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Comparison of the Effect of 5 Different Treatment Options for Managing Patellar Tendinopathy: A Secondary Analysis

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Abstract

Objective: Currently, no treatments exist for patellar tendinopathy (PT) that guarantee quick and full recovery. Our objective was to assess which treatment option provides the best chance of clinical improvement and to assess the influence of patient and injury characteristics on the clinical effect of these treatments. **Design:** A secondary analysis was performed on the combined databases of 3 previously performed double-blind randomized controlled trials. **Patients:** In total, 138 patients with PT were included in the analysis. **Interventions:** Participants were divided into 5 groups, based on the treatment they received: Extracorporeal shockwave therapy (ESWT) ($n = 31$), ESWT plus eccentric training ($n = 43$), eccentric training ($n = 17$), topical glyceryl trinitrate patch plus eccentric training ($n = 16$), and placebo treatment ($n = 31$). **Main Outcome Measures:** Clinical improvement (increase of ≥ 13 points on the Victorian Institute of Sport Assessment-Patella score) after 3 months of treatment. **Results:** Fifty-two patients (37.7%) improved clinically after 3 months of treatment. Odds ratios (ORs) for clinical improvement were significantly higher in the eccentric training group (OR 6.68, $P = 0.009$) and the ESWT plus eccentric training group (OR 5.42, $P = 0.015$) compared with the other groups. We found evidence that a high training volume, a longer duration of symptoms, and older age negatively influence a treatment's clinical outcome (trend toward significance). **Conclusions:** Our study confirmed the importance of exercise, and eccentric training in particular, in the management of PT. The role of ESWT remains uncertain. Further research focusing on the identified prognostic factors is needed to be able to design patient-specific treatment protocols for the management of PT.

Key Words: patellar tendinopathy, eccentric training, extracorporeal shockwave therapy, glyceryl trinitrate

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INTRODUCTION

Patellar tendinopathy (PT) (or jumper's knee) is a chronic overuse injury of the patellar tendon, which especially affects athletes performing sports that involve frequent jumping and landing.¹ Its prevalence varies from 14% in nonelite volleyball players and can be as high as 45% in elite volleyball players.^{2,3} The duration of symptoms is often long lasting,^{2–4} and the injury's chronic nature can have a tremendous impact on an athletic career. It sometimes even forces athletes to quit their sports career entirely.⁵

Many different treatment options have been suggested for the management of PT, including eccentric training, extracorporeal shockwave therapy (ESWT), and continuous topical glyceryl trinitrate (GTN).^{4,6–11} Although exercise therapy, and eccentric training in particular, is currently considered as the treatment of choice, it is not beneficial for all patients with PT.^{6,12} A review of different exercise programs

showed that eccentric training gives patients only a 50% to 70% chance of improvement of knee function and pain.¹³ As none of the other possible treatments seem to be superior, the question which treatment is most appropriate in managing PT thus remains unanswered. Moreover, it is not yet clear why some patients benefit from a certain treatment while others do not. "One size fits all" does not seem to apply when managing PT.¹⁴ Possibly, characteristics of the patients and the injury influence the outcome of different treatments. For example, the pathophysiological stage of the injury, according to the pathology continuum as described by Cook and Purdam,¹⁵ is likely to play an important role in a treatment's clinical outcome. In their work, they suggest that, for example, reactive tendinopathy as a result of acute overload may require load adjustment to give the tendon time to recover, whereas degenerative tendinopathy might benefit from interventions that restructure tendon matrix. However, they also state that clinical differentiation between the pathophysiological stages is difficult. Other clinical characteristics that have been suggested to play a role in a treatment's clinical outcome are training volume, body mass index (BMI), and male sex.^{4,9,16} However, limited evidence is available to support these suggestions.

In this study, a secondary analysis was performed on the combined databases of 3 randomized controlled trials previously conducted by our research group.^{9–11} Our goal was to assess which of these treatment options provides the best chance of clinical improvement. Secondly, patient and injury

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The authors report no conflicts of interest.

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characteristics were analyzed to see whether they influenced the clinical effect of these treatments.

METHODS

Study Design

A secondary analysis was performed on the combined databases of 3 randomized controlled trials conducted by our research group with comparable methods and homogeneous outcome variables.

