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SYSTEMATIC REVIEW

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Effect of exercise after a deep venous thrombosis: A systematic review

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Abstract

Post-thrombotic syndrome (PTS) is a common complication after deep vein thrombosis (DVT) and has a major impact on physical symptoms, quality of life (QoL) and economic costs. Relatively simple lifestyle interventions as physical exercise might reduce PTS severity and increase QoL. To evaluate the direct and long-term effects of physical activity in patients with an acute or previous DVT. We conducted a systematic review through an additional search from 2007 up to March 2022, to complement the comprehensive systematic review of Kahn et al. Articles evaluating the effect of exercise after a DVT including symptoms, QoL and the incidence and severity of PTS, were included. Quality of the studies was assessed using a GRADE-like checklist and results were reported according to the PRISMA Statement. Ten studies were included, seven randomized controlled trials and three cohort studies. We identified three types of physical activity based on timing and duration; (1) early mobilisation in the acute phase of the DVT; (2) short duration exercise 1 year after DVT and (3) prolonged exercise during follow-up after a previous DVT. Early mobilisation showed improvement in QoL and pain reduction and after 2 years it resulted in a significant reduction of PTS severity. Prolonged supervised exercise resulted in improvement of QoL. In addition, positive effects on symptoms of venous insufficiency and muscle functions were observed. None of the included studies reported an increased risk of PTS or worsening of symptoms due to physical activity. Physical exercise after a DVT is safe, improves QoL, reduces pain and decreases PTS severity. Lifestyle intervention such as guided individualized training programs can be a useful supplementary therapy for patients after a DVT or for PTS patients. Optimal training programs may be identified by further studies that improve patient-oriented outcomes for both adults and children after a DVT.

INTRODUCTION

Deep vein thrombosis (DVT) is a common condition, despite primary and secondary prevention, and may lead to the post-thrombotic syndrome (PTS). PTS can be described as a set of symptoms and signs of impaired venous outflow as a result of deep venous obstruction and/or reflux following a DVT.[1,2] It occurs in 20%–50% of DVT patients, of which 5%–10% develops severe PTS, including venous leg ulcers. PTS usually occurs in the first years after a DVT, but may develop even after 10–20 years.[2,3] PTS patients not only have a lower quality of life (QoL) compared to DVT patients without PTS,[2,4] they also impose a burden on the healthcare system due to high medical costs, lost workdays and loss of employment.[3] Different medical specialties such as general practitioners, dermatologists, phlebologists, angiologists and vascular surgeons encounter patients in different phases of the disease for treatment and interventions.

While a DVT has to be prevented by all means, once it occurs, the risk or severity of PTS can be decreased by different types of therapy, including optimisation of anticoagulant therapy, compression therapy, endovascular or surgical techniques to restore venous patency and lifestyle interventions such as weight loss and exercise.[3,5] Walking exercises improve ankle function and increase calve muscle pump (CMP) functionality, stimulating venous return.[6] On the other hand, impaired CMP functionality delays venous leg ulcer healing and increases its recurrence.[7]

Unfortunately, there is a misconception among patients and physicians that exercise is harmful in the acute and chronic phase after a DVT, while there is evidence to support the opposite.[8,9] A supervised exercise training program is recommended for PTS patients by the American Heart Association,[3] based on the findings of the review of Kahn et al.[9] We aimed to further evaluate the direct and long-term effects of physical activity in patients with an acute or previous DVT including symptoms, QoL and the incidence and severity of PTS.

METHODS

Search strategy and data sources

A systematic search of PubMed and Embase was performed until 14 March 2022. Limits to publication date were applied from 1 July 2007 based on the inclusion period (until July 2007) of the systematic review of Kahn et al.[9] The main search terms comprised thromboembolism, physical activity and randomized controlled trials (RCT; see Table S1 for the complete search strategy). We included studies from this review according to our selection criteria as mentioned in the next paragraph. The current review was reported according to the guidelines for reporting systematic reviews in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline.[10]

Study selection and eligibility criteria

We included studies that investigated the effect of exercise or physical activity in DVT patients (with an acute or previous DVT) on the incidence of PTS, indicators of PTS and QoL. Studies preferably used a general accepted and predefined, well-described definition of PTS, such as the definition recommended by the International Society on Thrombosis and Haemostasis (ISTH),[1] or a commonly accepted instrument to assess venous symptoms of PTS that is regularly used in the literature such as the Venous Clinical Severity Scores (VCSS). Studies focussing on other outcomes related to PTS development or symptoms (e.g. leg flexibility, leg circumference, recanalisation of the affected thrombotic veins) and/or QoL, were also included. Studies with more than 50% of the included patients having other causes of chronic venous insufficiency than DVT, were excluded. Studies published in another language than English were excluded, as well as review articles. Kahn et al.[9] conducted a complete and comprehensive review of the literature until July 2007.

Screening

Two authors (BR and MR), independently screened the search results, following a pre-determined protocol. First, studies were screened by title. If it was clear from the title that the study was not relevant for our review, no further screening was done. If the title was potentially relevant or unclear, the abstract was read. After all potentially relevant studies were selected by title and abstract, they were checked on availability and whether they matched the eligibility criteria using the full-text article. All full-text articles were screened independently by two reviewers (BR and MR). In case of disagreement, a third reviewer (CvM) was consulted.

Data extraction

Characteristics of each included study were extracted using a standard form and included the number of patients, mean age, sex, length of follow-up, type and duration of intervention, study population, study design and outcome tools used (presence and/or severity of DVT, presence and/or symptoms of PTS or PTS-related outcomes, QoL). Data were adopted and used as published in the original article.

Different primary and secondary outcomes were used in the included studies. In Table S2, a list with the most important primary and secondary outcomes that were used is shown. In this table we describe the outcomes such as PTS, chronic venous insufficiency and venous parameters along with their scoring methods. Moreover, questionnaires on QoL such as the VEINES-QoL or the SF-36 and on habitual exercise levels like the Godin Leisure Time Questionnaire are also shown and clarified.

