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REVIEW ARTICLE

May-Thurner syndrome: History of understanding and need for defining population prevalence

Michelle M. Harbin[1] | Pamela L. Lutsey[2]

[1]Laboratory of Integrative Human Physiology, School of Kinesiology, University of Minnesota, Minneapolis, MN, USA

[2]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA

Correspondence
Michelle M. Harbin, University of Minnesota, 1900 University Avenue S.E., 110 Cooke Hall, Minneapolis, MN 55455.
Email: Harb0085@umn.edu

Abstract

Patients with May-Thurner syndrome (MTS) are at elevated risk of developing an extensive left iliofemoral deep vein thrombosis (DVT; localized blood clot) due to an anatomical variant where the right common iliac artery compresses the left common iliac vein against the lumbar spine. While MTS was initially presumed to be rare when it was first anatomically defined in 1957, case reports of this syndrome have recently become more frequent, perhaps due to improved imaging techniques allowing for enhanced visualization of the iliac veins. Still, the population burden of this condition is unknown, and there is speculation it may be higher than generally perceived. In the present review, we (a) review history of how MTS became recognized, (b) describe practical challenges of studying MTS in population-based settings due to the specialized imaging required for diagnosis, (c) discuss why the contribution of MTS to DVT may be underestimated, (d) describe uncertainty regarding the degree of venous compression which leads to DVT, and (e) outline future research needs. Our goal is to raise awareness of MTS and spark additional research into the epidemiology of this condition, which may be an underappreciated causative venous thromboembolism risk factor.

KEYWORDS

deep vein thrombosis, epidemiology, iliac vein compression syndrome, pulmonary embolism, thrombophilia

1 | OVERVIEW OF MAY-THURNER SYNDOME (MTS) PATHOPHYSIOLOGY AND CLINICAL MANAGEMENT

Deep vein thrombosis (DVT) involves the development of a blood clot localized within the great veins of the body, commonly in the lower extremities.[1] In the presence of May-Thurner syndrome (MTS), also known as iliac vein compression syndrome or Cockett's syndrome, patients are predisposed to an iliofemoral thrombosis due to an anatomical variant in which the right common iliac artery overlies and compresses the left common iliac vein against the lumbar spine.[2-4] The chronic pulsatile compression from the right common iliac artery at the aortic bifurcation above the iliofemoral junction against the left common iliac vein results in impaired venous return and endothelial injury, leading to the deposition of elastin and collagen with subsequent possible obstruction and extensive DVT of the ipsilateral extremity.[5,6]

Clinical phases of MTS include a prolonged asymptomatic period of left iliac vein compression followed by the gradual development of an intraluminal venous fibrous band (ie, spur), which can subsequently progress to an acute unilateral left iliofemoral DVT that can be accompanied either with or without a pulmonary embolism (PE).[6,7] Patients that develop a left-sided DVT in the context of MTS are typically young adults that exhibit sudden swelling of the left lower extremity following surgery, during immobilization, or during

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TABLE 1 Prevalence estimates of May-Thurner syndrome