The Tendinopathy Of Patella Groningen Amsterdam Maastricht ESWT (TOPGAME) study by Zwerver et al (2011) was a multicenter, randomized, double-blind, placebo-controlled trial. The hypothesis tested was that ESWT was more effective than placebo ESWT in relieving pain and symptoms and improving function in actively competing jumping athletes with early symptomatic PT. Patients received either ESWT or placebo ESWT in 3 sessions at 1-week intervals. Two thousand impulses at a frequency of 4 Hz were administered in both groups, but in the placebo group, no transmission gel was applied so that shockwaves were not or hardly conducted.

Van der Worp et al (2014) conducted the Tendinopathy Of Patella SHOCKwave (TOPSHOCK) trial; a double-blind randomized controlled trial. The aim of this study was to compare the effects of focused shockwave therapy (FSWT) and radial shockwave therapy (RSWT) in addition to eccentric training for the treatment of PT. Patients received ESWT in 3 sessions at a 1-week interval. To the FSWT and RSWT groups, 2000 impulses at 4 and 8 Hz were delivered, respectively. The home-based eccentric exercise program started 2 weeks after the final ESWT treatment and consisted of single-leg squats on a decline board. Patients were instructed to perform 3 sets of 15 repetitions twice daily for 5 days a week.

Steunebrink et al (2013) studied the effect of GTN combined with eccentric training in patients with chronic PT and compared it with a placebo patch combined with eccentric training. This too was a randomized, double-blind, placebo-controlled clinical trial. In this trial, patients were instructed to wear the patch and simultaneously perform an eccentric training program at home, for which the instructions were equal to those given in the TOPSHOCK trial.

In contrast to the TOPGAME trial, in which no restrictions were given for either study group regarding sports participation, Steunebrink et al (2013) and Van der Worp et al (2013) both advised patients to reduce their sports activities during treatment.

More detailed descriptions of the designs, methods, and results of these studies have been published elsewhere.^{9–11,17,18}

Study Population

All patients who participated in the TOPGAME (n = 62), TOPSHOCK (n = 43), and GTN (n = 33) trials were included

in this secondary analysis, thus leading to a total of 138 patients.

Participants in the TOPGAME trial were recruited through the Dutch basketball, handball, and volleyball associations and through advertisements in newspapers, on websites, and at tournaments. Advertisements were also used in the GTN trial, as well as recruitment through outpatient departments (eg, general practitioners and physical therapists). By contrast, the TOPSHOCK trial included patients who visited the Sports Medicine Center of the University Medical Center Groningen.

The inclusion criteria of the 3 studies are presented in Table 1. The diagnostic criteria for PT were similar in all 3 studies: the presence of pain in the patellar tendon related to activity and/or thickening or tenderness on palpation. No imaging studies were used to confirm the clinical diagnosis. A wider age range was used in the TOPSHOCK and GTN trials compared with the TOPGAME trial. These 2 trials also included patients with a longer duration of symptoms than the TOPGAME trial. The TOPSHOCK trial also included participants who received bilateral treatment of the patellar tendon. Only the most affected tendon [lowest Victorian Institute of Sport Assessment-Patella (VISA-P) score] was included in the current secondary analysis.

Exclusion criteria were similar in all studies: acute knee injuries or other coexisting knee disorders, previous knee surgery or injection therapy, daily use of nonsteroidal anti-inflammatory drugs, and patients with contraindications for ESWT or GTN treatment (eg, pregnancy). Steunebrink et al (2013) also excluded patients who previously performed a heavy-load eccentric exercise program of the knee in the past 2 years and patients who were not able to perform the exercise program due to illness.

Study Groups

The 138 patients were divided into 5 categories based on the (placebo) treatment they received. The distribution of the participants into these treatment groups including the number of participants per group is shown in Figure 1. Because no differences were found between the FSWT and RSWT groups in the TOPSHOCK trial, these patients were merged in the same group, as both received shockwave therapy in combination with eccentric exercises.

Outcome Variable

The outcome of this study was clinical improvement (yes/no), defined as an increase of 13 points or more on the VISA-P score after 12 to 14 weeks of treatment.¹⁹ The Dutch VISA-P score, which assesses pain, function, and sports participation in patients with PT, was used as the primary outcome variable in all 3 studies. The follow-up measurement after 12 to 14 weeks of treatment was used to compare the effects of the different treatments.