Methodological quality assessment

Two authors (BR, MR) assessed the methodological quality of the included studies using a 13-item checklist with criteria based on a quality assessment instrument[11] and using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Studies received 1 point for each criterion that was met: 0–4 points was defined as a poor-quality study, 5–7 defined a fair quality study, 8–10 defined a good study and 11–13 defined a study of excellent quality. The items were classified into four factors: study aims and design, descriptions of treatment protocol, descriptions of methods, therapeutic/side effects and conduct of the study.

Summary measures

Variables are presented as mean or median with standard deviation (SD) or range if available, and dichotomous outcomes as percentages. Detailed explanations of results are presented in tables. p-values, odds ratio's and 95% confidence interval (CI) are presented if these statistics could be extracted from the original articles.

RESULTS

Study identification and selection

The search results are presented in a PRISMA flow diagram (see Figure 1). PubMed and the EMBASE database search resulted in 3154 publications. Search results were exported to EndNote and after eliminating duplicates and studies published before July 2007, 2506 publications were screened on title and, if necessary, on abstract, after which 100 studies remained. These studies were evaluated in more detail and 12 articles were left for full-text review. Three studies met the eligibility criteria.

Seven out of 10 studies included in the systemic review of Kahn met our predefined eligibility criteria. Two studies focussing on pulmonary embolisms and one study investigating the effect of compression therapy during exercise therapy, were not included in our review. In total, 10 studies were included in our systematic review for further analysis and assessment.[12-21]

Methodology quality assessment

Table 1 shows the results of the quality assessment. Table S3 provides a detailed overview of the conducted quality

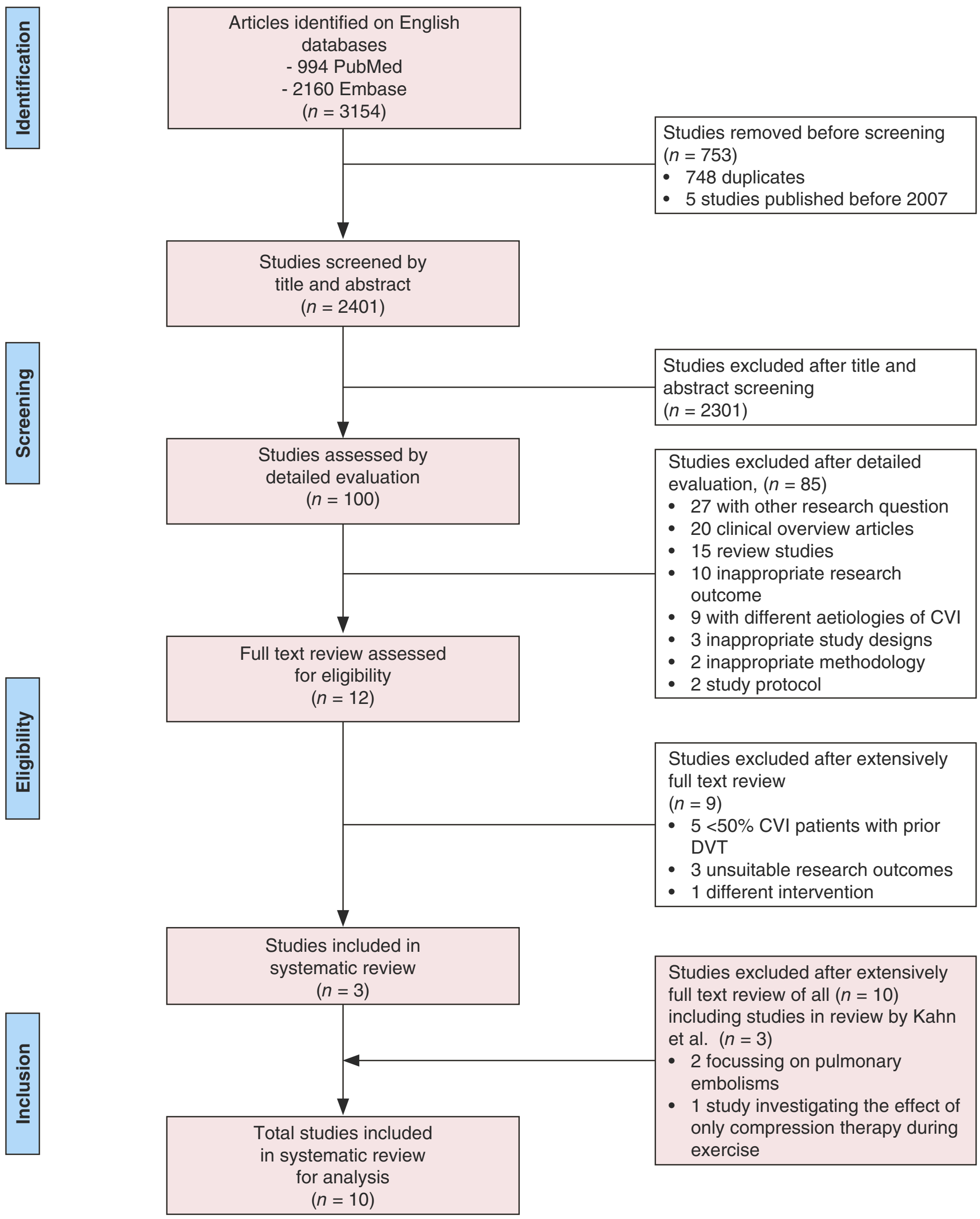

FIGURE 1 Flowchart study selection.

TABLE 1 Results of quality assessment of included studies.

