Phlebolymphology

ISSN 1286-0107

Vol 30 | No. 1 | 2023 | P1-56

No. 109

Phlebolymphology

Aims and Scope

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, is included in several databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, and news.

Correspondence

Editorial Manager
Hurrem Pelin YALTIRIK
Servier Affaires Médicales
35, rue de Verdun,
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 38 98
Email: hurrem-pelin.yaltirik@servier.com

Publication Director
Christophe CHARPENTIER
Suresnes, France

Publisher
Les Laboratoires Servier
50, rue Carnot,
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 60 00

Indexed in EMBASE, Index Copernicus, and Scopus.

ISSN 1286-0107

Content

Vol 30, No. 1, 2023 No. 109

Editorial

Dear Readers,

In this new issue of *Phlebolymphology*, you will find the articles as below:

Hypodermitis or lipodermatosclerosis (LDS) is a chronic inflammatory process of the dermis and subcutaneous layer in the legs of patients with advanced chronic venous disease (CVD). It is one of the clinical findings for class C4b in the CEAP classification (clinical, etiological, anatomical, and pathophysiological) of CVD; however, the cellular and molecular mechanisms responsible for progression of CVD and development of LDS remain unclear. **L. REINA-GUTIERREZ and A. SANJUANBENITO-REINA** ***(Spain)***, provide an up-to-date review on the epidemiology, pathophysiology, clinical manifestations, and management of hypodermitis or LDS.

Acute iliofemoral deep vein thrombosis is more symptomatic than a thrombosis distal to the common femoral vein and increases the risk of postthrombotic syndrome, which reduces quality of life and increases medical costs. To provide the best possible medical care, it all starts with identifying iliofemoral deep vein thrombosis. **M. J. E. VAN RIJN and J. M. BAKAS** ***(Netherlands)*** discuss the challenges, opportunities, and future perspectives for the treatment of iliofemoral deep vein thrombosis.

K. OZSVATH ***(USA)*** presents a literature review on the use of cyanoacrylate preparations – eg, VenaSeal, VenaBlock, and VariClose – within the venous system, preparations frequently used in the management of venous disorders; possible complications are also addressed.

A. JAWORUCKA-KACZOROWSKA ***(Poland)*** summarizes the potential etiologies of chronic pelvic pain (CPP) with a primary focus on gynecological issues, including pelvic venous disorders (PeVDs), an entity at the interface between gynecology and vascular surgery and an increasingly recognizable pathology.

Limited data are available on the prevalence of varicose veins and on risk factors for varicose veins during pregnancy. **S. D. AKSOY and colleagues** ***(Turkey)*** present the results of a recent observational study that was conducted to estimate the prevalence of varicose veins, identify the associated risk factors, and assess the impact on quality of life from varicose vein presence in pregnancy.

Enjoy reading this issue!

Editorial Manager
Dr H. Pelin Yaltirik

Phlebology has lost a master

In memory of Michel Perrin, MD (Editor in Chief of Phlebolymphology)

by Oscar Maleti, MD

A great vascular surgeon, Dr Michel Perrin, was particularly dedicated to research in phlebology, publishing prolifically, with nearly 500 articles, as well as chapters and books, during his career. His passionate dedication to the advancement of this field is evidenced by his service as president of most French societies and as an honorary member in most European societies for vascular diseases; he was the first president of the European Venous Forum (EVF), founded together with Andrew Nicolaides in 2000. Across the ocean, in the United States, he was an honorary member of both the American College of Phlebology (ACP) and the American Venous Forum (AVF).

An assiduous speaker at most international conferences, he brought his scientific thought to every continent. It is not surprising then that his delivery of the AVF's prestigious Eugene Strandness Memorial Lecture in 2005 was on the topic of "The Importance of International Collaboration for Developing a Scientific Approach in Venous Disease."

In recognition of his achievements in vascular medicine, he has received the highest awards, such as the Ratschow Memorial Medal in Germany, bestowed by the Curatorium Angiologiae Internationalis; the 2015 Gold Medal from the Saint-Petersburg Society of Phlebology (SPSP) in St. Petersburg, Russia; and in 2018, the inaugural Gold Medal awarded from the International Union of Phlebology (UIP).