Reference	Date	Study design	Patient population	Results
McMurrich[56]	1906	Autopsy study	Unselected population (n = 107)	35 (32.7%) of 107 veins had venous adhesions localized within the left common iliac vein
Ehrich and Krumbhaar[57]	1943	Autopsy study	Unselected population (n = 399)	95 (23.8%) of 399 veins exhibited obstructive abnormalities. Such abnormalities were less common among children and infants (4.7%), but were observed among 89 veins (33.8%) in cadavers over 10 years old
May and Thurner[2]	1957	Autopsy study	Unselected population (n = 430)	22% of 430 autopsies exhibited spur-like projections on the left common iliac vein
Cockett and Thomas[3]	1965	Case series	Patients with iliofemoral DVT (n = 35)	21 patients had a left iliofemoral DVT, among which 16 (76.1%) exhibited obstructions at the junction of the left common iliac vein with the vena cava, and localized to the point where the right common iliac artery anatomically overlies it
Negus et al[58]	1968	Autopsy study	Unselected population (n = 100)	Bands, or adhesions, that joined the anterior and posterior wall of the left common iliac vein were observed in 14 (14.0%) of the 100 unselected cadavers. Compression of the left common iliac vein where it is crossed by the right common iliac artery was present in 29 (53.7%) of the 54 normal phlebograms
Mickley et al[28]	1998	Case series	Patients with iliofemoral DVT (n = 77)	Iliac venous obstruction suggestive of venous spurs was present in 30 (49.1%) patients out of the total 61 patients with a left-sided iliofemoral DVT
Wolpert et al[84]	2002	Case series	Patients with left-sided lower extremity edema (n = 24)	Using MRV imaging, the presence of MTS was reported in 9 (37.5%) patients out of 24 patients that were symptomatic of a left lower extremity edema
Fraser et al[23]	2004	Case-control	Patients with DVT (n = 56), and controls (n = 28)	The prevalence of >50% compression on the left iliofemoral vein was higher in patients with a left iliofemoral DVT (n = 9, 56.3%) as compared to left femoropopliteal DVT (n = 1, 9.1%), right femoropopliteal DVT (n = 2, 16.7%), left isolated calf DVT (n = 1, 11.0%), right isolated calf DVT (n = 0; 0%), and control patients (n = 4, 14.3%)
Kibbe et al[68]	2004	Case series	Patients with abdominal pain (n = 50)	12 (24.0%) patients with abdominal pain had >50% compression of the left iliac vein, and 33 (66.0%) patients had >25% compression
Chung et al[69]	2004	Case series	Patients with iliofemoral DVT (n = 56)	Among the 44 patients with a left-sided iliofemoral DVT, 27 (61.3%) cases exhibited common iliac vein compression by the right common iliac artery
Raju and Neglen[91]	2006	Cohort	Patients with chronic venous disease (n = 4026 limbs)	938 limbs from 896 (22.2%) patients out of the total 4026 patients had iliac venous obstruction lesions

(Continues)

TABLE 1 (Continued)

Reference	Date	Study design	Patient population	Results
Friedrich de Wolf et al[37]	2013	Case series	Patients with venous disease (n = 63)	36 (57.1%) cases of MTS were identified in 63 patients with either venous claudication or venous disease
Liu et al[41]	2014	Cohort	Patients with left-sided chronic venous disease (n = 324)	48 (14.8%) cases of MTS were identified in 324 patients with left-sided chronic venous disease
Nazzal et al[82]	2015	Cross-sectional	Unselected population (n = 300)	>70% compression within the left iliac vein was present in 59 (19.6%) patients out of 300 asymptomatic patients; >50% compression was present in 134 (44.7%) patients
Choi et al[83]	2015	Cohort	Patients with DVT (n = 201)	137 (68.1%) cases of MTS were identified in 201 patients with a DVT that required endovascular treatment

Abbreviations: DVT, deep vein thrombosis; MRV, magnetic resonance venography; MTS, May-Thurner syndrome.

pregnancy and/or the postpartum period.[3,6,8-12] The occurrence of MTS in adolescents has also been documented in various case reports.[13-21] While MTS does occur among men, it is more common in females though the reason for this has not yet been completely explained.[22] Research suggests that a female's pelvis exhibits more of an accentuation of the lumbar lordosis that pushes the lower lumbar vertebrae anteriorly, thereby compressing the left common iliac vein against the right common iliac artery.[2,12,23]