Study	Poor quality (0–4)	Fairly good quality (5–7)	Good quality (8–10)	Excellent quality (11–13)
Jünger (2006)[12]			X (10 points)	
Blättler (2003)[13]		X (7 points)		
Partsch (2004)[14]		X (6 points)		
Kahn (2003)[15]		X (7 points)		
Shrier (2005)[16]			X (9 points)	
Shrier (2009)[17]			X (10 points)	
Isma (2007)[18]			X (9 points)	
Kahn (2011)[19]			X (8 points)	
Padberg (2004)[20]				X (11 points)
Hasan (2020)[21]		X (7 points)		

assessment, using a 13-item checklist.[11] One study was assessed as a study of excellent quality,[20] five were rated as good quality studies[12,16-19] and four studies were assessed as of fairly good quality.[13-15,21]

Study designs

We included three cohort studies[15-17] and seven randomized controlled trails (RCTs).[12-14,18-21]

Study characteristics

The characteristics of the studies are outlined in detail in Table 2. All 10 studies assessed the effect of physical exercise after a DVT with different primary and secondary outcomes. Exercise was investigated as habitual physical exercise levels, short interventional exercises or individualized long-term exercise programmes. To assess how exercise could affect patients with a (previous) DVT, we present the results of studies that investigated the effect of (1) early mobilisation in the acute phase of the DVT; (2) short duration exercise 1 year after DVT and (3) prolonged exercise during follow-up after a previous DVT.

Study results

A summary of the results of the included studies is presented in Table 3. As the outcomes differed among the 10 included studies, we summarized the results of all 10 studies individually. We ranked the studies in order of size according to the number of patients included or chronicity in case of follow-up studies.

Effect of early mobilisation in the acute phase of the DVT

A multicentre prospective study randomized 103 in-hospital patients, after a confirmed DVT, in an intervention group that could mobilize around the ward for at least 5 days and a control group that was prescribed strict bedrest.[12] Both groups were prescribed anticoagulation and compression stockings. The combined primary outcome consisted of relevant pulmonary embolisms (PE), diagnosis of PE, progression of thrombus, nosocomial infections, serious adverse events or death. Although not significant, less of the mobile patients reached the combined endpoint; 13.5% versus 28% bedrest patients ($p=0.09$) and the mobile patients less often had thrombus progression (7.7% vs. 20%, $p=0.09$). There was no significant difference between the groups in change of VAS pain scores at 12 days of follow-up.

In another RCT, 53 patients were randomized to (1) keep bedrest for 9 days, (2) perform walking exercises with therapeutic elastic stockings (TEK) or (3) perform walking exercises with compression bandages.[13] The QoL, the VAS pain score (in the compression bandage group) and reduction of oedema was significantly higher at Day 9 in the groups that did walking exercises. The relative risk of thrombus progression was lower in the exercise and compression groups ($p<0.01$).

The long-term follow-up was reported of these patients.[14] The two groups that immediately mobilized were combined and all patients were allowed to mobilize after 9 days and were stimulated to wear compression stockings for the next 2 years. Follow-up visits were performed in 70% of the patients. A significant lower median (interquartile range (IQR)) Villalta score was found in the two combined walking exercise groups (5 [3–6.5]) compared to the bedrest group (8 [6.5–11], $p<0.01$), despite a lower adherence to compression therapy for more than 1 year (50%) in the walking group compared with the bedrest group (73%). The incidence of PTS was lower in the exercise group (54%) compared with the bedrest patients (82%), although this was not statistically significant. No differences between the groups were found for pain scores, leg circumference and thrombus regression.

Effect of short duration exercise after a DVT

The single study included is a cohort study that analysed the effects of 30 min treadmill exercise in 41 patients with a DVT 1 year earlier,[15] of which 19 (46.3%) had PTS and 22 (53.7%)

did not. To examine whether the presence of PTS limited the ability to exercise, the primary outcome included VAS scores and muscle functions. No difference at baseline between patients was found in habitual activity levels using the Godin questionnaire. Severity of symptoms did not differ between the affected and unaffected leg after exercise and this was not influenced by the presence or severity of PTS. In PTS patients, there was a significant increase in muscle flexibility in the affected leg for the gastrocnemius muscle (4.5°, $p=0.003$) and the soleus muscle (5.7°, $p=0.001$) after treadmill exercise. Leg volume in PTS patients increased significantly more in their affected leg versus their unaffected leg (mean between leg difference + 53 ± 108 mL), compared with patients without PTS (mean between-leg difference − 15 ± 64 mL, $p=0.018$). The increase was most prominent in severe PTS.

Effect of prolonged physical exercise after a DVT

First, a cohort study of 301 patients evaluated whether the level of self-reported physical activity at 1 month after an acute DVT led to worsening of PTS severity at 4 months of diagnosis, defined by an increase of the Villalta score.[16] Three groups, (1) inactive (Godin score 0, $n=99$), (2) mild to moderate active (0–20, $n=97$) and (3) highly active (>20, $n=102$) were identified at 1 month after DVT. At 4 months follow-up no positive or negative effect on PTS severity was shown. Former active patients (Godin >0 pre DVT ($n=220$)) had self-reported activity levels at 4 months after DVT diagnosis that were either similar (42.3%, $n=93$) or showed an increase (13.2%, $n=29$), meaning that 44.5% ($n=98$) had a decreased activity level at 4 months. Fifty-five of those 98 patients stated that the decrease of their activity levels was due to exercise-induced leg symptoms, while the rest had reasons unrelated to their DVT.

The same research group investigated if the self-reported physical activity levels were associated with the risk of PTS occurrence at any moment within the first 2 years after DVT using the Villalta score[17] for 387 patients, an extended patient cohort of their prior study. Physical activity at 1 month after the DVT was not significantly associated with an increased risk of PTS occurrence in the next 2 years. Comparable results were shown after adjusting for potential confounders such as PTS severity, age, sex, BMI, pre-DVT physical activity level and disease-specific QoL scores. At 2 years follow-up, patients who had developed PTS were less physically active. This decrease in physical activity was greater among moderate and severe PTS patients than in patients with mild PTS ($p=0.002$).