TABLE 1. Inclusion Criteria of the TOPGAME, TOPSHOCK, and GTN Trials

TOPGAME Trial; Zwerver et al (2011)	TOPSHOCK Trial; Van der Worp et al (2013)	GTN Trial; Steunebrink et al (2013)
1. Presence of PT	1. Presence of PT	1. Presence of PT
2. Age: 18-35	2. Age: 18-50	2. Age: 18-40
3. VISA-P <80	3. VISA-P <80	3. VISA-P <80
4. Symptoms between 3 and 12 mo	4. Symptoms >3 mo	4. Symptoms between 3 and 24 mo

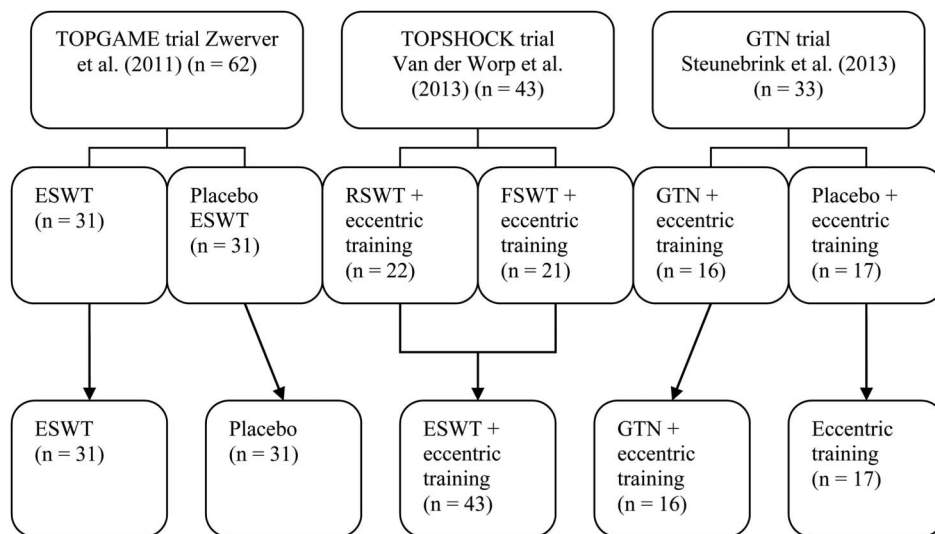


Figure 1. Flowchart illustrating the distribution of the study participants into 5 different treatment groups.

Measurements

Personal characteristics assessed at baseline included age, sex, length, weight, and number of training hours per week. Body mass index was calculated based on the given height and weight. Injury-related characteristics included duration of symptoms at baseline (months) and the VISA-P score, which was assessed at baseline and after 3 months of follow-up.

Data Analysis

Demographic characteristics of the study population were presented using descriptive statistics (mean values and SDs for normally distributed data, medians and ranges for skewed data, and numbers and percentages for quantities). These characteristics were shown for the different treatment groups and for patients with and without clinical improvement after 12 to 14 weeks. For the comparison of baseline characteristics and VISA-P scores after 3 months of treatment, 1-way analysis of variance (for normally distributed data) or Kruskal–Wallis and Mann–Whitney *U* tests (for skewed data) with Bonferroni corrections were used. Univariable logistic regression analyses were performed for patient characteristics and the different treatment groups to assess their effect on clinical improvement. Odds ratios (ORs) with 95% confidence intervals and *P* values were presented. A multivariable logistic regression model was used to correct for possible confounders. In this model, the treatment group and the significant variables at the univariate level were added. Based on the number of events, we were able to enter 2 more variables in the multivariable model. The selection of these 2 variables was made after running different models to make sure that the predictive ability of the final model was sufficient (based on overall accuracy percentages and Nagelkerke *R* square test). The model with the best predictive ability (highest Nagelkerke *R* square test) was selected. A standard method (Enter) was used.

Data were analyzed using SPSS version 22 (SPSS Inc, Chicago, Illinois). Differences were considered statistically significant at $P < 0.05$. *P* values < 0.10 were considered as a trend toward significance.

RESULTS

Of the 138 patients included in the analysis, 52 patients (37.7%) improved clinically after 3 months of treatment based on their VISA-P score.

The baseline characteristics and clinical results of the different treatment groups are shown in Table 2. Patients who received GTN in combination with eccentric training and those who only performed eccentric exercises were significantly older than those who only received ESWT treatment ($P = 0.003$ and $P = 0.002$, respectively). Patients in the ESWT + eccentric training groups had a significantly longer duration of symptoms and a lower baseline VISA-P score compared with all other groups ($P < 0.001$). The difference in the VISA-P score between the groups was no longer significant after 3 months of treatment. No differences were found between the groups regarding sex, BMI, and number of training hours per week.

