

## REVIEW

# The Effectiveness of Early Mobilization in Hospitalized Patients with Deep Venous Thrombosis

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**ABBREVIATIONS**

DVT=deep venous thrombosis  
LMWH = low-molecular weight heparin  
PE=pulmonary embolism  
PTS=post-thrombotic syndrome

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**ABSTRACT**

Deep venous thrombosis (DVT) is a common problem among hospitalized patients. It places the patient at risk for pulmonary embolism (PE) and post-thrombotic syndrome (PTS). In particular, up to 50% of patients with proximal DVT of the lower extremity develop PE. Because of the high mortality rate, there is a great concern from physiotherapists and physicians regarding patient's treatment in the hospital setting. Thus, the purpose of the present review is to examine the effectiveness of early mobilization in acute leg DVT of the lower extremity in hospitalized patients. Current evidence shows that early mobilization, i.e., walking and/or exercising, with anticoagulation and leg compression may be encouraged in patients with acute DVT. Recent studies reported the benefits of reduction in pain and edema, with improvement in quality of life when using the therapeutic strategy of early mobilization in patients with DVT. Early mobilization does not appear to increase the risk of developing PE, progression of an existing DVT, or developing a new DVT. Further research with larger hospitalized patient samples is required to determine the appropriate time in which ambulation should be initiated after DVT, and whether exercise (regular or vigorous) or no exercise is more effective for DVT, PE, and PTS.

**INTRODUCTION**

Deep venous thromboembolism (DVT) has been a serious concern for hospitalized patients causing significant morbidity and mortality in northern Europe, United States, and Canada.<sup>1</sup> DVT results from a combination of venous stasis, vein injury, and increased coagulation activity, referred to as Virchow's triad.<sup>2</sup> This medical situation places the patient at risk for pulmonary embolism (PE), and post-thrombotic syndrome (PTS).<sup>3,4</sup> Post-thrombotic syndrome comprises the signs and symptoms that may occur as long-term complications of DVT. Up to 50% of patients with DVT involving the proximal deep veins of the lower extremities develop PE<sup>5</sup> and the overall incidence of PTS is 20–50%.<sup>6</sup> Because of the high mortality rate of VTE, therapists' greatest concern is the primary care for the patient during initial management of DVT, particularly in the hospital setting.<sup>5</sup> Thus, it becomes necessary to investigate therapeutic approaches following diagnosis of DVT to reduce the high morbidity rate of VTE.

Patients with myocardial infarction, ischemic stroke, congestive heart failure, chronic

obstructive pulmonary disease, underlying malignancy, trauma, and patients undergoing surgical procedures appear to be at increased risk for developing DVT in the hospital setting.<sup>7</sup> Critically ill patients have an increased risk of lower extremity DVT compared with other hospitalized patients.<sup>8,9</sup> A study with critical ill patients showed that mechanically ventilated patients with sudden episodes of hypotension, tachycardia, or hypoxia may have undetected PE.<sup>10</sup> Unsuspected PE may also contribute to difficulty of weaning patients from mechanical ventilation.<sup>11</sup> The significance of DVT in critically ill patients is major, because these patients are likely to have serious consequences of even small pulmonary emboli.<sup>12</sup> Furthermore, patients with DVT have a longer duration in mechanical ventilation, intensive care unit stay, and hospital stay than patients.<sup>12</sup> Therefore, it is worth investigating the appropriate therapeutic approach of DVT and the possible risks of PTS and PE, particularly, in the hospital setting.

Prolonged immobilization has been associated with DVT in critically ill patients.<sup>13</sup> In particular; neurosurgical intensive care patients are vulnerable to the development of DVT because they are immobilized due to their neurological deficits. This immobility is confounded by many other situations that add to physical deconditioning, such as administration of sedative agents and muscle atrophy from prolonged bed rest.<sup>14</sup>

Over the past decades, patients with acute DVT in the lower limbs were traditionally immobilized. This approach was motivated by the fear of dislodging an unstable thrombus and causing PE and by the belief that inactivity relieves local pain and swelling. On the other hand, bed rest promotes stasis, an element of Virchow's triad. Also, immobilization can lead to secondary complications, i.e., muscle weakness and atrophy, reduction of muscle endurance, pain and discomfort, respiratory problems, and can thus be detrimental for patients. Early mobilization has been recently considered an appropriate therapeutic approach for the acute stage of DVT. Therefore, it is important to investigate the benefits of early mobilization and to examine how safe this approach may be in terms of preventing the development of new thrombi, PE and PTS or the progression of already existing thrombi.