Throughout his career, he was integrally involved in weaving the very fabric of the tools used to classify and to communicate about venous disease. Indeed, envisaging a better classification, he participated in the creation of the CEAP (clinical, etiological, anatomical, and pathophysiological) classification system for chronic venous disease, becoming its promoter in Europe; and in 1998, he organized a meeting around classification of recurrent varicose veins (REVAS). He participated in creation of the VEIN-TERM consensus document that defines the terms used in phlebology and of the SYM Vein consensus document on venous symptoms, finishing in 2018 with publication of the VEIN GLOSSARY, which defines more than 1000 terms used in phlebology and which has been translated into 6 languages.

His deep enthusiasm extended far beyond medicine, to history, cuisine, and culture. Michel was highly educated in other fields, including naval history. An expert in naval battles, he was often invited to lecture on this subject. Other loves included great French wines, but also those of Tuscan and Piedmontese origin, and cooking, with a particular appreciation of Italian food, especially pasta and charcuterie—including sweet ham and Emilian salami, and with what could best be described as a veneration for culatello. He also had an unbridled passion for the cathedral of Modena, whose history he learned to the point that he became an expert on the subject, which he would describe in detail as we listened to one of his favorite composers, Mahler.

Michel's vivacity did not stop with the manner in which he pursued his interests but encompassed as well his fighting spirit, commitment to work, and sense of humor. Never did he allow the limitations imposed on him from his health weigh on others; despite those, he continued to attend congresses with unheard of tenacity. Indeed, Michel did not know a day without work, choosing to spend a few hours at least working even on Sundays, Christmas, and Easter. And yet, in the many meetings in Modena with other phlebologists—Bob Kistner (USA), Andrew Nicolaides (UK), Bo Eklöf (Sweden), Peter Neglén (Cyprus), our mutual friend Jérôme Guex (France), and many others—Michel was the pivot around which humor revolved. While being frank and honest in his opinions and interactions with others, his commitment to friendship, as to all his passions, was total.

Michel was Editor in Chief of Phlebolymphology.

Phlebology has lost a master.

Phlebolymphology Vol 30 | No.1 | 2023

Management of hypodermitis or lipodermatosclerosis: an up-to-date review

Lourdes Reina-Gutierrez, MD

Medical Doctor specialized in Angiology and Vascular Surgery, Head of the Angiology and Vascular Department of University Hospital Central de la Cruz Roja, Madrid, Spain and Professor of Medicine Grade in Alfonso X el Sabio University

Alfonso Sanjuanbenito-Reina, MD

Medical Doctor at University Hospital Ramon y Cájal, Madrid, Spain

ABSTRACT

Hypodermitis or lipodermatosclerosis (LDS) is a chronic inflammatory process of the dermis and subcutaneous layer in the legs of patients with advanced chronic venous disease (CVD). It is one of the clinical findings for class C4b in the CEAP classification (clinical, etiological, anatomical, and pathophysiological) of CVD. The cellular and molecular mechanisms responsible for progression of CVD and development of LDS remain unclear. Endothelial injury activates leukocytes, causing a perivascular inflammatory process that affects the dermis and hypodermis in the context of chronic venous hypertension. LDS presents 2 clinical stages: the acute phase and a chronic condition. The acute phase is characterized by the appearance of an erythematous, indurated, and warm plaque with intense local pain that is poorly demarcated in the inner surface of the lower leg. The chronic phase presents a demarcated, thickened, and indurated skin with a constriction of the distal leg that imparts the shape of an inverted champagne bottle. Ulcers may develop in this phase. The diagnosis is based on clinical findings and is frequently misdiagnosed with cellulitis and other panniculitides in the acute phase, delaying optimal treatment. Ultrasound examination with probes used in routine venous examination of lower limbs can easily identify the histopathologic changes that affect the dermis and subcutaneous layer in CEAP class C4b CVD. The treatment must focus on eliminating the ambulatory chronic venous hypertension through conservative and invasive measures and controlling the factors that determine the onset or progression of CVD.