In regard to treatment, due to the mechanical, pulsatile nature of the obstruction from the right common iliac artery, patients respond poorly to conservative anticoagulation medicine therapy alone.[3,6,24,25] Endovascular treatment, consisting of catheter-directed thrombolysis using urokinase, was initially reported to be a safe and effective treatment for patients with an iliofemoral DVT in 1994.[26] Among patients with an underlying venous stenosis, follow-up venography consisted of either balloon angioplasty alone, or angioplasty with permanent stent placement.[26] Since then, catheter-delivered thrombolytics and percutaneous mechanical thrombectomy, either with or without angioplasty and stent placement, has been standard of care for patients symptomatic with MTS.[6,24,27-42] Studies that have evaluated stenting of the left common iliac vein report low morbidity, no mortality, a long-term high patency rate, and a low rate of in-stent restenosis.[35,43-52] Postoperative therapy for MTS includes anticoagulation for at least 3 months to prevent rethrombosis, and a retrievable inferior vena cava filter may also be considered for patients with a preexisting pulmonary embolism.[6,50,53]

2 | METHODS: IDENTIFICATION AND SELECTION OF THE LITERATURE

Relevant literature was identified by means of an electronic database (PUBMED), using the following search terms: "May-Thurner syndrome OR iliac venous compression syndrome AND venous thrombosis." This search was supplemented by hand searching of bibliographies of published studies, as well as previous reviews of MTS and DVT. Anatomical description of MTS was provided in autopsy studies, and later in case reports and case-control studies that utilized venography or other imaging methodologies. Information regarding diagnosis and endovascular treatment was provided in case reports, case series, and reviews of the literature.

3 | HISTORY OF UNDERSTANDING

In 1851, Rudolf Virchow first proposed that the increased incidence of venous thrombosis within the left lower extremity was a result of the right common iliac artery compressing the left common iliac vein.[54,55] In the early 1900s, McMurrich[56] reported that 32.7% of 107 cadavers from an unselected population exhibited obstructions, or adhesions, within the left common iliac vein (Table 1). In 1943, Ehrich and Krumbhaar[57] studied the iliac venous system among 399 cadavers, and reported that left iliac vein obstruction occurred in

TABLE 2 Diagnostic testing and imaging in the context of May-Thurner syndrome

Imaging technique	Reference	Study date	Study design	Sample size (n)	Conclusion	Limitations
Abdominal/pelvic CT	Kibbe et al[68]	2004	Case series	50	Abdominal and pelvic CT imaging, as well as CT venography, utilizing narrower cuts (3- to 5-mm) can accurately visualize iliac venous compression, stenotic lesions, and collateral pathways. Advantages of CT over contrast venography include enhanced feasibility, clearer imaging of the pelvic veins and the formation of collaterals, and a shorter exam time	Ionizing radiation exposure, and difficulties with appropriately timing the imaging sequence to optimal contrast opacification of the iliac veins. Iliac spurs may be too difficult to visualize during CT imaging with 10-mm cuts; narrower cuts may be required for diagnosing MTS
	Oguzkurt et al[70]	2005	Case series	24		
	Oguzkurt et al[15]	2006	Case report	1		
	Oguzkurt et al[71]	2008	Case-control	68		
	Duran et al[72]	2011	Case report	1		
	Carr et al[74]	2012	Case control	47		
	Kalu et al[77]	2013	Case report	1		
CT venography	Chung et al[69]	2004	Case series	44		
	Jeon et al[73]	2010	Case series	30		
	Foit et al[76]	2013	Case report	1		
	Liu et al[41]	2014	Cohort	324		
	Kuo et al[80]	2015	Case series	42		
	Bozkaya et al[81]	2015	Case series	23		
	Choi et al[83]	2015	Cohort	201		
MRV	Wolpert et al[84]	2002	Case series	24	MRV can image iliac venous compression and can estimate the degree of venous collateral flow	MRV cannot be performed in patients with metallic implants. Research suggests MRV has low reproducibility for detecting iliac venous compression. MRV has not undergone prospective validation for detection of iliac vein lesions
	Fraser et al[23]	2004	Case-control	84		
	Gurel et al[85]	2011	Case report	1		
	Budnur et al[86]	2013	Case report	1		
	McDermott et al[87]	2013	Case series	214		
	Friedrich de Wolf et al[37]	2013	Cohort	63		
IVUS	Ahmed and Hagspiel[88]	2001	Case report	2	IVUS has high sensitivity in imaging iliac venous compression, and has therapeutic use in guiding the deployment of stents	IVUS is not appropriate as a screening test because it is used as an adjunct to contrast venography in the diagnosis and endovascular management of MTS
	Forauer et al[89]	2002	Case series	16		
	Neglen and Raju[90]	2002	Case series	304		
	Raju and Neglen[91]	2006	Cohort	4026		
	Oguzkurt et al[16]	2007	Case report	1		
	Canales and Krajcer [92]	2010	Case report	1		