Accordingly, the purpose of the present review is to examine the role of early mobilization in hospitalized patients with DVT.

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#### PHYSIOLOGICAL CHANGES DUE TO MOBILIZATION

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The biological condition of the endothelium plays a central role in the pathophysiology of DVT, and the hypertensive stasis due to prolonged immobilization in patients with DVT is likely to impair the endogenous endothelial fibrinolytic activity.<sup>15-17</sup> Particularly, experimental studies in humans have recognized the fibrinolytic properties of the healthy endothelium,<sup>18</sup> whereas other studies have consistently shown that: (a) recanalization

after DVT is inversely related to the levels of endothelium derived factors that inhibit the fibrinolytic system;<sup>19</sup> (b) vascular inflammation is associated with a reduced fibrinolytic response to venous occlusion;<sup>16</sup> and (c) exercise training reduces the impairment in fibrinolytic activity in patients with peripheral arterial disease.<sup>20</sup> In a recent study it was demonstrated that exercise suppresses shear-induced platelet activation and subsequent polymorphonuclear leukocyte adhesion to platelets deposited at sites of vascular injury under flow, thus reducing the risk of vascular thrombosis and inflammation.<sup>21</sup> The reduction of platelet and leukocyte functions and the promotion of endothelial fibrinolytic activity reduce the risk of vascular thrombosis.<sup>17</sup>

Inactivity of the venous system pump mechanism provided by lower limb muscles contributes to formation and propagation of thrombus.<sup>22</sup> The potentially beneficial effects of mobilization are related to the calf muscle pump theory and to muscle training. Particularly, during muscle contraction, there is increase in ejection ability, facilitating venous outflow, which in turn reduces the gradient of hydrostatic pressure that is responsible for edema formation; in addition, there is an improvement in muscle perfusion, thus enhancing the potential of muscle action.<sup>23</sup> External compression of the leg associated with a walking program might provide reduction in blood hydrostatic pressure and, consequently, lead to reduction in venous signs and symptoms.<sup>24</sup>

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#### EFFECTS OF EARLY MOBILIZATION

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Several studies have investigated the effect of mobilization (ambulation and/or exercise) on all aspects of VTE, i.e., pain and swelling of patients with DVT, thrombus growth/extension/propagation, PE and PTS. The results of various studies that examined the effect of immediate ambulation and/or exercise on speed of pain and edema resolution in DVT are contradictory. Indeed, pain and swelling associated with DVT were more reduced in the walking group than in the bed-rest group 9 days after initiating ambulation.<sup>24</sup> In addition, Blättler and Patsch,<sup>25</sup> in their randomized controlled trial, reported that the pain level and the difference between the circumferences of both calves were significantly more reduced in the walking with compression groups compared with the bed-rest group. Another two experimental studies examined during a short-term follow-up, the change in leg symptoms in patients with acute DVT after starting early walking.<sup>26,27</sup> Although in the first study<sup>26</sup> early walking did not influence the rate of improvement of acute leg pain, in the other study,<sup>27</sup> early walking was associated with greater improvement in acute pain and quality of life. Nevertheless, due to equivocal current results, future studies including many patients and using appropriate methodologies should be conducted to examine the effect of early mobilization on pain and edema in patients with DVT.