Keywords

chronic venous disease | chronic venous insufficiency | hypodermitis | hypodermitis sclerodermiformis | indurated cellulitis | lipodermatosclerosis | panniculitis | sclerosing panniculitis

Phlebolymphology. 2023;40(1):6-25.

www.phlebolymphology.org

Definition

Hypodermitis or lipodermatosclerosis (LDS) is a chronic inflammatory process characterized by the induration of the dermis, hypodermis, and sometimes the superficial fascia in the legs of patients with chronic venous disease (CVD).[1-4]

Various terms have been used through the years to delineate this condition. Huriez et al were the first to recognize and describe LDS in 1955. They called it hypodermitis sclerodermiformis and believed that the disease was caused by cellulitis in patients with venous insufficiency.[5] Other terms such as sclerosing panniculitis and indurated cellulitis have been used to describe the same entity, whereas the term LDS has become the preferred nomenclature in the United States and the United Kingdom.[2-4]

LDS is a form of lobular panniculitis without vasculitis associated with CVD.[6] The panniculitis or hypodermitis is defined as the focal inflammation of the cellular subcutaneous layer or hypodermis. It can be caused by multiple causes. The best way to classify the different types of panniculitis is from a histopathological point of view. Panniculitis can be lobular or septal, depending on where the initial inflammatory process originates, and each one of them can be classified as with or without vasculitis. These patterns can overlap, particularly in more advanced stages of the disease, comprising all areas of the subcutaneous layer, which is defined as mixed or diffused panniculitis (*Table I*).[6,7]

Lobular

With vasculitis

- **Erythema induratum of Bazin.**
- **Erythema nodosum leprose.**
- **Lucio disease.**
- **Crohn disease.**

Without vasculitis

- **Immune:**
  - Lupica panniculitis.
  - Hypocomplementemia panniculitis.
  - Panniculitis associated with dermatomyositis.
  - Panniculitis associated with rheumatoid arthritis.
  - Lipoatrophic panniculitis.
- **Enzymatic:**
  - Pancreatic panniculitis.
  - Panniculitis associated with deficit of alfa-1-antitripsina.
- **Neoplasic:**
  - Histiocytic cytophagic panniculitis.
  - Panniculitis associated with lymphoma and leukemia.
- **Physical panniculitis:**
  - Panniculitis caused by cold.
  - Chemical panniculitis.
  - Traumatic fat necrosis.
- **Infectious panniculitis:**
  - Panniculitis caused by atypic mycobacteria.
  - Panniculitis caused by subcutaneous mycosis.
- **Panniculitis associated with deposits:**
  - Fat
    - › *Sclerema neonatorum.*
    - › *Fat necrosis of newborn.*
    - › *Post steroids panniculitis.*
  - Calcium
    - › *Calcified panniculitis of renal insufficiency.*
  - Uric acid
    - › *Gout panniculitis.*
  - Cholesterol
    - › *Hemorrhagic panniculitis secondary to cholesterol embolus.*
- **Eosinophilic panniculitis.**
- **Weber-Christian Disease.**
- **Subcutaneous lipogranulomatosis.**
- **Lipodermatosclerosis.**
- **Lipodystrophy.**
- **Panniculitis in other diseases.**

Septal

With vasculitis

- **Nodosum polyarteritis.**
- **Superficial migrans thrombophlebitis.**
- **Leukocytoclastic vasculitis.**

Without vasculitis

- **Nodosum erythema.**
- **Subacute migrans nodular panniculitis.**
- **Eosinophilic fasciitis.**
- **Scleroderma panniculitis.**

Table 1. **Histopathologic classification of panniculitis.**

Based on reference 6: Sánchez-Saldaña et al. *Dermatol Peru*. 2006;16(3):36-61.
Based on reference 7: Bondi et al. Paniculitis. In: Fitzpatrick TB ed. *Dermatología en Medicina General*. 5 ed. Éd. Medica Panamericana; 2001:1341-1356.

