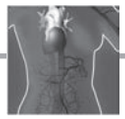
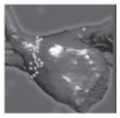


How should we treat May–Thurner syndrome and other causes of iliac vein obstruction? Examining the evidence

May–Thurner syndrome most commonly refers to left-sided iliofemoral vein obstruction caused by compression of the left common iliac vein between the right common iliac artery and lumbar vertebrae. However, other forms of May–Thurner syndrome have been described, and May–Thurner syndrome is part of a larger spectrum of venous disease, iliac vein obstruction. May–Thurner syndrome and other forms of iliac vein obstruction can present with acute iliofemoral deep vein thrombosis or chronic venous symptoms of pain, swelling, skin changes and ulceration. The treatment of May–Thurner syndrome and other forms of iliac vein obstruction has evolved with the advancements of endovascular surgery.

KEYWORDS: iliac vein compression ■ iliac vein obstruction ■ iliofemoral deep vein thrombosis ■ May–Thurner syndrome ■ venous stent

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May and Thurner originally described intimal abnormalities or 'spurs' in the proximal left iliac vein in a very large series of cadaver dissections [1]. May and Thurner proposed that this abnormality, thought to be due to compression by the overlying right iliac artery, accounted for the fourfold increase in left-sided iliofemoral deep vein thromboses (IFDVTs) compared with right-sided IFDVTs. Since that time, other variants of iliac vein compression have since been described; it is recognized that iliac vein obstruction can be associated with both acute IFDVT as well as symptoms of chronic venous insufficiency. With the advent of endovascular treatment options, the source of iliac vein compression has become less important to treatment options, and therefore the term 'nonthrombotic iliac vein lesion' is often used to refer to cases of iliac vein stenosis secondary to external compression. In addition, the distinction between thrombotic and nonthrombotic causes of iliac vein obstruction may make little difference in terms of treatment options and outcomes of iliac vein obstruction.

Iliac vein obstruction from May–Thurner syndrome (MTS) and post-thrombotic etiologies may be more prevalent than previously thought. Some studies estimate that MTS is associated with 37–72% of all IFDVTs [2–4] and an increasing number of iliac vein interventions are also being performed for symptoms of chronic venous insufficiency. Therefore, an understanding of the natural history and treatment of IFDVT and chronic venous insufficiency is an inherent part of treating iliac vein obstruction.

Iliofemoral deep vein thrombosis

IFDVTs carry a worse prognosis than other lower extremity deep vein thromboses (DVTs) in terms of resolution, pulmonary embolism (PE), recurrence and post-thrombotic syndrome (PTS) [5–10]. IFDVTs show only 10–30% recanalization rates with anticoagulation alone [38–41] and lower extremity venous reflux occurs in close to 90% of patients [11–14]. IFDVTs may account for two-thirds of all PEs from DVTs and carry up to a 50% risk of PE [8,15]. Patients with proximal DVTs have a two-to-three-fold relative risk of recurrent thromboembolism compared with patients with distal DVTs [16,17], and IFDVT carries a 2.4-fold increase in recurrent VTE risk compared with all proximal DVT [18]. Furthermore, IFDVTs may be associated with PTS rates of 50% despite compliance with anticoagulation and compression [19,20]. Worse outcomes for patients with IFDVTs have prompted interest in more aggressive treatment regimens to help decrease long-term sequela of the disease. Given the poor prognosis of IFDVT compared with other lower extremity DVTs, the investigation and treatment of MTS and other causes of iliac vein obstruction in patients presenting with IFDVTs has been advocated as potentially reducing long-term recurrence and long-term sequela.

Treatment of IFDVT

■ Anticoagulation

Systemic anticoagulation remains the cornerstone of any treatment profile for IFDVT and markedly reduces recurrent PE and mortality [21]. It has long been accepted as standard of care that the duration of therapy and the particular

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agent must be tailored to the individual patient based on a number of clinical factors as assessed by the clinician. Current recommendations for the treatment of DVT are provided by the American College of Chest Physicians and are rigorously reviewed and updated every few years. The current guidelines, the 9th edition, were published in February 2012 [22].

Newer oral anticoagulants are now available and emerging as viable alternatives to warfarin for treatment of acute DVTs. Of the new oral anticoagulants, rivaroxaban and dabigatran have been demonstrated in randomized control trials and a systematic review to be as effective as warfarin in preventing overall death, death from pulmonary embolism, and recurrent DVT and pulmonary embolism [22–26]. Rivaroxaban is a direct factor Xa inhibitor with once a day dosing, and dabigatran is direct thrombin inhibitor that is dosed twice daily.