Another RCT randomized 72 patients to investigate the effect of supervised physical exercise on venous symptoms and recanalisation of the prior thrombosed vein after a first episode of acute DVT.[18] All patients received anticoagulation therapy and TEK whereas the intervention group ($n=32$) in addition performed daily walking exercises and weekly supervised exercises for 6 months. Of the total of 67 (93%) patients who completed follow-up, the Björgell phlebographic score showed no statistically significant difference at 6 months between the intervention group 3.0 (SD 4.9) and the control group 1.1 (SD 2.8). Overall, QoL on a VAS scale of 0–100 improved and calf circumference in cm was reduced in both groups without any significant difference between the groups. There were no reports of recurrent DVT, PE or other complications.

In an RCT studying the effect of a 6-month supervised exercise training program to improve leg strength, leg flexibility and overall cardiovascular fitness, 43 patients diagnosed with PTS at least 6 months after a DVT were randomized into an intervention group ($n=21$) and a control group ($n=22$).[19] A significant between-group difference in disease-specific QoL, using the VEINES-QoL questionnaire, was shown in favour of exercise of 4.6 points (95%CI: 0.54–8.7, $p=0.03$). A difference of 3 points was considered clinically relevant. The effect of exercise on severity of PTS was not significantly different between the exercise group and the control group. However, the physical component score on the SF-36, leg strength and quadriceps flexibility were all statistically significant in favour of the exercise group.

Next, 30 male veterans with chronic venous insufficiency (CVI), 50% of whom had a history of DVT, were included in a RCT to compare the effect of a structured exercise program, consisting of individualized physical training sessions versus TEK only.[20] The 17 patients in the intervention group followed weekly training sessions for 3 months, after which they were encouraged to continue for another 3 months. Of the 28 (93%) patients who completed follow-up, there was a significant difference in venous ejection fraction ($p=0.03$), residual volume fraction ($p=0.03$) and measurements of the isokinetic peak torque per body weight, used to test muscle strength of different angular velocities at both slow ($p=0.05$) and fast speed ($p=0.03$), all in favour of the exercise group. No effect was found on CVI severity, functional mobility or QoL.

To investigate the feasibility of an individualized exercise program for paediatric and adolescent patients after an acute DVT, 23 patients (age 7–21 years) were randomized into two groups at 3 months after diagnosis.[21] Both groups were educated on the positive effects of physical exercise and were stimulated to exercise. The intervention group was also stimulated to increase activity level by 25% for 8 weeks to each individual's target level based on their baseline activity level of the previous 4 weeks tracked by a Fitbit tracking device. After the 8-week 'active' period patients could choose to maintain their increased exercise levels or return to their baseline levels. Besides feasibility, change in PTS score, assessed by the Manco–Johnson Instrument, was measured. A higher score indicates worse PTS severity. In total 15 of 23 patients completed the trial, and only 3 of 11 patients in the intervention group followed the 8-week prescribed regimen. During the trial self-reported physical activity did not differ between the groups, although the mean change (SD) in PTS scores at 6 months follow-up in the intervention group was 0.0

TABLE 2 Study characteristics.

Study	Study design	Study aim	Patient population, + inclusion criterium, – exclusion criterium	Intervention	Comparison	Main outcomes	Follow-up
Jünger (2006)[12]	Multicentre prospective RCT	To study the effect of mobilisation directly after a DVT	+ Presence of a proximal DVT diagnosed with duplex sonography or phlebography + In-patients and admitted for a DVT, at least 6 days hospitalized + Anticoagulation and compression therapy similar in both groups – Lysis therapy/thrombectomy – Concurrent symptomatic PE	Instruction to mobilize on the ward for at least 5 out of 6 days after DVT diagnosis	Strict bedrest for at least 5 out of 6 days	• Combined primary endpoint (clinically relevant PE, diagnosis of PE, progression of thrombus, nosocomial infection, serious adverse events, death) on final examination on Day 10–12. • Occurrence of single events of primary endpoint • Degree of leg pain (VAS scale, 0–100)	12 days
Blättler (2003)[13]	Single-centre RCT	To study the effect of immediate compression therapy and ambulation on PTS development	+ Mobile patients with DVT + Symptoms <14 days – Therapy already started – Thrombolysis/thrombectomy indicated	I: Inelastic compression therapy and walking for 9 days II: Elastic compression therapy and walking for 9 days	III: Bed rest up to 9 days without compression therapy	• Pain scores at 9 days • Leg circumference • DVT-related QoL • Recanalisation	9 Days
Partsch (2004)[14]	Single centre RCT (same cohort as Blattler et al.[14])	To study the effect of immediate compression therapy and ambulation on PTS development	+ Mobile patients with DVT + Symptoms <14 days – Therapy already started – Thrombolysis/thrombectomy indicated	I: inelastic compression therapy and walking for 9 days II: elastic compression therapy and walking for 9 days	III: Bed rest up to 9 days without compression therapy	• PTS severity (Villalta score) at 2 years • Pain scores • Leg circumference • Recanalisation	2 years
Kahn (2003)[15]	Single-centre prospective cohort study	To study the effect of exercise on venous symptoms and the effect of PTS on exercise	+ Subjects with a first episode of unilateral DVT at least 1 year earlier – Symptomatic pulmonary embolism – Unable to do treadmill exercises	Treadmill walking or running that caused sweating and mild tachypnoea for max. 30 min	• Comparison of post and pre-exercise symptoms • Comparison affected and non-affected leg • Comparison between patients with and without PTS	• Severity of individually venous symptoms after 30 min • Ligament flexibility • Muscle fatigability • Leg volume	30 min
Shrier (2005)[16]	Multicentre prospective cohort study	To study the effect of physical activity 1 month after DVT on PTS severity and activity 4 months later	+ New diagnosis of DVT, confirmed with duplex ultrasound or contrast venogram – Unable to adhere to the study protocol – Expected life span <1 year	N/A	N/A	• Δ PTS severity between 1 and 4 months visit (Δ Villalta score > 0) • Change in self-reported physical activity level (Godin Questionnaire)	4 months
Shrier (2009)[17]	Multicentre prospective cohort study (same cohort as Shrier et al.[19]) Single centre RCT	To study the effect of physical activity 1 month after DVT on PTS severity and activity 2 years later	+ New diagnosis of DVT, confirmed with venous duplex ultrasound or contrast venogram – Unable to adhere to the study protocol – Expected life span <1 year	N/A	N/A	• Development of PTS (Villalta score) over 2-year period. • Self-reported physical activity level (Godin Questionnaire)	24 months
Isma (2007)[18]	Single centre RCT	To study the effect of supervised exercise on recanalisation after DVT by phlebography, QoL and leg circumference	+ New diagnosis of DVT with phlebography. – Other disease or earlier thrombosis – Age > 75 years – DVT diagnosed only by ultrasonography – Inadequate phlebography for severity-scoring of the thrombosis	Six months of daily walking exercise and weekly supervised exercise	Standard DVT treatment only	• Recanalisation on phlebography at 6 months • Quality of life • Calf circumference	6 months
Kahn (2011)[19]	Two-centres RCT	To study the effect of exercise training after a DVT on QoL and PTS severity	+ Unilateral symptomatic DVT + Diagnosis >6 months + Presence of PTS – Contra-indication for exercise training – Expected life span <6 months – Pregnant or lactating – Open venous leg ulcer – Unable to visit check-ups	Six-month supervised and individualized exercise training program designed to improve cardiovascular fitness and leg strength and flexibility	One-hour education session on PTS with monthly phone follow-ups to simulate attention and contact received by the intervention group. Patients were asked to not alter their habitual activity level	• Venous disease-specific quality of life at 6 months • Severity of PTS (Villalta score) • Physical component of functional health and well-being (SF-36 PCS) • Leg strength • Quadriceps flexibility	6 months

