<td>Echo type II</td>
<td>21.5 ± 6.2</td>
</tr>
<tr>
<td>Echo type III</td>
<td>14.2 ± 7.5</td>
</tr>
<tr>
<td>Echo type IV</td>
<td>17.5 ± 9.9</td>
</tr>
<tr>
<td>Echo types I and II</td>
<td>68.3 ± 16.8</td>
</tr>
<tr>
<td>Maximum tendon thickness, mm</td>
<td>9.9 ± 2.0</td>
</tr>
</tbody>
</table>

IQR, interquartile range; VISA-A, Victorian Institute of Sport Assessment–Achilles. Values are mean ± SD unless otherwise indicated.
series of eccentric drops to be certain that the technique was correct. The patients performed the exercises at home, and during the follow-ups we checked whether the technique was correct. The first 4 weeks, the patients were advised to gradually increase the frequency of eccentric drops with the aim to reach a maximum compliance during the program. After 4 weeks the original 12-week eccentric exercise program started, so in total the eccentric exercises were performed for 16 weeks. The patients were instructed to perform 180 repetitions/d. They were informed that these exercises commonly cause pain and that they should accept this if it was not disabling. Increasing load was advised when the exercises could be carried out without any discomfort. This could be performed using weights in a backpack or with calf-muscle machines. We advised to start with 2 kg (4.4 lb) and increase by 2 kg (4.4 lb) when the exercises could be performed without discomfort. All patients were instructed to avoid weight bearing sporting activities for the first 8 weeks. After 8 weeks, gradual return to sport activities was encouraged if pain allowed.

**Outcome Measurements**

All patients completed a questionnaire consisting of clinical outcome measures, and subsequently UTC measurements were performed at baseline and after 2, 8, 16, and 24 weeks.

The severity of symptoms was evaluated by a researcher using the VISA-A questionnaire. The VISA-A score ranges from 0 to 100, 0 denoting *no activity and maximum pain* and 100 denoting a perfect score of *maximum activity and no pain*. This validated and disease-specific questionnaire, which quantifies pain and activity level, was completed with minimal assistance of a single researcher. To evaluate the long-term results (mean follow-up 2.2 y), this questionnaire was completed once more by e-mail.
The UTC measurements (UTCimaging, Stein, The Netherlands) were done using a standardized protocol described and illustrated in a previous study.4 The patients lay prone on an examination table with their feet hanging over the edge. With a holding device the ankle was positioned in a standardized angle of dorsiflexion, thereby stretching the Achilles tendon. A standoff with scan gel was applied to the limb under investigation, and subsequently a high-resolution 10-MHz linear-array transducer (Smartprobe 10L5, Terason 2000, Teratech, USA) was moved manually along and perpendicular to the Achilles tendon’s long axis over a distance of 9.6 cm.

Custom-designed software (UTCimaging, Stein, The Netherlands) was used for data collection and analysis. Every 0.2 mm, transverse images were captured with constant settings (focusing, brightness, contrast, and gain). The digital-scan data were stored on the hard disk of a computer and compounded to a 3-dimensional data block that provided the tomographical visualization of the Achilles tendon in 3 planes of view: transverse, sagittal, and coronal. Furthermore, the processing of contiguous transverse images by means of custom-designed algorithms facilitated the discrimination of 4 echo types. Echo types I and II are generated from a single ultrasound reflection, belong to typically 1 interface structure, and therefore represent more or less organized tendon bundles. Echo types III and IV are generated by multiple reflections that interfere as a consequence of multiple interfaces and represent smaller, disorganized, and more fibrillar structures or even amorphous tissue that has typically been described in tendinotic tissue. The method has been extensively described and validated in equine tendons5 and to a lesser extent tested and displayed in tendinopathy patients versus a control group.4

The thickest part of the tendon in the anteroposterior direction was determined, and subsequently the border of the Achilles tendon was discriminated in the grayscale image.4 At this site, the proportions of the 4 echo types in the transverse cross-section were defined, and the echo types were also calculated 2 mm proximal and distal from this position. An average of the echo types in these 3 cross-sections was used in the overall tendon assessment.