■ Ambulation

Historically, physicians were reluctant to allow patients with lower extremity DVT out of bed for fear of dislodging a clot or the negative effects of dependency. Evidence now clearly shows that early ambulation is not only safe, but likely beneficial for patients [27,28].

■ Compression

At the turn of this century, compression therapy for the treatment of DVT was an afterthought. Since then, two randomized control trials and a Cochrane Database meta-analysis have demonstrated a 50% relative risk reduction and a 23% absolute risk reduction of developing PTS with 2 years of compression therapy [29–31].

Catheter-directed thrombolysis & thrombectomy

Emerging evidence continues to support an aggressive approach to clearance of lower extremity DVT. Catheter-based thrombectomy is one such aggressive technique aimed at clearing the vein of thrombus in the acute setting. A 2012 meta-analysis and systematic review reported significantly better outcomes for catheter-directed thrombolysis and thrombectomy (CDT) of IFDVTs compared with anticoagulation, with relative risk of PTS at 0.19 (0.07–0.48), venous obstruction 0.38 (0.18–0.37) and venous reflux 0.39 (0.16–1.0) [32].

The largest randomized trial of CDT therapy to date [20], the CaVenT study, included 20 Norwegian institutions that randomized 209 patients with first-time acute (21 days) IFDVT to conventional treatment or conventional treatment plus alteplase infusion (max 96 h). There was an absolute risk reduction of 14.4% in PTS at 24 months in patients randomized to CDT. Iliofemoral patency showed an absolute increase of 18.5% at 6 months in the CDT patients. The number needed to treat to prevent one episode of PTS was 7.

Diagnosis of MTS & other causes of iliac vein obstruction

The diagnosis of MTS requires a high index of suspicion. It is often possible to demonstrate left iliac vein compression on magnetic resonance venography or computed tomography venography. However, this finding is fairly nonspecific given the high incidence of left iliac vein compression in asymptomatic patients [33].

The diagnosis of MTS and other causes of iliac vein obstruction in patients presenting with acute left leg DVT is often made by venogram after venous thrombolysis or thrombectomy. However, investigation of the iliac veins may also demonstrate iliac vein stenosis in patients presenting with symptoms of chronic venous insufficiency. While venography is the traditional approach for identifying iliac vein stenosis, several authors advocate the routine use of intravascular ultrasound, citing poor sensitivity of ascending venography at diagnosing iliac vein stenosis/obstruction compared with intravascular ultrasound (IVUS) [34,35].

Venography or IVUS may show obvious stenosis of the left common iliac vein in the characteristic area of right common iliac artery crossover, often with large collateral veins. During fluoroscopy, multiple oblique projections may be needed to demonstrate this stenosis, as the compression may be in the antero-posterior dimension and not appreciated on standard AP fluoroscopy views. In addition, other variants of iliac vein obstruction has been reported that involve more distal compression of the left common iliac vein by the left hypogastric artery, and compression of the right iliac vein by the right common iliac artery [35].

Alternatively, venography may show a more subtle sign of left iliac vein compression, known as a venous spur. Three different types of venous spurs have been identified: medial (central), lateral and diaphragm. Correlation with intraoperative findings has demonstrated that these venous spurs represent flow-limiting intimal changes within the iliac vein. Venous spurs are probably reactive changes of the vein to chronic compression. The presence of a venous spur is the characteristic feature of MTS as described by May and Thurner [1]. The diagnosis of venous spurs has

generally been made with contrast venography; however, the utility of IVUS in demonstrating venous spurs has also been demonstrated [36].

Treatment MTS in patients presenting with IFDVT

As in all cases of IFDVTs, the risks and benefits of anticoagulation versus removal of thrombus using thrombolysis/thrombectomy need to be considered. When proceeding with more aggressive treatment of IFDVT in patients with suspected MTS, initial efforts are directed restoring patency of the iliofemoral veins. In the acute period, surgical thrombectomy, mechanical thrombectomy and catheter directed thrombolysis have all been described for restoring patency of iliofemoral thrombosis with good results [4,37–42].

A key question is whether evidence of MTS on completion venography or IVUS after acute IFDVT mandates treatment of the compressed iliac vein or whether anticoagulation alone is sufficient. While there are no randomized trials on this subject, case series have documented poor patency rates with both anticoagulation and percutaneous venoplasty compared with venous stents [43]. The presence of a venous spur may also require definitive treatment as case studies suggest 73% of patients with untreated venous spurs will have recurrent thrombosis of the iliac vein compared with 13% of patients with treated venous spurs [39].