The baseline characteristics of patients with and without clinical improvement after 12 to 14 weeks of treatment and the results of the univariable logistic regression analyses are presented in Table 3. Extracorporeal shockwave therapy in combination with eccentric training increased chances of clinical improvement compared with placebo treatment. Eccentric training alone was also more likely to improve clinical symptoms than placebo treatment (trend toward significance).

The simple logistic regression analyses showed that a higher baseline VISA-P score decreased chances of clinical improvement. Furthermore, patients spending more than 2 hours per week on training at baseline were less likely to demonstrate clinical improvement than those who trained less than 2 hours per week.

Multivariable logistic regression analysis showed that both eccentric training alone and ESWT combined with eccentric training increased the odds for clinical improvement (Table 4). Patients in the eccentric training group were more likely [OR 6.7 (1.6–27.6)] to improve compared with placebo treatment, when corrected for confounding variables. Shockwave therapy combined with eccentric training also showed an increased chance of clinical improvement compared with placebo [OR 5.4 (91.4–23.2)]. Furthermore, a longer duration of symptoms, older age, and a higher number of training hours

TABLE 2. Baseline Characteristics of the Placebo, ESWT, ESWT + Eccentric Training, GTN + Eccentric Training, and Eccentric Training Groups

	Placebo	ESWT	ESWT + Eccentric Training	GTN + Eccentric Training	Eccentric Training
N (%)	31 (22.5%)	31 (22.5%)	43 (31.2%)	16 (11.6%)	17 (12.3%)
Personal characteristics					
Male/female, n (%)	21/10 (67.7/32.3)	20/11 (64.5/35.5)	32/11 (74.4/25.6)	11/5 (68.8/31.2)	14/3 (82.4/17.6)
Age (yr), median (range)	26.0 (18.0 to 35.0)	23.0 (17.0 to 34.0)	26.4 (18.5 to 47.9)	33.0 (17.0 to 54.0)*	35.0 (18.0 to 51.0)†
BMI median (range), kg/m ²	24.0 (18.6 to 29.6)	23.6 (18.8 to 35.5)	24.3 (17.6 to 30.8)	23.9 (19.8 to 27.4)	25.4 (19.4 to 32.1)
Training hours, n (%), h/wk					
0-2	11 (35.5)	10 (32.3)	25 (58.1)	8 (50.0)	7 (41.2)
>2	20 (64.5)	21 (67.7)	18 (41.9)	8 (50.0)	10 (58.8)
Clinical characteristics					
Duration of symptoms, median (range), mo	8.0 (1.0 to 12.0)	8.0 (1.0 to 12.0)	24.0 (3.0 to 300.0)‡	6.7 (1.4 to 25.9)	8.3 (3.2 to 25.9)
VISA-P at baseline, mean (SD)	62.4 (13.4)	59.4 (11.7)	48.3 (17.3)‡	63.0 (16.4)	67.8 (10.9)
VISA-P at 3-month follow up, mean (SD)	66.3 (19.0)	66.8 (16.2)	61.0 (22.6)	73.0 (15.3)	73.6 (20.7)
VISA-P difference, median (range)	0.0 (-17.0 to 44.0)	6.0 (-25.0 to 42.0)	12.0 (-47.0 to 62.0)	8.0 (-16.0 to 56.0)	13.0 (-26.0 to 24.0)
Clinical improvement, n (%)	8 (25.8%)	9 (29.0%)	21 (48.8%)	5 (31.2%)	9 (52.9%)

* Significantly different from the ESWT group ($P = 0.003$).
† Significantly different from the ESWT group ($P = 0.002$).
‡ Significantly different from all other groups ($P < 0.001$).

per week decreased chances of clinical improvement in the multivariable model (trend toward significance).

DISCUSSION

The main finding of this secondary analysis was that only 52 (37.7%) patients improved clinically after 3 months of

treatment. Regarding the different treatment options, we found that eccentric training alone and a combination of eccentric training and ESWT were more likely to achieve clinical improvement compared with ESWT alone, GTN in addition to eccentric training, and placebo treatment. The secondary aim was to identify patient and injury characteristics that influence a treatment's clinical outcome. Our results