Regarding the effect of early mobilization on thrombus growth and/or occurrence of PE, Aldrich and Hunt<sup>28</sup> concluded in their review that early ambulation is suggested in patients with DVT. The authors recommended that these patients may safely begin ambulation once appropriate anticoagulation medication has been instituted, i.e., the patient may begin walking within the first 24 hours after he/she has begun medical treatment for DVT. A clinical experimental study compared bed rest for 9 days without compression with walking exercises using either compression stockings or bandages in patients with proximal DVT.<sup>25</sup> Thrombus size was assessed by duplex ultrasound examination on days 0 and 9. Progression of thrombus length in the femoral vein was seen in 40% after bed rest and in 28% with walking and compression.<sup>25</sup> Regarding change of thrombus length, the difference between bed rest and walking with compression was statistically significant.<sup>25</sup> Two other randomized controlled trials also examined thrombus extension in patients with acute DVT after about 10 days walking.<sup>27,29</sup> The relative risk of thrombus progression associated with early walking was 0.38 [95% confidence interval (CI): 0.13-1.15],<sup>29</sup> and 0.56 (95% CI: 0.20-1.57),<sup>27</sup> suggesting a trend but not a clear benefit of walking on decreasing the risk of thrombus progression. In another experimental study, bed rest with immobilization and lack of compression therapy in patients with DVT was associated with higher incidence of thrombosis progression and new cases of PE at 30 days.<sup>17</sup> In this study,<sup>17</sup> all patients in the exercise group were encouraged to perform active walking exercises as much as possible for at least 3 times a day wearing class II compression stockings (20-40 mm Hg) during night and day. In theory, the positive effects of compression are added to those of early mobilization because of rhythmic acceleration of venous flow velocity due to muscle pump function, thus preventing venous stasis. However, this study was a single-center retrospective analysis, which contained several sources of potential bias (e.g., patients were not randomly allocated, missed many cases of PE, and sensitivity of the echocardiography was poor). Regarding thrombus propagation, another retrospective multicenter study showed that thrombus propagation was observed in about 20% of patients when late mobilization was applied, whereas thrombus propagation fell to 1% when mobilization was applied immediately, particularly, 10 days earlier than the bed-rest group.<sup>30</sup> Finally, Junger et al<sup>31</sup> compared the outcome of mobilization against strict bed rest in patients with acute proximal DVT in their prospective, randomized, open and multicenter trial. Fifty patients in the immobilized treatment group were prescribed strict bed rest for at least 5 days. Fifty-two patients of the mobile treatment group were instructed to immediately start moving around on the ward during the minimum 5-day initial phase. A progressive thrombosis or new thrombus was found in 7.7% of cases in the immediate mobile group and 20.0% of cases in the immobile group which was immobilized for 4 days. No incidence of fatal PE due to mobilization was detected.<sup>31</sup> Based on the results of

the above studies, mobilization associated first with administration of low-molecular weight heparin (LMWH) has been proposed for DVT patients immediately after diagnosis.<sup>31,32</sup>