Abbreviations: CT, computed tomography; IVUS, intravascular ultrasound; MRV, magnetic resonance venography; MTS, May-Thurner syndrome.

33.8% of cadavers that were over 10 years old. Unlike McMurrich, who proposed that such obstructions at the site of the compression on the left common iliac vein were congenital in origin,[56] Ehrich and Krumbhaar[57] concluded these obstructions were acquired because they were composed of elastin and collagen, and were more common with increasing age.

It wasn't until 1957 that this syndrome was anatomically described, when the researchers May and Thurner[2] reported that 22% of 430 cadavers exhibited this anatomical variant with localized intraluminal fibrous bands, referred to as spurs, on the left common iliac vein. May and Thurner[2] further postulated that these spurs were acquired from the chronic compression on the left common iliac vein via the overriding right common iliac artery. The pulsatile compression from the right common iliac artery was thought to cause increased irritation of the endothelium, which subsequently caused cell proliferation and the development of spurs within the left common iliac vein.[2] In a different autopsy study, Negus et al[58] reported that these fibrous bands, or adhesions, joined the anterior and posterior wall of the left common iliac vein, and occurred among 14% of the 100 cadavers. Despite the fact that 54 cadavers had normal venous smooth muscle and did not have collateral veins, 29 (53.7%) of the 54 cadavers with normal iliac veins exhibited compression via the right common iliac artery, as evidenced by the presence of a partially translucent groove at the proximal end of the left common iliac vein.[58]

While initial research on MTS was based on autopsy studies from unselected populations, in 1965 Cockett and Thomas were the first researchers that studied living patients symptomatic of an acute iliofemoral DVT from iliac vein compression syndrome, and used venography to describe the nature of the compression. These patients exhibited pigmentation, induration, and ulceration, as well as swelling and widespread pain of the entire left leg.[3] The average age of the patients with MTS was 23 years old, and half of the cases were under 20 years at onset.[3] The mode of onset of DVT occurred following a brief immobilization period, either postoperative, postpartum, or subsequent to a minor injury.[3] The most common location of compression occurred at the mouth of the left common iliac vein where the right common iliac artery crossed over it.[3] It was also demonstrated by Cockett and Thomas that the venous spur is an irreversible process, because the surgical repositioning to relieve the compression did not induce iliac vein recanalization.[3] Cockett further postulated that patients could remain asymptomatic for an extended period of time, due to the development of collateral veins that facilitated the bypass of the narrowed left common iliac vein.[3,4,59]

4 | DIAGNOSIS OF MAY-THURNER SYNDROME

Physical examination is insufficient to diagnose MTS, and the accuracy of Doppler ultrasound in imaging venous spurs among patients with suspected MTS is not convincing;[6,29,30,60] it is technically difficult to image venous compression and stenosis via ultrasound due to the deep location of the iliac veins.[61] Given the widespread use of ultrasound to confirm the presence of an acute DVT,[60,62,63] many iliofemoral DVT cases associated with MTS could potentially go undiagnosed. As such, a challenge of MTS, which has likely hampered attempts to quantify prevalence of this condition, is related to the necessity of invasive imaging for accurate diagnosis.

Contrast venography using transvenous pressure measurements is the gold standard test used to diagnose MTS;[64] the formation of collateral veins and a pressure gradient that is >2 mm Hg across the iliofemoral stenosis at rest are hallmarks of MTS.[24,41,65] However, venography is typically not performed unless thrombolysis is anticipated, owing to its invasive nature and postprocedural complications (eg, phlebitis).[66] Besides venography, other imaging techniques, such as multidetector computed tomography (CT) scans,[15,41,67-83] magnetic resonance venography (MRV),[23,60,84-87] and intravascular ultrasonography,[16,88-93] have been used to image iliac venous compression and are described in Table 2.