Despite the high rethrombosis rate of patients presenting with IFDVTs associated with MTS, randomized control trial of venous stents versus anticoagulation are missing, and long-term data is scarce. Case series on iliac vein lesions associated with IFDVT usually combine patients with acute and chronic iliac vein occlusions. In addition, patients with MTS are often grouped with patients demonstrating iliac vein obstruction from post-thrombotic and extrinsic compression etiologies. Examination of the literature shows that thrombolysis or thrombectomy followed by iliac vein stent for acute IFDVT associated with MTS often demonstrates initial success rates and one year primary patency rates greater than 90% [2,4,38,43–49]. However, mean follow-up times are generally short (less than 2 years), and few studies provide hemodynamic data or data on subsequent development of PTS. Therefore, data regarding long-term patency of iliac venous stents can only be extrapolated from trial addressing obstructive iliac vein lesions in patients presenting with symptoms of chronic venous insufficiency rather than acute IFDVT.

MTS in patients presenting with chronic Iliac vein obstruction

In contrast to patients presenting with acute left leg IFDVT, a much larger group patients present with chronic symptoms of lower extremity pain, edema or ulcerations without acute DVT. These patients may or may not endorse a previous history of DVT. While there are no absolute criteria for investigation of iliac vein obstruction in patients demonstrating symptoms of chronic venous insufficiency, there are findings that may suggest a proximal obstruction. Raju *et al.* describe a greater than 50% positive predictive value for the following findings in identifying limbs with iliac vein obstruction on IVUS examination [50]:

- >4 mmHg venous pressure elevation with exercise;
- >6 mmHg reactive hyperemia at rest;
- Lack of respiratory phasicity in common femoral vein (CFV) on venous duplex ultrasound scan;
- Iliac vein lesion seen on venography.

Alhalbouni *et al.* also described that 59% of patients with venous ulcers that fail to heal after 3 months of compression therapy and surgical correction of superficial reflux will demonstrate iliac vein obstructive lesions [51].

Technical success and mid-to-long-term patency (1–6 years) for stenting of iliac venous lesions in the treatment of chronic venous disease appears good, with most studies reporting close to 90% success rates and 71–93% primary patency [50–55]. Most series also demonstrate significant clinical improvement with iliac vein stenting [50–53,55,56].

Most series of iliac venous stents combine venous obstruction secondary to MTS, post-thrombotic etiologies, and obstruction secondary to external compression. Some reports suggest that MTS patients may have improved ulcer healing rates and stent patency compared with patients with post-thrombotic iliac vein obstruction [50,53]. High rates of ulcer healing are reported after stenting of iliac vein obstruction despite concomitant deep vein reflux, although ulcer healing rates are higher in patients without deep venous reflux [35]. Concerns that iliac vein stenting can worsen deep vein reflux and lead to clinical deterioration of the affected limb do not seem to be supported by hemodynamic data [57].

Large series of iliac vein stents for chronic venous symptoms report ulcer healing rates of 54–62% [50,55,56]. Despite improved quality-of-life measurements and low morbidity, these results are

somewhat surprising given large trials and meta-analyses have demonstrated that that 64–84% of venous ulcers heal within 3 months using compression therapy alone [58,59]. Proponents of iliac venous stenting for chronic venous symptoms assert that the 54–62% ulcer healing rates after iliac venous stents occur in patients with ulcers refractory to conventional treatment [50,51]. Therefore, it appears that evaluation and stenting of iliac vein stenosis for chronic venous symptoms may best be reserved for patients that are refractory to compression therapy on a case-by-case basis.

Endovascular approach to treatment of MTS

The popliteal vein is the preferred access site in cases of acute IFDVT associated with iliac vein obstruction and allows lysis of femoral vein DVTs. There is more variation in access sites for post-thrombotic iliac vein obstruction. Given the rarity of isolated iliac vein DVTs [60] the CFV is often involved in the original IFDVT and is often abnormal in chronic MTS associated with previous DVTs. In such cases, the popliteal vein is the best access site as several authors report extending venous stents to the CFV. Surprisingly, the use of stents across the inguinal ligament may not adversely affect patency rates [45]. Other authors support the use of the ipsilateral CFV as the initial access site [54,55].

Self-expanding stents are used in the treatment MTS to resist restenosis from iliac artery or inguinal ligament compression. The Wallstent® (Boston Scientific, MA, USA) is the most common stent described for this purpose. Although, there is a wide range of stent diameters used, the most common sizes utilized are 10–14 mm. Despite the use of self-expanding stents, central migration of stents has been reported [2,61], which underscores the importance of using appropriately sized stents [52]. In addition, shortening of self-expanding venous stents during deployment can make precise positioning somewhat challenging. While some authors advocate the use of IVC filter insertion during the original lysis [38], other series report no clinically significant PEs in patients undergoing lysis without IVC filter insertion [2,4,45,46]. There is no consensus regarding the use of anticoagulation versus venous stents. Although some authors report good patency rates with antiplatelet agents alone, others advocate anticoagulation when treating complex iliac vein lesions [55,62,63].