More specifically about the frequency of PE, Aschwanden et al,<sup>33</sup> in an open-label, randomized, parallel group study, randomized 129 patients with DVT to either strict immobilization for 4 days or to ambulate for  $\geq 4$  hours per day. All patients were screened for PE at baseline and daily during the 4-day observation period. The frequency of PE at baseline was 53% and 44.9% in the immobile and the mobile groups, respectively. During the 4-day observation period, new PEs were found in 10.0% and 14.4% of the immobilized and ambulating patients, respectively. As this difference was not statistically significant, the authors concluded that immobilization is not superior to early mobilization, thus suggesting that early mobilization is safe. Similarly, Partsch et al<sup>34</sup> with a prospective study and Schellong et al<sup>35</sup> with a randomized controlled trial reported that when ambulatory patients with acute DVT first receive properly dosed LMWH and then they are encouraged to walk with appropriate compression bandages or stockings, the threat of PE is minimal. In Kahns' et al<sup>36</sup> systematic review and meta-analysis which combined the results of all four previous experimental trials,<sup>25,33-35</sup> it appeared that early walking was associated with a relative risk of symptomatic or asymptomatic PE after 10 days of 1.16 (95% CI: 0.66-2.05), and thus the authors concluded that immediate exercise compared with bed rest was associated with a similar short-term risk of PE in patients with acute DVT. A recent systematic review and meta-analysis examined the effects of early ambulation on the development of PE and progression/development of a new thrombus in patients with acute DVT.<sup>37</sup> Ambulation and compression was compared to bed rest and compression.<sup>25,32,33,35</sup> The relative risk for development of new PE was 0.63 (95% CI: 0.34-1.19)<sup>32,35</sup> and 1.36 (95% CI: 0.57-3.29)<sup>25,33</sup>, thus suggesting a similar risk for the two methods. In the same meta-analysis, researchers evaluated the progression of a previous thrombus or the development of a new thrombus in the available studies.<sup>25,32</sup> Individual relative risks for ambulation and compression versus bed rest and compression and ambulation and compression versus bed rest alone were 0.39 (95% CI: 0.13-1.14) and 0.56 (95% CI: 0.20-1.57), respectively, thus indicating a similar risk for the compared methods. Therefore, the results of this meta-analysis<sup>37</sup> suggest that early ambulation does not harm patients diagnosed with DVT. However, before any clinical judgment regarding the treatment is made, it is necessary to weigh the potential advantages and disadvantages of ambulation.<sup>37</sup> Patients should also be closely monitored for changes in their status when being ambulated during the initial acute phase.<sup>36</sup> Nevertheless, clinicians should be confident that ambulating patients with DVT does not appear to increase the risk of developing a new PE, progression of an existing DVT, or developing a new DVT.<sup>36</sup>

Regarding the effect of early mobilization on PTS, it has

been shown that exercise may help to exacerbate the symptoms of patients diagnosed with PTS.<sup>38</sup> Indeed, in subjects with PTS, Kahn et al<sup>38</sup> found that performing exercises did not exacerbate symptoms and resulted in improved flexibility in the affected leg. They reported that treadmill or similar exercise is unlikely to make symptoms of PTS worse, and may improve flexibility.<sup>37</sup> In this experimental study,<sup>37</sup> patients, who had a first episode of unilateral DVT at least 1 year earlier and were categorized as having (1<sup>st</sup> group), or not having PTS (2<sup>nd</sup> group), exercised on a treadmill set at a 5% incline for as long as they were able up to a maximum of 30 minutes. In another experimental study,<sup>39</sup> mobile patients with PTS who received compression therapy had significantly lower Villalta scores than patients who were prescribed bed rest and no compression therapy. Recently, Kahn et al<sup>40</sup> conducted a randomized controlled 2-center pilot trial to assess the feasibility of a multicenter-based evaluation of a 6-month exercise training program to treat PTS. The intervention was an exercise training program consisting of a 6-month program with strengthening, stretching and aerobic components designed to improve leg strength, leg flexibility and overall cardiovascular fitness. Thirty-nine patients attended 15 one-on-one sessions with an exercise trainer (3 sessions per week in the first two weeks, 2 per week in the third week, 1 per week in the fourth week and 1 per month thereafter).<sup>40</sup> The first three sessions lasted 60 minutes, and subsequent sessions lasted 45 minutes. This trial included only young, well-educated and active patients, and the authors found that exercise training may improve the symptoms of PTS. Finally, a multicenter study that included a prospectively followed cohort of 301 patients of all ages<sup>41</sup> showed that patients with higher levels of self-reported habitual physical activity at one month tended to have less severe post-thrombotic symptoms, but this difference did not attain statistical significance. Nonetheless, future clinical trials with larger hospitalized samples may confirm the positive role of mobilization on PTS.

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## GUIDELINES AND PERSPECTIVES

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Buller et al<sup>42</sup> reported that the American College of Chest Physicians did not recommend bed rest in the guidelines for treating acute DVT, but rather recommended ambulation with compression as tolerated by the patient after starting anticoagulation. Patients who are not hemodynamically stable should be first stabilized. Patients should wear elastic compression stockings with a pressure of 30 to 40 mmHg at the ankle for 2 years after an episode of DVT and a course of intermittent pneumatic compression for patients with severe edema of the leg resulting from PTS should be employed.<sup>42</sup> However, a joint guideline from the American College of Physicians and the American Academy of Family Physicians does not make recommendations about ambulation for therapy of PE.<sup>43</sup> Table 1 shows the recent evidence-based clinical practice guidelines

**TABLE 1.** Evidence-Based Clinical Practice Guidelines from the American College of Chest Physicians. Antithrombotic Therapy and Prevention of Thrombosis.