To determine the location of an area with decreased tendon structure, the tendons on UTC imaging at baseline were also divided into 5 regions (postero-medial, antero-medial, antero-lateral, postero-lateral, and central).4 This procedure was executed with an automatic program in UTCimaging. A line was drawn through the largest width of the tendon, and perpendicular to this line, a second line was defined as the longest distance in an anterior to posterior direction. The intersection of these 2 lines was used as the center of an oval area in the middle of the tendon. A cutoff of 99% echo types I and II was used to determine whether a location was defined as an area with decreased tendon structure. This was determined with use of segmentation, which was based on the persistence of features characteristic of echo type III or IV over a longer distance (25 contiguous images, 4.8 mm) than previously described in the equine and human studies (9 contiguous images, 1.6 mm).4,5

**Statistical Analysis**

It was estimated that an increase in VISA-A score of 12 points would be clinically relevant, with a standard deviation of the VISA-A score of 15 points.10,16 We calculated that a sample of 25 was required to detect this increase with a power of 80% with 2-sided testing at a significance level of 5%. All data were normally distributed, so changes in VISA-A score and UTC echo types were analyzed with paired t tests and correlations were evaluated with Pearson correlation tests.

The researcher who performed the analyses was blinded to the patients’ clinical status. The analyses were performed with the use of SPSS software (version 16.0.1; SPSS Inc, Chicago, IL), and significance was assumed when P values were less than .05.

**Results**

**Single Point in Time**

In total, 115 UTC scans were analyzed at all time points. The proportions of echo types I and II did not correlate with the corresponding VISA-A scores (P = .32, r = –.09). At baseline, non-structure-related echo types (III and IV) were found on the posteromedial (n = 23), posterolateral (n = 20), anterolateral (n = 14), anteromedial (n = 21), and central (n = 15) sites.

**Changes Over Time**

The mean (SD) VISA-A score increased significantly by 11 (20) points after 24 weeks (P = .01). After a mean follow-up of 2.2 years, the mean (SD) VISA-A score significantly increased by 14 (21) points (P = .004). The mean (SD) percentage of echo types I and II decreased nonsignificantly by 0.3% (13) after 24 weeks (P = .92). The mean changes in the VISA-A score and the percentage of echo types I and II are displayed in Figure 2, and the mean change in separate echo types is shown in Figure 3. The absolute changes over time and confidence intervals of the VISA-A score and the UTC echo types are displayed in Table 2.

An increased percentage of structure-related echo types I and II after 24 weeks was not correlated with an increase in VISA-A score after 24 weeks (P = .94, r = –.02) or after a mean of 2.2 years (P = .98, r = .09; Figures 4 and 5). The baseline percentage of echo types I and II did not correlate with an increase in VISA-A score after 24 weeks (P = .76, r = .07) or after a mean of 2.2 years (P = .76, r = .07).

There was a correlation between the VISA-A score at baseline and the VISA-A score at 24 weeks (P = .002, r = .61) and at 2.2 years follow-up (P = .001, r = .71; Figures 6 and 7).
Figure 2 — There was a slight but significant increase in Victorian Institute of Sport Assessment–Achilles (VISA-A) score after 24 weeks, but there was no significant change in echo types I and II in this time period. Error bars denote SDs.

Figure 3 — Progression of echo types I to IV. There were no significant changes in any echo type from baseline to 24 weeks. Error bars denote SDs.

Table 2  Changes Over Time in the VISA-A Score and the UTC Echo Types I and II, Mean (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 wk</th>
<th>8 wk</th>
<th>16 wk</th>
<th>24 wk</th>
<th>Mean 2.2 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISA-A score</td>
<td>47</td>
<td>50 (–2 to 8)</td>
<td>52 (–1 to 11)</td>
<td>54 (–1 to 15)</td>
<td>58 (3–20)*</td>
<td>60 (5–24)*</td>
</tr>
<tr>
<td>Percentage of UTC echo types I and II</td>
<td>68</td>
<td>72 (–3 to 9)</td>
<td>71 (–7 to 7)</td>
<td>75 (–0.3 to 9)</td>
<td>70 (–6 to 5)</td>
<td>NA</td>
</tr>
</tbody>
</table>

VISA-A, Victorian Institute of Sport Assessment–Achilles; UTC, ultrasonographic tissue characterization; CI, confidence interval. There was a slight but significant improvement in the severity of symptoms, measured with the VISA-A score. There was no significant change in tendon-structure organization, measured with UTC echo types I and II.