TABLE 2 (Continued)

Study	Study design	Study aim	Patient population, + inclusion criterium, – exclusion criterium	Intervention	Comparison	Main outcomes	Follow-up
Padberg (2004)[20]	Single centre RCT	To study the effect of a supervised exercise program on calf muscle strength and haemodynamics	+ Patients with advanced CVI (CEAP 4–6) + CVI evidence with duplex ultrasound or APG – Painful or excessive (>4 cm) ulceration – Recognized non-compliance – Absence of an objective evidence of a venous cause – Recent acute thrombosis – ABI < 0.9	Three months of structured supervised exercise program followed by 3 months of unsupervised exercise and compression stockings	No additional exercise with compression stockings	• Calf pump function • Calf muscle strength • VCSS • Quality of life	6 months
Hasan (2020)[21]	Pilot RCT	To study the eligibility of and compliance to exercise therapy in children and adolescents as well as the PTS incidence and QoL in this group	+ outpatient subjects between 7 and 21 years of age with a new, first lower extremity DVT – Unable to exercise – Contra-indications to increasing activity that could impair existing medical conditions	16 week period with 8 weeks of individualized physical aerobic activity and education on benefits of physical activity initiated 3 months post DVT	Habitual activity after education on benefits of physical activity and encouragement to exercise	• Feasibility outcomes: eligibility, consent, compliance and trial completion • Changes in PTS (Manco-Johnson Instrument) • Changes in QOL	9 months

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; EF, ejection fraction; IQR, interquartile range; NS, not significant; OR, odds ratio; PTSs, post-thrombotic syndrome; QoL, quality of life; RVF, residual volume fraction; SD, standard deviation; SEM, standard error of the mean; VAS, visual analogue scale; VCSS, Venous Clinical Severity Score.

(SD = 0.50) versus an increase of 1.3 (SD = 0.8) in the control group ($p < 0.05$).

DISCUSSION

In this review of 10 studies focussing on physical exercise after a DVT, we found that the relatively 'simple' intervention of exercise had positive effects on both short- and long-term outcomes. Short-term outcomes after early mobilisation in the acute phase of the DVT included a reduction in PTS severity, an increase in QoL and a reduction of pain and oedema. Long-term outcomes after exercise training in the chronic phase after a DVT continued to improve QoL as several secondary outcomes associated with severity of PTS such as improved venous haemodynamics and enhanced muscle strength and muscle flexibility. Interestingly, higher levels of physical activity did not result in an increase of PTS severity. Patients with PTS tend to have a lower activity level than patients without PTS, which is more prominent with increasing PTS severity. In paediatric and adolescent patients adherence to a supervised physical exercise program proved to be difficult for this younger patient group.

Based on their systematic review of 2008 Kahn et al.[9] already promoted a positive role for exercise in patients with an acute or previous DVT without worsening of PTS symptoms. Our review supports these conclusions. Moreover, both Kahn et al. in their review and others also studied the incidence of complications like PE or recurrent venous thrombotic events (VTE), which did increase with increased physical exercise.[2,5] The additional studies we included in this review did not described these possible side effects. The positive effect of exercise on QoL was found both for exercise in the acute phase of a DVT, as well as in patients that had already developed PTS. The RCT performed by Kahn in 2011 confirmed the conclusions from their 2008 review and showed that a well supervised 6-month exercise training program in PTS patients improved QoL, leg strength and quadriceps flexibility, the latter being associated with improvement of venous return.[6]

Shrier et al.[17] demonstrated that nearly half of the previously active patients had a reduction in physical activity level after a DVT and patients appeared to be less active with increasing PTS severity. This might be out of fear for worsening of symptoms or to avoid pain, which both are known to predict low physical activity in leg ulcer patients.[22] 25% of patients in the cohort study of Shrier with reduction of their physical activity levels after DVT diagnosis stated that exercise-induced leg symptoms were responsible for this reduction. A session of treadmill exercises in another study showed no worsening of symptoms in the patient's affected leg compared to the unaffected leg. Worsening or development of PTS after longer follow-up was not shown in any study in our review. Thus, the specific cause of being less active after a DVT, or in case of PTS, is unclear and should

TABLE 3 Patient characteristics, main results and conclusion per study.