- Early ambulation of patients with acute deep vein thrombosis (DVT)
- In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C).

*Remarks:* If edema and pain are severe, ambulation may need to be deferred. As per next section, we suggest the use of compression therapy in these patients.

- In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).

*Remarks:* Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed post-thrombotic syndrome (PTS) and find the stockings helpful. Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.

- Physical treatment of patients with PTS
  - In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C).
  - In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B)

From: Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ. Antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 suppl):7S.

and recommendations from the American College of Chest Physicians.<sup>44</sup>

The prescription of rest in bed for patients with DVT did not reduce the incidence of PE to the extent of significantly influencing clinical evolution.<sup>28,32,33,35</sup> When the progress of patients left to rest in bed is compared with that of patients who had early walking, there is no significant difference in PE occurrence,<sup>24,33-35,39,45</sup> although it is claimed that immediate mobilization contributes to reduction in thrombus progression.<sup>24,31</sup> Therapists must weigh the risk of ambulation that may potentially cause PE against the alternate treatment of bed rest, which is certainly with its own risks, i.e., bed rest can result in loss of aerobic capacity and may also decrease leg muscle strength, range of movement, and general function.<sup>37</sup> An exercise training program may also be an effective treatment for PTS, with improvement in venous disease-specific quality of life and severity of PTS symptoms and signs.<sup>38</sup>

Research indicates that first starting treatment with LMWH and then early walking may be suggested in patients with acute



DVT provided they have adequate cardiopulmonary reserve and no evidence of PE. A history of previous DVT is not a contraindication to regular exercise. The use of compression is reasonable given that they were used in the successful trials. For therapists who are not familiar with the application of a strong and well-fitting short stretch bandage, good quality class II–III compression stockings may be an alternative. Compression should be recommended for at least 1 year. Then it may be decided if it should be maintained, depending on the residual signs and symptoms.<sup>32</sup>

Immediate ambulation after starting anticoagulation and a range of motion exercises are useful techniques for decreasing DVT. They are simple to use and do not increase the risk of bleeding, making them ideal for most hospitalized patients. Foot and ankle exercises encourage plantar and dorsiflexion to improve venous return. They do not require anything other than patient adherence and willingness to perform exercises every day. For those patients who are unable to perform foot and ankle exercises, passive range of motion is an appropriate substitute. The use of these exercises is safe for all patients except for those with musculoskeletal injuries.<sup>13</sup>

The results of the existing studies suggest that the potential role of ambulation and/or exercise as a treatment modality for DVT should be further explored.<sup>35</sup> Future studies should confirm the positive effect of mobilization on pain and edema of an acute DVT and on the PTS. Further randomized trials are required to investigate if more vigorous exercise training initiated early after DVT is safe and whether regular exercise can be an effective treatment for the PTS. More research should also explore the appropriate time to begin ambulation after diagnosing DVT. Lastly, in future research, double-blind designs should be used with sufficiently long follow-up periods.

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### CONCLUSION

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After starting appropriate anticoagulation, mobilization with appropriate leg compression in patients with DVT: (a) improves endurance which results from increased aerobic capacity; (b) reduces muscular effort due to improved strength; (c) reduces pain, swelling and discomfort via improved function of the calf muscle pump; (d) improves musculoskeletal function via increased flexibility of ankle and knee joints; and (e) improves quality of life. Current knowledge suggests that early ambulating patients with DVT do not appear to have an increase risk of developing a new DVT, progression of an existing DVT, PE or PTS. Nevertheless, further intensive research in large heterogeneous samples of hospitalized patients is required to confirm the beneficial effects of mobilization on DVT, PE and PTS.

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