*Significant change from baseline.
Figure 4 — Relationship between change in symptoms at short term and change in tendon structure. An increased percentage of structure-related echo types I and II after 24 weeks was not correlated with an increase in Victorian Institute of Sport Assessment–Achilles (VISA-A) score after 24 weeks ($P = .94, r = -.02$). Dots represent individual cases, and the fit line shows the linear relationship.

Figure 5 — Relationship between change in symptoms at long term and change in tendon structure. An enhanced percentage of structure-related echo types I and II after 24 weeks was not correlated with an increase in Victorian Institute of Sport Assessment–Achilles (VISA-A) score after a mean of 2.2 years ($P = .69, r = .09$). Dots represent individual cases, and the fit line shows the linear relationship.
Figure 6 — Relationship between severity of symptoms at baseline and at short-term follow-up. There was a correlation between the Victorian Institute of Sport Assessment–Achilles (VISA-A) score at baseline and the VISA-A score at 24 weeks follow-up ($P = .002$, $r = .61$). Dots represent individual cases, and the fit line shows the linear relationship.

Figure 7 — Relationship between severity of symptoms at baseline and at long-term follow-up. There was a correlation between the Victorian Institute of Sport Assessment–Achilles (VISA-A) score at baseline and the VISA-A score at a mean of 2.2 years follow-up ($P < .001$, $r = .71$). Dots represent individual cases, and the fit line shows the linear relationship.
Tendon Structure in Chronic Tendinopathy

Discussion

In this first prospective observational study on the effects of an eccentric-exercise program with use of UTC to quantitatively measure tendon integrity, we could not demonstrate an improvement in tendon structure after 24 weeks. The mean VISA-A score increased slightly but significantly. The severity of symptoms was not related to the tendon structure at a single point in time or in change over time. The degree of tendon-structure disorganization at baseline was not predictive for the change in severity of symptoms after 24 weeks, but the VISA-A score at baseline was a predictor for the VISA-A score at midterm and long-term follow-up.

These findings are important because many researchers have reported on the relationship between structural changes of the tendon and symptoms.\(^4,^{14,17–22}\) It is known that normal tendons are characterized by a regular echo pattern, whereas hypoechoic lesions resulting from collagen disorganization are frequently described in cases of tendinosis.\(^3\) In 1 retrospective study,\(^13\) there were indications that the presence of hypoechoic areas led to a slower recovery in patients with Achilles tendinopathy. In a prospective study,\(^14\) ultrasonography was performed before the start of conservative treatment, and the authors found that there was no statistically significant relationship between overall clinical outcome and the degree of ultrasonographic abnormality. In addition, in the current study we found that the degree of ultrasonographic tendon-structure disorganization cannot predict clinical outcome using standardized outcome measures. These findings are in line with cohort studies that reported that symptoms do not mirror ultrasonographic appearances,\(^17–19\) although in asymptomatic individuals they may be of value in predicting the development of Achilles tendon pain.\(^23\)

Indeed, these study results show that symptoms and function may improve within 6 months but improvement of tendon structure may take more time. The results of our study, in which a quantified and standardized ultrasonographic method was used, confirm previous (qualitative) findings. UTC has been used previously as a follow-up instrument in equine studies. Several studies in horses with standardized surgical lesions induced in normal flexor tendons, without underlying degenerative changes, revealed that healing processes can be monitored quantitatively by means of UTC. The quality of repair could be quantified in vivo by means of UTC, and these features corresponded significantly with both histomorphology and tensile properties (postmortem) 24 weeks postsurgery.\(^24,25\)

Previous prospective cohort studies reported that all patients had structural ultrasonographic changes (hypoechoic area or irregular fiber structure) at baseline, but at long-term follow-up (means of 28 and 46 mo) after a 12-week eccentric exercise program, many tendons showed a normalized tendon structure on qualitative assessment with concurrently high patient satisfaction.\(^20,26\) These studies used real-time ultrasonography, whereas we used standardized UTC methods. In our study, the tendon structure did not change within 24 weeks after eccentric-exercise treatment. There may be a few reasons for this discrepancy. The first hypothesis is that structural changes of the tendon may not occur within this short period. With use of a microdialysis technique it was found that a 12-week eccentric-exercise program for the treatment of Achilles tendinopathy resulted in increased collagen synthesis (peritendinous type I collagen) without an increased degradation.\(^27\) These findings suggest a short-term regenerative effect of eccentric-exercise therapy on a molecular or fibrillar scale, but it is unknown whether this collagen will be organized into hierarchically arranged tendon bundles.\(^28\) This process may be time consuming, and future studies should be carried out to evaluate whether the UTC appearance will ever become normalized at all, after tendons have been symptomatic. A limitation of this study is that we did not evaluate long-term tendon-structure organization.