Study	Characteristics	Outcomes	Conclusions
1. Effect of early mobilisation in the acute phase of the DVT			
Jünger (2006)[12]	$N=103$ 52 = mobile 51 = immobile Mean age: 60 years Male 56%	**Occurrence of primary outcome (combined events), *n* (%)** Mobile group 7 (13.5%) vs. immobile group 14 (28%) $p=0.088$ (95%CI: −0.301 to 0.010) **Number of thrombus progression or new thrombus events, *n* (%)** Mobile group 4 (7.7%), vs. immobile group 10 (20%) $p=0.088$, 95%CI not mentioned **Number of clinically relevant/symptomatic PE events, *n* (%)** Mobile group 1 (1.9%) vs. immoblie group 5 (10%) $p=0.109$, 95%CI not mentioned **Number of deaths, *n* (%)** Mobile group 0 (0%) vs. immobile group 0 (0%) **Mean (±SD) VAS scores (0 to 100) for leg pain from day 1 vs. final examination (day 10 to 12)*** Mobile group: 54.1 (±30.4) vs. 20.7 (±19.2) Immobile group: 41.0 (±26.8) vs. 14.0 (±11.1) **Intention-to-treat analysis*	A trend was found in favour of mobilisation with less events, especially number of thrombus progression and relevant PE, although not significant No significant difference in pain reduction
Blättler (2003)[13]	$N=53$ 17 = bedrest 18 = stockings and mobilisation* 18 = bandage and mobilisation* **stockings + bandage = compression group* Mean age: unknown Male: unknown	**Pain scores (VAS scale)*** Mobile + only bandage vs. bed rest $p<0.05$[a] **Oedema (difference of mean lower leg circumference)*** Mobile + compression group vs. bedrest $p<0.001$[b] **DVT-related QOL*** Mobile + compression group vs. bed rest $p<0.05$[b] **Relative risk (95%CI) on thrombus progression** Mobile + compression group 6/27 22% vs. bedrest 4/10 40% RR 0.56; 95%CI: 0.20 to 1.57; NS **No exact numbers provided, data presented in figures in article*	The combination of mobilisation and compression therapy directly after DVT diagnosis reduced pain and oedema and improved QOL at 9 days
Partsch (2004)[14]	$N=37$ of 53 left after 2 years FU 11 = bedrest 13 = stockings and mobilisation 13=bandage and mobilisation Mean age: 56 years Male: 62.0%	**Median (IQR) PTS severity (Villalta score) after 2 years** Mobile: 5 [3 to 6.5] vs. bedrest: 8 [6.5 to 11] $p<0.01$ **Incidence of PTS development (Villalta ≥ 5) after 2 years** Mobile 14/26 (54%) vs. bedrest 9/11 (82%) RR 0.66; 95%CI: 0.42, 1.03; NS **Median (IQR) difference of pain (VAS scale) after 2 years** Bedrest 15 (8.5 to 35) vs. stockings and mobile 20 (7 to 23.5) vs. bandage and mobile 17 (7 to 26.5) NS **Median (IQR) difference of pain by Lowenberg test (mmHg) after 2 years** Bedrest 20 (0 to 15) vs. stockings and mobile 0 (−10 to 30) vs. bandage and mobile 0 (−17.5 to 40) NS **Median (IQR) difference of calf circumference (cm) between DVT leg and contralateral leg after 2 years** Bedrest 1.5 cm (0.5 to 1.75) vs. stockings and mobile 0.5 cm (−1 to 1.5) vs. bandage and mobile 1.0 cm (−0.25 to 2) NS **Percentage of recanalisation, progression or regression of the primary extension of DVT after 2 years** Mobile group: no thrombi 58.3%, unchanged 33.3%, progress 8.3% Bed rest group: no thrombi 54.5%, unchanged 36.4%, progress 9.1% NS	The combination of mobilisation and compression therapy directly after DVT diagnosis decreased severity of PTS at 2 years

TABLE 3 (Continued)