Surgical approach

With the high success rate of endovascular techniques, surgical treatment of MTS has become rare. However, multiple surgical approaches have been described.

Broadly, surgical procedures fall into the two categories of bypass and reconstruction. Bypass options include the femoral–femoral bypass with saphenous vein (Palma–Dale procedure), femoral–iliac, and iliocaval bypasses. While case series are generally small, the Palma procedure has a 70–83% 2–5-year patency rates [64–66]. Iliocaval and femorocaval bypasses demonstrate lower patency rates of 40–64% [64–66] at 2 years and can be performed with autologous vein or ePTFE. Several authors have advocated temporary or permanent arteriovenous fistulas to produce faster flow through venous bypasses; however, results are controversial [65]. Reconstruction options involve patch angioplasty of the stenotic iliac vein, removal of endoluminal webs/senechiae, and mobilization/reconstruction of either the iliac artery or vein. Again, evidence is limited to small case series and patency rates are similar to venous bypasses [67].

Conclusion

Lower extremity symptoms due to iliac vein compression are more common than previously thought. In addition to acute IFDVTS, iliac vein compression can also present with symptoms of chronic venous insufficiency, such as pain, edema, venous claudication, skin changes and ulcers. While MTS appears to be a leading cause of iliac vein obstruction, post-thrombotic stenosis and external compression are other recognized causes.

Multiple case series suggest that treatment of acute IFDVTs in patients with iliac vein compression can be performed with good technical success and mid-term results using catheter directed thrombolysis/thrombectomy combined with venous stents. Improved outcomes of IFDVTs treated with CDT combined with high rethrombosis rates in cases of iliac vein obstruction treated with angioplasty and anticoagulation without venous stenting have led to a fairly aggressive treatment of iliac vein obstructions presenting with acute IFDVTs.

The use of venous stents in patients with symptoms of chronic venous insufficiency and evidence of iliac vein obstruction has also become more widespread. Several case series report technical success rates and primary patency rates greater than 90%; however, reports with longer follow-up demonstrate lower primary patency rates of 71–79% [55,56]. The correction of iliac vein obstruction may lead to ulcer healing and clinical improvement in cases refractory to conventional treatment; however, there has not been

any randomized comparisons of iliac venous stents versus diligent compression therapy and treatment of lower extremity superficial venous reflux. While guidelines for treatment of chronic iliac vein obstruction are missing, a recent review of the literature by Raju encompassing 1500 patients undergoing iliac venous stents has been performed. This review makes a grade 1B recommendation for iliac vein stenting in patients with disabling symptoms in whom conservative therapy has failed, and a a 2B recommendation for iliac vein stenting in patients with less severe symptoms [68]. At this time, the investigation and treatment of iliac vein obstruction for chronic symptoms is perhaps best reserved for patients with significant symptoms that are refractory to compression therapy.

Future perspective

The treatment of iliac vein obstruction causing acute IFDVT may prevent recurrent thrombosis and therefore reduce development of PTS. However, the use of iliac vein stents to improve chronic venous symptoms needs to be compared with conventional treatment in a randomized controlled trial. The most compelling evidence for endovascular treatment of chronic iliac vein obstruction currently consists of case series of patients who have achieved suboptimal relief with conventional treatment and who improve with subsequent endovascular intervention. Therefore, a randomized controlled trial of endovascular intervention versus continued compression may clarify the optimal treatment of chronic venous symptoms caused by iliac vein obstruction.

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Executive summary

Background

- May–Thurner syndrome represents one type of iliac vein obstruction and can lead to acute iliofemoral deep vein thrombosis or symptoms of chronic venous insufficiency.

Causes of iliac vein obstruction

- Compression by overlying artery (May–Thurner).
- Extrinsic compression.
- Post-thrombotic stenosis or occlusion.

Treatment of iliofemoral deep vein thrombosis

- Prompt anticoagulation should be started with low molecular weight or unfractionated heparin followed by transition to warfarin or a new-generation anticoagulant (i.e., dabigatran or rivaroxaban).
- 30–40 mmHg compression stockings should be worn for 2–3 years.
- Early ambulation is beneficial.
- Early removal of thrombus burden through thrombolysis may decrease incidence of post-thrombotic syndrome.

Treatment of iliac vein obstruction

- Stenting of iliac vein obstruction causing acute iliofemoral deep vein thrombosis may reduce recurrent thrombosis.
- Stenting of iliac vein obstruction causing chronic venous symptoms may lead to improvement of symptoms, but there are no randomized comparisons to conventional therapy.

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▪▪ **Review and analysis of trials of chronic iliac venous stents.**