5 | POSSIBLE UNDERESTIMATION OF CONTRIBUTION OF MTS TO THE POPULATION BURDEN OF DVT

Clinically recognized MTS accounts for only 2% to 5% of all DVTs.[6,55,94] This is despite evidence that venous spurs on the left common iliac vein are present in one half to two thirds of patients with left-sided iliofemoral DVT.[23,69,71] It has been speculated that the percent of DVTs due to MTS may be much higher than clinically recognized. This suspicion is supported by the disproportionately greater incidence of left-sided DVT,[95-97] clinical studies that report significant iliac venous compression occurs in the majority of patients with left DVT,[3,23,55,57] and presence of fibrous spurs in 22% to 33% of cadavers.[2,57] However, no population-based studies have yet been conducted to document the prevalence or incidence of MTS.

One possible reason for underdiagnosis of MTS is that it may be overshadowed by other more easily recognized risk factors. For instance, individuals with MTS may not be symptomatic until provoked during instances of increased hypercoagulability, such that may occur during immobilization following surgery, after prolonged travel, during pregnancy, or during the postpartum period.

Another potential reason for the underdiagnoses relates to the relative difficulty in diagnosing this condition. As detailed above and in Table 2, although contrast venography is the gold standard for diagnosing MTS,[65] it is time and resource intensive, invasive, requires contrast, and can result with postprocedural complications.[98] Because of these limitations, venography has never been used as a systematic screening tool, and is only implemented during situations in which follow-up thrombolytics treatment is anticipated.[64] Doppler ultrasound, though widely used in the initial diagnosis of DVT because it is non-invasive and does not require radiation or contrast,[99] is not a candidate for MTS screening because it is not sensitive enough to detect non-occlusive thrombosis and intraluminal spurts within the iliac veins. When weighting the strengths and limitations of various options that could be used to obtain

population-level estimates of the incidence and prevalence of MTS, clear contenders include using either pelvic CT scans, CT venography, or MRV. Though expensive, they are noninvasive, do not require contrast and are low burden.

6 | UNCERTAINTY IN THE DEGREE OF VENOUS COMPRESSION THAT LEADS TO DVT

The reference standard for diagnosing MTS has been venography depicting narrowing of the left common iliac vein secondary to external compression, with intraluminal changes that are suggestive of spur formation.[71] An issue with this diagnosis is that it lacks a precise definition for the degree of compression that may designate a patient at high risk for developing a DVT. Furthermore, it has been postulated that left common iliac venous compression may be a normal anatomic variant.[68,71,79,84] Table 3 presents comparisons of the degree of iliofemoral venous compression between MTS patients and controls. As an example, in a case-control study, Carr et al[74] reported an average stenosis of 68% among 21 patients with a DVT due to MTS, while the 26 age-matched controls had an average stenosis of 52%. The odds of DVT were increased by a factor of 2.18 for each 10% increase in left iliac venous stenosis.[74] This strongly suggests that greater iliofemoral venous stenosis is associated with increased DVT risk; but, the wide range of compression between patient groups suggests that the degree of stenosis alone is but one determinant in the development of a DVT.

Considering the prior text, anatomic compression on the left iliac vein may not be sufficient for diagnosing MTS; compression even in excess of 50% may be a common finding in patients that are asymptomatic of venous thrombosis.[71] Oguzkurt et al[71] proposed that a threshold of 70% iliofemoral compression demonstrates severe constriction and underlying MTS among patients with a left iliofemoral DVT. Conversely, DVT can also occur when there is <70% iliac venous compression, and it is difficult to decipher whether or not there is underlying MTS at these compression levels. In sum, given the relatively high incidence of this anatomic finding in the general population and the relatively low incidence of lower extremity DVT in the general population, it has been suggested that mild venous compression alone may not represent an increased risk of development of DVT. The current lack of knowledge of the degree of venous compression and stenosis that precipitates a DVT has complicated attempts to quantify the extent to which iliofemoral compression is a risk factor for DVT.