Study	Characteristics	Outcomes	Conclusions
2. Effect of short duration exercise after a DVT			
Kahn (2003)[15]	$N = 41$ (19 with PTS) Mean age: 51 years Male = 57.8%	**Difference after-before exercise in symptom rating in cm on a VAS scale, all patients** Affected leg: −0.01 to +0.52, NS Unaffected leg: −0.04 to +0.44, NS *Outcomes were not influenced by presence or severity of PTS* **Mean difference after exercise from preexercise of leg volume (mL ± SD), all patients** Affected leg: +76 mL ± 110, $p < 0.001$ + 59 mL ± 82, $p < 0.001$ Unaffected leg: +59 mL ± 82, $p < 0.001$ + 76 mL ± 110, $p < 0.001$ **Mean difference in leg volume (mL ± SD) after exercise, affected leg vs. unaffected leg, only PTS patients** Affected leg +53 ± 108 mL vs. unaffected leg −15 ± 64 mL, $p = 0.018$ *More severe PTS gained more volume in the affected leg* **Mean difference in muscle flexibility after exercise between affected leg and unaffected leg in PTS patients vs. non-PTS patients** Gastrocnemius flexibility: +4.5°, $p = 0.0029$ Soleus flexibility: +5.7°, $p = 0.0011$ No correlation between change in leg volume and change in muscle flexibility was found for gastrocnemius muscle $R^2 = 0.03$ or soleus muscle $R^2 = 0.07$)	Treadmill exercises did not worsen symptoms in patients with or without PTS in their affected leg compared to their unaffected leg Exercise led to a greater mean leg volume in patients with PTS in their affected leg compared to their unaffected leg In PTS patients exercise led to a greater increase in muscle flexibility between the affected and unaffected leg compared to non-PTS patients
3. Effect of prolonged physical exercise after a DVT			
Shrier (2005)[16]	$N = 301$ Mean age: 55 years Male: 50%	**Adjusted OR[c] for worsening of PTS (ΔVillalta score > 1) after 4 months (95%CI) according to activity level at 1 month*** No physical activity: OR = 1.0 (reference) Mild–moderate active group: OR = 0.93 (0.47 to 1.87) Highly active group: OR = 0.52 (0.23 to 1.15) **When worsening was recalculated as ΔPTS > 0 as compared with > 1, the results were similar but the evidence for a gradient effect was stronger: OR mildly to moderately active = 0.76 (0.40, 1.44), and OR highly active = 0.52 (0.26, 1.03).* **Change in physical activity level at 4 months among active patients (Godin score at 1 month > 0 (*n* = 220))** 42.3% ($n = 93$) reached the same physical activity level 13.2% ($n = 29$) had increased physical activity levels 44.5%% ($n = 98$) had decreased physical activity levels* **Exercise-induced leg symptoms were reported as the cause in 25% (n = 55) of all previously active patients*	An increase in habitual physical activity 1 month after DVT did not worsen PTS at 4 months Nearly half of all previously active subjects had a decrease in physical activity level, with exercise-induced leg symptoms being the cause in 25% of all former active patients
Shrier (2009)[17]	$N = 387$ Mean age: 58 years Male: 50.5%	**Adjusted OR[d] for developing PTS within 2 years after DVT (95%CI)*** Mild to moderate activity levels within 1 month after diagnosis: 1.64 (0.85 to 3.15) High levels of activity within 1 month after diagnosis: 1.33 (0.68 to 2.06) **Data of patients with 'no activity' not provided* **Association between occurrence of PTS and physical activity level at 2 years follow-up[e], proportion, % (95%CI)*** **No activity (Godin = 0 at 2 years):** None to mild PTS 19.6 (13.6 to 25.6) Moderate to severe PTS 42.4 (29.2 to 55.7) **Mild to moderate activity level (Godin = 1 to 20 at 2 years)** None to mild PTS 24.9 (19.0 to 30.9) Moderate to severe PTS 20.6 (10.5 to 30.8) **High activity level (Godin > 20 at 2 years)** None to mild PTS 55.5 (48.8 to 62.2) Moderate to severe PTS 36.9 (24.0 to 49.8) **Overall difference of physical activity between none to mild* vs. *moderate to severe PTS was statistical significant, p = 0.002*	The level of exercise in the first month after DVT was not associated with the 2 years risk of developing PTS Patients with PTS had lower activity level than patients without PTS. This was more prominent with increasing PTS severity

(Continues)

TABLE 3 (Continued)

Study	Characteristics	Outcomes	Conclusions
Isma (2007)[18]	$N = 72$ Mean age: 54 years Male: 52%	**Median calf circumference of affected leg (cm (range)) at 6 months follow-up** Exercise group 38 cm (25.5 to 48) vs. control group 36 cm (32.5 to 44) NS **Median QoL (VAS score 0-100 mm (range)) at 6 month follow-up** Exercise group 4 (0 to 74) vs. control group 7.5 (0 to 95) NS **Mean phlebographic DVT score (Björgel score (SD)) after 6 month follow-up** Exercise group 3.0 (4.9) vs. control group 1.1 (2.8) NS	No difference in calf circumference, QoL or phlebographic score was seen after daily exercise training for 6 months
Kahn (2011)[19]	$N = 43$ Mean age: 46 years Male: 44.4%	**Mean difference of VEINES-QoL (SD) from baseline to 6 months** Exercise group 6.0 (5.1) vs. control group 1.4 (7.2) Between group difference 4.6 points (95%CI: 0.54 to 8.7) $p = 0.027$ **Mean difference of PTS severity from baseline to 6 months; Villalta score (SD)** Exercise group −3.6 (3.7) vs. control group −1.6 (4.3) Between group difference − 2.0 points (95%CI: −4.6 to 0.6) $p = 0.14$ **Mean difference on SF-36 PCS scale (SD) from baseline to 6 months** Exercise group 5.6 (7.7) vs. control group 0.2 (7.6) Between group difference: 5.4 points (95% CI: 0.5 to 10.4) $p = 0.03$ **Mean difference of leg strength from baseline to 6 months; number of heel lifts (SD)** Exercise group 5.2 (10.6) vs. control group −2.5 (10.8) Between group difference: 7.7 (95% CI: 0.7 to 14.7) $p = 0.03$ **Mean difference of quadriceps flexibility from baseline to 6 months; degrees (SD)** Exercise group 10.2 (20.5) vs. control group 0.3 (6.6) Between group difference: 9.9 (95% CI: −1.0 to 20.7) $p = 0.04$	Six-month exercise training improved the disease specific QoL, leg strength, quadriceps flexibility and the physical component of health-related QoL, but not Villalta score
Padberg (2004)[20]	$N = 30$ (50% with prior DVT) Mean age: 70 years Male: 100%	**Mean difference in calf pump functions from baseline to 6 months (% (±SEM))** Ejection fraction (EF): Intervention group 3.5 ± 2.7 vs. control group −1.4 ± 2.1 $p = 0.03$ Residual volume fraction (RVF): Intervention group −8.8 ± 4.6 vs. control group 3.4 ± 2.9 $p = 0.03$ **Mean difference in muscle strength (peak torque/body weight) at slow speed from baseline to 6 months (number (±SEM))** Intervention group 3.1 ± 1.4 vs. control group −1.0 ± 1.1 $p = 0.05$ **Mean difference in muscle strength (peak torque/body weight) at fast speed from baseline to 6 months (number (±SEM))** Intervention group 2.8 ± 0.9 vs. control group −0.3 ± 0.6 $p = 0.03$ **Mean difference of VCSS score from baseline to 6 month (total (±SEM))** Intervention group −0.3 ± 0.9 vs. control group 0.1 ± 1.0 $p = 0.51$ No difference in QoL between both groups (data not shown)	After exercise training, the EF increased significantly and the RV decreased significantly Both slow and fast peak torque, to measure calf muscle strength, improved in the affected legs of patients receiving exercise regimen The exercise program did not lead to any differences in venous severity score or QOL