The Vein Glossary[8] has defined hypodermitis as one of the signs associated with chronic venous insufficiency (CVI) and one of the clinical findings in class C4b of the CEAP classification (clinical, etiological, anatomical, and pathophysiological; *Table II*).[9] The Vein Glossary defined it as follows: "It consists of an inflammatory, edematous, fibrotic plaque of the medial lower third of the lower leg. It can be associated with stasis purpuric dermatitis and atrophie blanche. Often extremely painful, it can be the start of an ulcer."[8]

Ulceration rate associated with LDS was estimated to be around 13% in a retrospective study.[3] Kirsner et al proposed that the degree of thickening was associated with the appearance of a venous ulcer.[1] The degree of skin thickening associated with LDS around the ulcer has been found to be predictive of a difficulty in healing.[10] The larger the area of LDS, the greater the risk of re-ulcération in patients with CEAP class C5.[11]

C (Clinical Manifestations), **E** (Etiology), **A** (Anatomic Distribution), **P** (Pathophysiology)			
C0	No visible or palpable signs of venous disease	C4a	Pigmentation or eczema
C1	Telangiectasias or reticular veins	C4b	Lipodermatosclerosis or atrophie blanche
C2	Varicose veins	C4c	Corona phlebectatica
C2r	Recurrent varicose veins	C5	Healed
C3	Edema	C6	Active venous ulcer
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease	C6r	Recurrent active venous ulcer

Table II. CEAP classification system and reporting standard revision 2020.
Hypodermitis or lipodermatosclerosis is one of the clinical findings for CEAP class C4b.
After reference 9: Lurie et al. *J Vasc Surg Venous Lymphat Disord*. 2020;8:342-352. © 2020, Society for Vascular Surgery.

Prevalence

Based on epidemiological studies, the prevalence of class C4b in the general population varies from 2.1% to 13.2% depending on the country and the sex (*Table III*).[12] A systematic review identified 32 studies from 6 continents including >300 000 adults and found a pooled C4 prevalence of 4%.[13] Approximately 10% of CVD patients will develop LDS.[14-16]

Based on case studies, patient series, and randomized controlled trials (RCTs), middle aged and elderly women are more frequently affected by LDS. In addition, LDS also was associated with obesity in some of these studies, and although it may appear as bilateral, it is more often a unilateral lesion.[1-3,11,17-19,20-28] In a retrospective analysis of 97 patients with acute and chronic LDS, 87% were women, predominantly middle aged, 66% were obese, and 85% were either overweight or obese. Bilateral involvement was found in 45% of cases.[2] Patients with morbid obesity have more advanced CVD, caused by an increased abdominal pressure, a decreased calf muscle function, and inactivity. In addition,

CEAP class	Men			Women		
	France	*Germany*	*Poland*	*France*	*Germany*	*Poland*
C2	23.7	12.4	51.6	46.3	15.8	47.7
C3	1.1	11.6	9.2	2.2	14.9	10.5
C4	4.0	3.1	13.2	2.1	2.7	10.3
C5	1.4	0.6	4.2	0.7	0.6	2.2
C6	0	0.1	2.1	0	0.1	1.1

Table III. Prevalence of chronic venous disease (percentage of population) stratified by CEAP clinical class (C2-C6).
See in particular the prevalence of C4 CEAP clinical class.
Abbreviation: CEAP, clinical, etiological, anatomical, pathophysiological classification system. After reference 12: Nicolaides et al. *Int Angiol*. 2018;37(3):191-192. © 2018, Edizioni Minerva Medica.

popliteal vein compression during hyperextension of the leg during standing has been observed.[29-31] Together with these mechanical factors, obesity is associated with a systemic proinflammatory state that impairs venous and lymphatic return, contributing to the onset and worsening of CVD and lymphedema.[32]

Elderly patients more often suffer advanced stages of CVD due to associated comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, right heart failure, and obesity; and often, a decreased calf muscle function caused by immobility, stroke, and locomotor system diseases.[33]

Physiopathology

The macrovascular complications associated with CVD progression are well recognized; however, the cellular and molecular mechanisms responsible for the development of LDS and subsequent venous ulceration remain unclear.