TABLE 3. Simple Logistic Regression Analysis: ORs for Clinical Improvement

	No Clinical Improvement	Clinical Improvement	OR (95% CI)	P
Personal characteristics				
Sex, m/f, n (%) (female = ref)	58/28 (67.4/32.6)	40/12 (76.9/23.1)	1.61 (0.73-3.54)	0.236
Age, median (range), yr	26.5 (17.0-54.0)	26.0 (17.0-51.0)	1.00 (0.96-1.04)	0.859
BMI, mean (SD), kg/m ²	24.3 (3.3)	24.0 (3.2)	0.97 (0.87-1.08)	0.582
Training hours, n (%), h/wk				
0-2 (=ref)	32 (52.5)	29 (47.5)		
>2	54 (70.1)	23 (29.9)	0.47 (0.23-0.95)	0.035*
Clinical characteristics				
VISA-P at baseline, median (range)	65.0 (16.0-84.0)	56.5 (15.0-82.0)	0.97 (0.95-0.99)	0.013*
Duration of symptoms, median (range), mo	10.0 (1.0-300.0)	8.0 (1.4-60.0)	0.99 (0.98-1.01)	0.441
Treatment, n (%)				
Placebo (=ref)	23 (74.2)	8 (25.8)		
ESWT	22 (71.0)	9 (29.0)	1.18 (0.39-3.60)	0.776
ESWT + eccentric training	22 (51.2)	21 (48.8)	2.74 (1.01-7.48)	0.048*
GTN + eccentric training	11 (68.8)	5 (31.2)	1.31 (0.35-4.93)	0.693
Eccentric training	8 (47.1)	9 (52.9)	3.23 (0.93-11.25)	0.065†

* Significant difference ($P < 0.05$).
† Trend toward significance ($P < 0.10$).
95% CI, 95% confidence interval.

TABLE 4. Multivariable Logistic Regression Analysis: ORs for Clinical Improvement

	OR (95% CI)	P
Treatment (placebo = ref)		
ESWT	1.05 (0.33-3.30)	0.934
ESWT + eccentric training	5.42 (1.39-21.23)	0.015*
GTN + eccentric training	1.74 (0.41-7.33)	0.449
Eccentric training	6.68 (1.62-27.62)	0.009*
Baseline VISA-P	0.98 (0.95-1.01)	0.137
Duration of symptoms, mo	0.96 (0.94-1.00)	0.022†
Training hours, h/wk		
(0-2 = ref)		
>2	0.47 (0.20-1.10)	0.083†
Age, yr	0.95 (0.90-1.00)	0.048†

* Significant difference ($P < 0.05$).
† Trend toward significance ($P < 0.10$).
95% CI, 95% confidence interval.

showed that a longer duration of symptoms, older age, and a higher number of training hours per week at baseline negatively influenced the clinical outcome.

Our findings that patients performing an eccentric training program were more likely to achieve clinical improvement are in accordance with previously published work. Reviews of the literature on the treatment of PT concluded that eccentric training using a 25-degree decline board should be the treatment of choice for patients with PT.^{6,12} Furthermore, in patients with Achilles tendinopathy eccentric exercises may have a positive effect on tendon structure in both the short and long terms.²⁰⁻²² This, however, remains a subject of debate because conflicting evidence has also been reported.^{23,24} The current recommendations that eccentric training should form the basis of the treatment of PT are thus supported by our results. We acknowledge, however, that growing evidence exists for the beneficial effects of other exercise programs for the treatment of PT.²⁵⁻²⁸ For example, Kongsgaard et al (2009) showed improvement of pain and function after 12 weeks of both heavy slow resistance training and eccentric training in patients with PT. Moreover, patients performing heavy slow resistance training showed a reduction in tendon abnormalities on ultrasound and changes in extracellular matrix, indicating an increased collagen turnover. In that study, eccentric training did not improve tendon structure.²⁹ Based on our data, we cannot recommend one exercise therapy program over another.

The multivariable analysis suggests a beneficial effect of the combination of ESWT and eccentric training. The positive effect of this combined treatment was formerly demonstrated by Peers³⁰ in 2003. However, before we can conclude that ESWT in addition to eccentric training is a promising treatment for patients with PT, there are some remaining questions that need further attention. First, it is difficult to determine to what extent ESWT plays a part in the positive outcome in this treatment group. It is possible that the eccentric training program rather than the ESWT treatment was responsible for the effect that was measured, especially because ESWT as a solitary treatment did not seem to have a beneficial effect. Given the lower OR for the combined treatment of ESWT with eccentric training compared with eccentric training alone, one might even suggest that ESWT

negatively influences the beneficial effect of eccentric training. Moreover, the exact working mechanism and effects of ESWT on tendon tissue have not yet been clarified. Presumably, ESWT influences nociceptive response and neovascularization in tendon tissue, but articles studying this subject are not conclusive.³¹ Further research is therefore needed to establish the effects of ESWT on tendon tissue and to determine its role in the treatment of PT.