TABLE 3 (Continued)

Study	Characteristics	Outcomes	Conclusions
Hasan (2020)[21]	$N = 23$ Mean age: 15 years Male: 48%	**Adherence to the allocated intervention and overall activity** Only 3 of the 11 patients adhered to prescribed activity during active study phase No differences in self-reported physical activity scores between groups during entire trial In postintervention phase, only 20% of all patients maintained target activity levels **Mean change of PTS score from baseline to 6 months of follow-up (mean Manco-Johnson Instrument score (SD))** Intervention 0.0 (0.50) vs. control group +1.3 (0.8) $p = 0.0017$ **Mean change of total QoL score from baseline to 6 months of follow-up (mean QoL score (SD))** Intervention +5.5 (14.3) vs. control group +24.5 (14.2) $p = 0.023$ **Elastic compression stocking use at 6 months follow-up** Intervention group 44% vs. control group 85%	Enrolment and randomisation of paediatric DVT patients of prescribed exercise therapy was feasible; however, adherence and retention was low Activity lowered PTS score The control group had a statistical significant better mean QoL score than the intervention group although both showed a substantial increase in QoL scores

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; IQR, interquartile range; NS, not significant; OR, odds ratio; PTSs, post-thrombotic syndrome; QoL, quality of life; SD, standard deviation; SEM, standard error of the mean; VAS, visual analogue scale; VCSS, Venous Clinical Severity Score.

[a]In favour of the mobile and bandage (combined) group.

[b]In favour of the mobile and compression (combined) group.

[c]Adjusted for age, sex, pre-DVT physical activity level and venous disease-specific QOL at 1 month.

[d]Adjusted for age, sex, body mass index (BMI) and pre-DVT physical activity level (baseline Godin score) and disease severity at 1 month.

[e]Scored on the Godin questionnaire.[14]

be further elucidated in future studies, along with the role of physicians, trainers and supervisors could play.

In most trials, both PTS occurrence and severity was scored using the Villalta scale. Though recommended by the ISTH, this is a subjective scale and might have been interpreted differently by different assessors.[1] Moreover, this scoring modality does not cover all important aspects of PTS, such as venous claudication. Many studies investigated however more important variables, such as venous haemodynamic parameters and symptoms apart from the Villalta score. Many studies did emphasized the importance of quality of life, which is an increasingly important outcome in chronic diseases as PTS. Since PTS imposes a great burden on patients' QoL, the improvement of QoL due to exercise which was found in several trials, is promising.

Post-thrombotic syndrome not only reduces QoL, it also impose a burden on the healthcare system with significant financial consequences, especially in case of venous leg ulcers.[3,4] The consumption of care from both in-hospital and home care organisations increases medical costs and the combination of direct and indirect societal costs leads to considerable economic burden.[23] The positive outcomes in this review can be of great importance to potentially reducing these costs. Several studies have found a long-term positive effect of physical exercise on preventing worsening of PTS, venous symptoms and QoL. That exercise therapy can have a long-lasting effect suggests that this could be an inexpensive tool to reduce those costs, although this should be the focus of further research.[3]

In paediatric patients leg discomfort and a lack of motivation and time appeared to be reasons for their inability to adhere to prescribed exercise schedules. As this was a pilot study with few patients primarily focussing on the feasibility of physical exercise programs in paediatric patients, the results of the PTS and QoL scores must be interpreted with caution. Moreover, this study showed the difficulty for younger patients to adhere to a physical activity program. More knowledge on how to motivate paediatric patients after a DVT to exercise is necessary to overcome these concerns.

The limitations of this review are due to the heterogeneity in methods and outcomes of the included studies and therefore a meta-analysis could not be performed. For example, instead of using the Villalta score for PTS as primary outcome, a significant number of trials investigated surrogate endpoints, like leg or joint flexibility, leg circumference or recanalisation of the affected vein. These outcomes can be associated with venous disease severity,[6] but do not automatically imply the presence of PTS or indicate the severity of PTS. In some studies, no associations were found between physical exercise and PTS, while a positive association was found between exercise and some secondary endpoints.

Although most studies included exclusively active or former DVT patients, one of the studies included 50% of patients with causes of CVI other than a previous DVT.[20] This must be taken into account when analysing and comparing their results. Apart from the studies by Shrier et al., all studies were performed in <100 patients which is low when considering the high prevalence of DVT. The studies by Shrier et al. were performed in >300 patients, although these were cohort studies and so did not randomize patients to intervention and control groups. The authors only recorded the levels of habitual activity. In the cohort study of Shrier just 71% of the patients reached the end of the 2-year follow-up.[17] Strict inclusion and exclusion criteria (e.g. exclusion of older patients, inclusion of only veterans or a fairly good tolerance to exercise) could also have influenced the outcomes, as this is not a representation of the average patient suffering from PTS. Moreover, of the included children in the pilot RCT 83% was overweight, which might have introduced significant bias in a study on physical activity. Lastly, exercise exposure among the trials was often not verified accurately.

CONCLUSION

The relatively 'simple' intervention of exercise has positive effects in the acute and chronic phase after a DVT, on both short- and long-term outcomes. A positive recommendation for treating PTS with a supervised exercise program, has been incorporated in the American Heart Association document on the prevention, diagnosis and treatment of PTS.[2] In analogy to peripheral arterial disease, physical exercise therapy could be a good supplementary therapy for DVT patients. Because patients may have an anxiety towards physical activity, especially when this temporarily increases pain or leg swelling, physicians should explicitly tell their patients exercise is not harmful. Further research is needed, focussing on the effects of different supervised exercise programs as part of the treatment for acute DVT as well as for patients suffering from PTS. With the upcoming popularity of activity tracking devices and the availability of apps, motivating patients to exercise and track lifestyle interventions may become much more easily accessible as well as more playful and fun.

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SUPPORTING INFORMATION

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