On a microcirculatory level, chronic venous hypertension produces an endothelial injury with recruitment of inflammatory cells, increased permeability, and exit of proinflammatory molecules, cells, and proteins to the interstice. The resulting perivascular inflammatory process affecting the hypodermis leads to fat necrosis and fibrosis of the skin that is defined as LDS or hypodermitis (*Figure 1*).[34-37]

Inappropriate endothelial activation in CVD is a mechanism common to other cardiovascular diseases and diabetes. A recent epidemiological study in 12 423 CVD patients found a clear association between CVD and an increased risk of cardiovascular disease and all-cause mortality. This association was reported at each stage of CVD, and the risk increased proportionally with higher CEAP classes.[25,38] Epigenetic factors that cause microcirculation deterioration and inflammation can contribute to venous and lymphatic disease such as obesity, diabetes, poor lifestyle and nutritional habits, postural changes, calf pump dysfunction, drug intake, trauma, stress, and a dysfunctional autonomic nervous system.[39]

The venous and lymphatic systems work as a unit, the overloading of one being compensated by the other. Moreover, the overloading and failure of one produces the failure of the other.[40] Lymphoscintigraphy is normal in early stages of CVD, but later it shows pathologic findings and lymph flow impairment, leading to inflammation.[39] This inflammation arises when lymphatics cannot cope with the interstice overload of fluid and proinflammatory molecules and cells.[39]

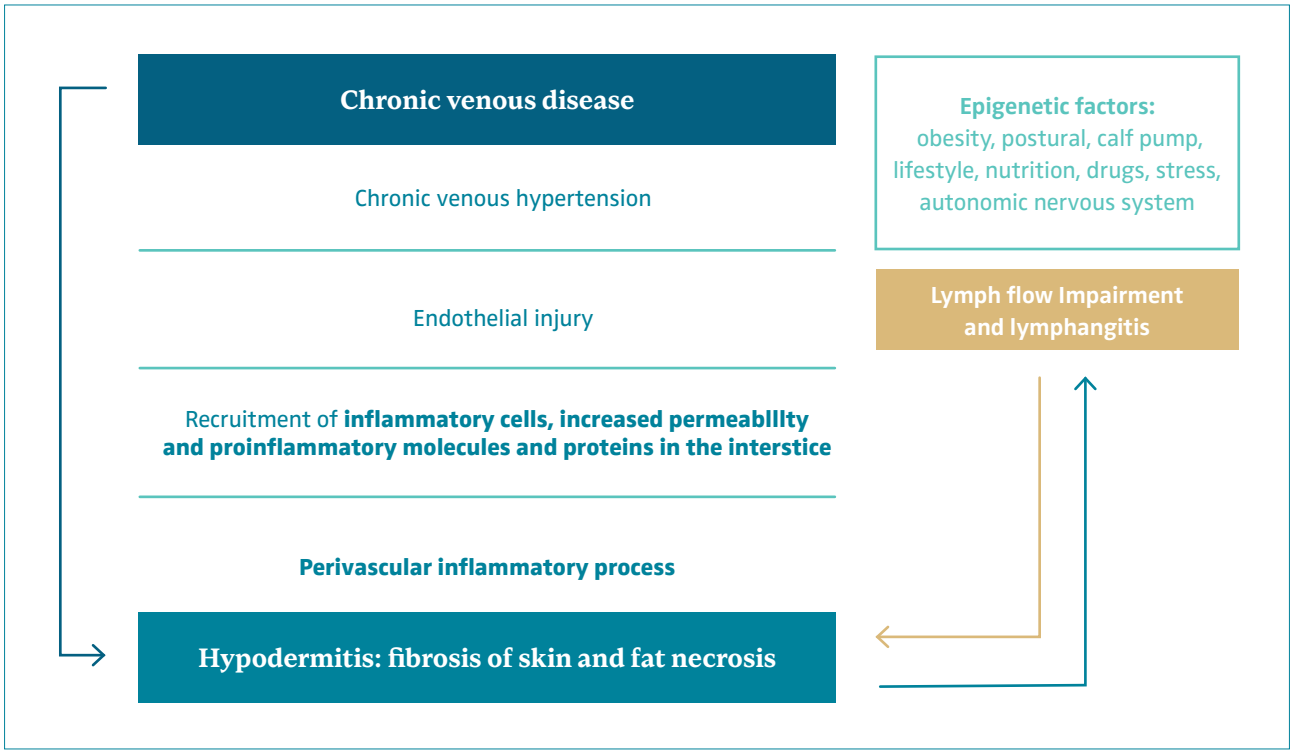
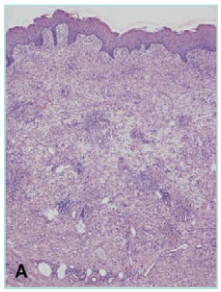