7 | NEED GREATER UNDERSTANDING OF THE EPIDEMIOLOGY OF MTS

Given that MTS may be an underappreciated contributor to DVT, future research should quantify the prevalence of left iliac venous compression and intraluminal venous spurs among apparently healthy adults (ie, 18-50 years old) in a population-based study. CT venography may be an appropriate imaging technique for such a study. If the prevalence is determined to be reasonably high, it would be interesting to prospectively (over the course of several years) repeat measurements of the iliac veins, as this would provide insight of how venous compression and intraluminal spur formation changes with age. This information may be useful in identifying high-risk individuals that are predisposed to venous thrombosis in the context of MTS. Concurrent measurements of D-dimer could also be conducted in order to assess whether concentrations of this biomarker of hypercoagulability correlates with the degree of iliac venous compression. Were that the case, D-dimer may have predictive value in estimating DVT risk among individuals with MTS. Studying racial and ethnic differences

TABLE 3 Comparisons on the degree of iliofemoral venous compression and stenosis between May-Thurner syndrome patients and controls

Reference	Subject population	Results
Oguzkurt et al[70]	MTS patients (n = 10), and controls (n = 14)	The average percent stenosis of the left common iliac vein was 68% in the MTS patient group. Average diameter of the origin of the left iliac vein (3.5 mm) in patients with MTS was significantly smaller relative to that of the control group (11.5 mm)
Oguzkurt et al[71]	MTS patients (n = 34), and age- and sex-matched controls (n = 34)	Average iliofemoral venous compression was 74% and 28% among patients with MTS and controls, respectively. Among the 34 patients with MTS, 32.3% (n = 11) had <70% compression and 67.6% (n = 23) had >70% compression
Carr et al[74]	Patients with a left-sided DVT (n = 21), and age-matched controls (n = 26)	Average compression on the left iliac vein was 68% and 52% for DVT patients and controls, respectively. The odds of a DVT increased by a factor of 2.18 for each 10% increase in left iliac venous compression
Chen et al[79]	DVT patients (n = 79), and controls (n = 218)	Patients with a left-sided DVT (n = 60) had an average compression on the left iliac vein of 77%. In comparison, patients with a right-sided DVT (n = 19) and control patients had an average venous compression of 38% and 49%, respectively. The odds of a DVT increased by a factor of 2.78 for each 10% increase in left iliac venous compression

Abbreviations: DVT, deep vein thrombosis; MTS, May-Thurner syndrome.

in the prevalence of iliac venous compression and MTS might help explain why African Americans are at elevated risk of DVT.[100] A case-crossover analysis could also be conducted among individuals that developed an iliofemoral DVT due to MTS, as this study design may identify additional risk factors (eg, oral contraception, recent surgery, immobilization) that trigger DVT in the context of MTS.

In sum, many uncertainties exist regarding the prevalence of MTS and its pervasiveness in DVT, and it is possible that MTS underlies a greater proportion of DVT events than commonly perceived. As we await findings from studies that would shed light on the questions raised above, we hope to raise awareness about MTS as a potential underlying factor for DVT, especially in young adult women symptomatic of an extensive left iliofemoral DVT with no previous history of hypercoagulability.

CONFLICT OF INTEREST

The authors have no disclosures.

AUTHOR CONTRIBUTIONS

No funding for this review paper was provided, and no payment was received to produce this manuscript. MMH wrote the first draft of the manuscript, and submitted it for publication. PLL provided subject matter expertise and a critical review of the manuscript. All authors have seen this manuscript, and give approval of this version to be published.

ORCID

Michelle M. Harbin https://orcid.org/0000-0003-2590-3874
Pamela L. Lutsey https://orcid.org/0000-0002-1572-1340

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