Given the positive effect of eccentric training on chances of clinical improvement, it is rather difficult to explain why GTN in combination with eccentric training did not show the same positive results. With an overall compliance of 70% reported by both Steunebrink et al (2013)¹⁰ and Van der Worp et al (2013),¹¹ we considered a lower compliance to the training program an unlikely explanation for the difference in the clinical outcome. Although quite speculative, the quality of exercise performance within the GTN group might have been lower compared with the eccentric training and ESWT with eccentric training groups. This could have negatively influenced the potential beneficial effects of the training program, as was described by Fortington et al.³² We hypothesized that the significantly lower Visual Analogue Scale (VAS) score (more pain) at baseline within the GTN group compared with the eccentric training group as reported by Steunebrink et al¹⁰ could have influenced the clinical outcome. However, after additional analyses, no correlation was found between the VAS score at baseline and clinical improvement on the VISA-P score after 12 weeks of treatment (not shown). The reason for the difference in outcomes between this treatment group and the other eccentric training groups therefore remains unknown.

Regarding the prognostic factors for clinical improvement, we found that a high training volume, a longer duration of symptoms, and older age had a negative influence on a treatment's clinical outcome. The negative influence of a high training volume on clinical improvement has been previously suggested by Visnes et al (2005) and Zwerver et al (2011).^{4,9} The mechanical overload of the tendon, caused by a high training volume, is likely to interfere with a treatment's potential beneficial effect. Moreover, because overload is a causal factor for developing tendinopathy, it seems appropriate to adjust load, especially in the acute stage of tendinopathy.¹⁵ This implies that in clinical practice

physicians should not only prescribe a medical treatment but also advise the patient to (temporarily) adjust training volume. The negative influence of older age and longer duration of symptoms can be linked to the stage of pathology. An older person tends to have stiffer tendons that more often have characteristics of the degenerative stage of pathology. The latter is also seen in patients with more chronic symptoms of PT. In both cases, the tendon's capacity to adjust and heal tends to decrease, complicating its treatment.¹⁵ Other factors related with poorer outcomes of lower limb tendinopathies may be an impaired muscle–tendon function, impaired kinetic chain function, biomechanical factors, and changes in neurovascular structure.³³

In the current study, only 37.7% of the patients improved clinically after 3 months of treatment. This result shows that PT remains a challenging condition. Currently, no conservative treatment exists for this injury, which guarantees quick and full recovery. The low number of patients who improve clinically suggests that a more differentiated treatment and individualized programs are necessary to improve clinical results.²⁷

To our knowledge, this is the first study to compare the effect of these multiple treatment options for PT on clinical improvement of symptoms in a secondary analysis on original data. Three double-blind randomized controlled trials with comparable methods and homogeneous outcome variables were included in this study. The primary outcome variable was the presence of clinical improvement based on an improvement of at least 13 points in the VISA-P score. This threshold was chosen as minimal important change based on previous work.¹⁹ The VISA-P questionnaire has proven to be a reliable instrument for evaluating outcomes in patients with PT and was specifically designed for this purpose.^{34,35} Previous studies evaluating the effect of eccentric training alone and ESWT followed by eccentric training have shown that clinical improvement can be demonstrated after 12 weeks of follow-up using VISA-P scores.^{30,36,37}

This study has some potential limitations. The selected trials for this secondary post hoc analysis included different populations in their original studies because of different ways of recruitment. We cannot exclude that (unmeasured) differences between the populations influenced our results, despite the fact that we corrected for possible confounding variables in our multivariable regression analysis. Also, other differences between the trials, such as the diagnosing physician, the physical therapist, outcome assessors, and medical centers involved, may have influenced the results. Because of the limited sample size, these variables could not be included in the model. Other possible limitations are the use of a home-based exercise program rather than a supervised exercise program, although a compliance of 70% was reached in both the TOPSHOCK and GTN trials and that no long-term results were studied.

CONCLUSIONS

In conclusion, only a small percentage of patients improved clinically after 3 months of treatment. In our analysis, eccentric training provides the highest chances of clinical improvement in patients with PT. The role of ESWT remains uncertain.

Furthermore, we found evidence that a high training volume, a longer duration of symptoms, and older age

negatively influence a treatment's clinical outcome and should therefore be taken into account during treatment. Further research focusing on these prognostic factors is needed to be able to design patient-specific treatment protocols for the management of PT.

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