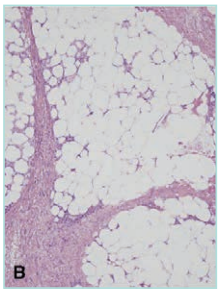
Figure 1. Physiopathology of hypodermitis.

Histopathology

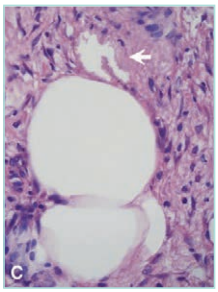
Hypodermitis is characterized by a progressive septal fibrosis and necrosis of the fat lobules (*Figure 2*).[3,22,23,41,42] An infiltrate with dilated vascular spaces is seen at first in the dermis. Thickening of the septa with discrete inflammation and necrosis of adipocytes in the center of the lobule can be observed. As the disease progresses, the septa become fibrosed, and this fibrosis progressively extends into the lobules, obliterating the adipocytes. Within the dermis, lobulated and tortuous thick-walled blood vessels, erythrocyte extravasation and siderophages, perivascular lymphocytic infiltrate with foamy macrophages and plasma cells, and dermal atrophy can be seen. Hemosiderin has been found to always be present in LDS skin.[43]



Diffuse and discrete perivascular infiltrate with dilated vascular spaces in the dermis.



Septal panniculitis with markedly thickened fibrotic septa extended into the fat lobules.



Necrosis of the adipocyte in the center of the lobule. The adipocytes are substituted by a pseudomembrane with fibrosis of the dermis and the subcutaneous layer.

Progressive septal fibrosis and necrosis of the fat lobules.

Figure 2. Histopathology of hypodermitis characterized by a progressive septal fibrosis and necrosis of the fat lobules.

Images from reference 41: Chan et al. *J Am Acad Dermatol*. 2008;58(3):525-527.

Clinical manifestation

LDS presents 2 clinical stages or phases according to the clinical manifestations: the acute-subacute phase and a chronic condition.[1,2,23,24,44] The acute phase is characterized by the appearance of an erythematous and slightly indurated and warm plaque with intense local pain that is poorly demarcated in the inner surface of the lower leg (*Figure 3*). This **acute stage** is usually misdiagnosed as cellulitis, thrombophlebitis, morphea or erythema nodosum. The **chronic phase** is characterized by a demarcated, thickened, and indurated skin involving the gaiter region caused by extensive sclerosis of the dermis and subcutaneous tissue of the lower leg. Usually, progressive fibrosis leads to a constriction of the distal leg and imparts the characteristic shape of an inverted champagne bottle (*Figures 4 and 5*). The skin can be darkly hyperpigmented although it is not invariably so. Areas of atrophie blanche within LDS skin can also be present (*Figure 6*). Ulcers may develop in this phase. With advanced sclerosis and regression of the acute inflammatory reaction, pain tends to be duller and aching, being more frequent when the patient walks or exercises.[1,2,4,22] In a retrospective study of 97 patients, Bruce et al found pain in the lower limb to be the most common symptom of LDS, seen in 43% of patients.[2]

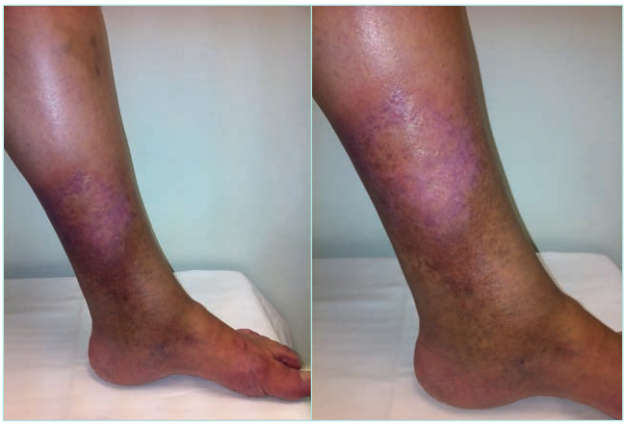


Figure 3. Acute hypodermitis or lipodermatosclerosis. Chronic venous disease of CEAP class C4b. An inflammatory plaque poorly demarcated in the inner surface of the lower third of the lower leg, which is often extremely painful.