The second hypothesis is that the study population is different than those in the previous studies. In our study, 72% of the patients were involved to some degree in sports activity. It is known that sedentary individuals benefit less from eccentric-exercise therapy than active people.\(^11\) The increase in VISA-A score in our study may therefore be lower than in previous studies that used this outcome measure in an active population.\(^10,29\) This finding might be explained by the fact that the VISA-A score also quantifies activity level, but there may be other reasons why sedentary people do not benefit. It is suggested that compliance to the eccentric exercises may play a role in the outcome.\(^10\) However, in our study compliance was not recorded, which could be regarded as a limitation. In addition to activity level, the VISA-A score quantifies pain. However, surrounding tissues may be more important than intratendinous collagen as a source of pain. Alfredson\(^7\) stated that surrounding tissues like nerves and blood vessels may be changed after eccentric-exercise therapy and therefore result in decreased pain perception. In addition, in cases of paratenon pathology only moderate intratendinous changes may be observed, but clinically this may result in more pain and reduced function.\(^4\)

The location of tendon disorders may be another subject of interest. Gibbon et al\(^30\) reported that most ultrasonographic midportion disorders (91%) were found in the medial segment. They concluded that these disorders are a result of repetitive hyperpronation of the foot. We found lesions on the postero medial side in all tendons. The biomechanical cause of these findings may be related to abnormal alignment, but soleus muscle traction can be another cause because this deep calf muscle attaches to the Achilles tendon in this region, probably leading to torsion of structures during repetitive loading.\(^31\) The study design makes it impossible to confirm these hypotheses.

We previously found that there is a higher chance of having symptoms in the presence on UTC of more echo types III and IV, representing loss of normal tendon structure.\(^4\) However, based on the findings in the current study, the quantity of baseline tendon-structure disorganization
is not related to the clinical outcome at short- or long-term follow-up. A hypothesis is that pain is not necessarily related to the restoration of bundle organization, at least not 24 weeks from baseline. Repair of tendon structure in degenerative tendon tissue probably takes much more time and is preceded by molecular processes that result in improvement of symptoms. We found that there was a relationship between the VISA-A score at baseline and at final follow-up. Therefore, clinical examination remains the cornerstone of evaluating the progress of symptoms in tendinopathy, and ultrasonographic imaging may not be useful for predicting symptoms. These findings are relevant for daily clinical practice, but they also lead to additional questions that could be a focus in future studies. In tendinopathy research, accurate information about the long-term progress in large-cohort studies is lacking. It is unknown whether patients have a constant clinical progression or a more fluctuating course of symptoms over time. It could be hypothesized that a normalized tendon structure does not result in recurrence of symptoms. Another problem is the limited information about the relationship between the severity of symptoms and previous activity levels. It might be that a slight decrease in activity level results in a more fluctuating course of symptoms over time. It could be attributable only to the effects of eccentric-exercise therapy. Furthermore, we did not record compliance to the eccentric exercises. It is known that in an active population more than a quarter of patients report performing the exercises at less than half of the prescribed intensity. It would have been interesting to relate reported compliance to change in tendon structure.

Conclusions

In previous studies, there were conflicting results regarding the predictive value of ultrasonographic disorders on clinical outcome after conservative treatment. A problem may be the lack of standardization of conventional ultrasonography, which is influenced by machine settings, transducer handling, and interpretation by the observer. Therefore, UTC was previously transferred from equine-validated tests to human Achilles tendons. With this prospective cohort study we found that tendon structure does not improve in the short term after eccentric exercises in Achilles tendinopathy. Furthermore, tendon structure is not related to the clinical severity of symptoms at a single point in time or in change over time.

References