Abbreviation: CEAP, clinical, etiological, anatomical, pathophysiological classification system.
Images from: University Hospital Central Cruz Roja Collection.

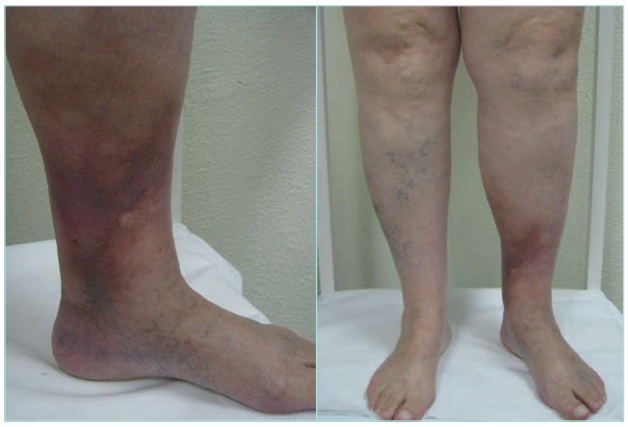


Figure 4. Chronic hypodermitis or lipodermatosclerosis. Chronic Venous Disease of CEAP class C4b.

A well-demarcated area of hyperpigmented, thickened, and indurated skin involving the gaiter region of the lower leg caused by extensive fibrosis and sclerosis of the dermis and subcutaneous tissue of the lower leg. Usually, fibrosis leads to a constriction of the distal leg giving to the leg the appearance of an inverted champagne bottle. An ulcer may develop.

Abbreviation: CEAP, clinical, etiological, anatomical, pathophysiological classification system.
Images from: University Hospital Central Cruz Roja Collection.

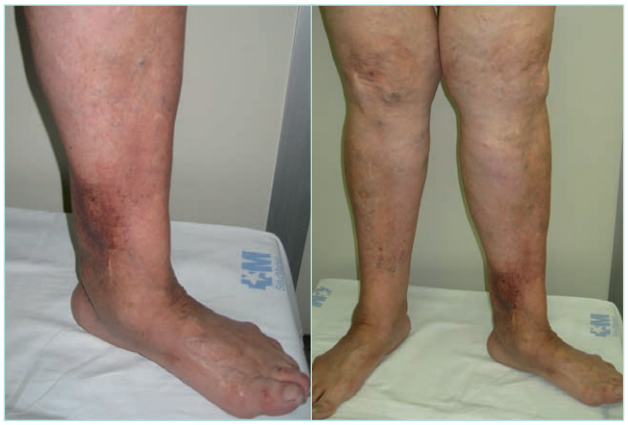


Figure 5. Chronic hypodermitis or lipodermatosclerosis. Fibrosis and sclerosis of the dermis and the subcutaneous layer that manifests as an induration of the skin and the sign of the inverted champagne bottle. It can be the start of an ulcer.

Images from: University Hospital Central Cruz Roja Collection.

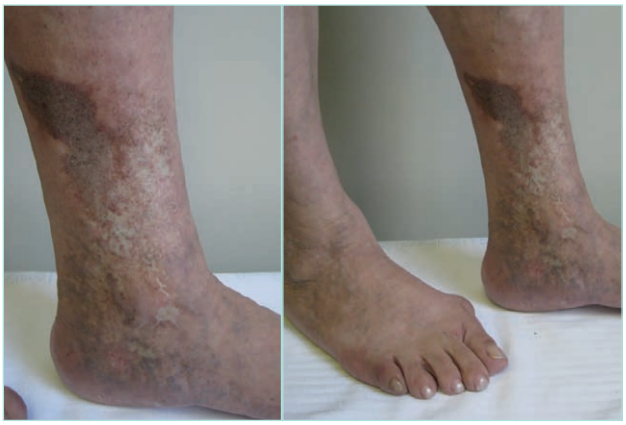


Figure 6. Chronic hypodermitis or lipodermatosclerosis. It can be associated with stasis purpuric dermatitis and atrophie blanche.

Images from: University Hospital Central Cruz Roja Collection.

The chronic phase most often develops following the acute phase (in months or even more than a year) or may occur independently. It is unclear whether each patient with chronic LDS undergoes an acute phase. Based on patient history, it appears that an acute phase is not necessary or that its severity may be variable, thus a patient may not recall such a phase or have sought medical attention.[1,4] Once installed, acute inflammatory phases can occur again during the chronic phase, named the ''acute on chronic'' form of LDS.[4,44] In the retrospective case-control study of Suehiro et al, in 6 legs out of 30, acute LDS recurred 9 (3-38) months after the initial attack, exclusively in legs with persistent induration, hyperpigmentation, and edema.[28] In CVD, LDS is usually a chronic condition in which acute phases may occur.[44]

Clinical diagnosis

The diagnosis of LDS is clinical. However, although chronic LDS is readily recognized clinically, acute lesions are frequently misdiagnosed since they lack the sharp demarcation, hard consistency, and sometimes obvious clinical signs of venous disease associated with chronicity.[22] Such early and evolving lesions may be clinically confused with cellulitis, erysipelas, lymphangitis, morphea, superficial venous thrombophlebitis, erythema nodosum, erythema induratum, and a range of other panniculitides.[22,23]

The acute phase is frequently mistaken as a cellulitis and treated ineffectively with antibiotics. The key points to differentiate acute LDS from cellulitis/erysipelas are the absence of fever, systemic symptoms, inguinal lymphadenopathy, normal laboratory inflammatory parameters such as leukocytes, and lack of antibiotic treatment effectiveness.[22] The diagnosis of lower-limb cellulitis is incorrect in as many as one-third of patients. The most common disorders mistaken for lower-limb cellulitis are venous eczema, LDS, and lymphedema.[45]

Erythema nodosum is observed especially on the anterior aspects of the lower legs, and erythema induratum is found mainly on the calves. Panniculitis during lupus erythematosus course usually appears on the trunks or arms.[22,23]

Biopsy

Biopsy can provoke a nonhealing ulcer; therefore, a histologic study is only recommended in selected cases to do a differential diagnosis with other panniculitis or diseases.

Skin ultrasound examination

Skin ultrasound examination, a ''noninvasive biopsy,'' is an excellent morphological evaluation of the cutaneous (epidermis and dermis) and subcutaneous layers, using the same probes dedicated to routine vascular investigation.[46] The author of this review refers the readers to the publication of Caggiatti et al[46] to further investigate this topic.

Findings in normal skin are illustrated in *Figure 7*.[46] The epidermis appears as a thin hyperechoic band because of the echoes created between the gel and the skin surface. The papillary dermis (PD) appears as a thin and low-echogenic band parallel to the skin surface, immediately below the hyperechoic epidermis. It is called the ''subendothelial-low-echogenic-band'' (SLEB). The hypoechogenicity of the PD is related to its high water content. The reticular dermis (RD) appears as a regular band, with homogeneous thickness and echogenicity. The echoes from the reticular layer originate from the boundaries between the collagen fibers and the surrounding ground substance and cells.

In normal conditions, the dermo-hypodermic junction (D-HJ) appears as an uninterrupted line, easily recognizable thanks to the marked difference in echogenicity of the RD and the subcutaneous layer (*Figure 7*). The subcutaneous tissue consists of hypoechoic fat lobules separated by echolucent connective trabeculae. The prevalence of adipose tissue makes the subcutaneous layer markedly less echogenic than the overlying dermis. The thickness of the trabeculae varies greatly between individuals and within the same subject, depending on the evaluated area (*Figure 7*).[46]

Hypodermitis is characterized by inflammatory edema in initial phases and liposclerosis in advanced cases. The ultrasound pattern is greatly variable, with different combinations of cutaneous and subcutaneous changes. To simplify the matter, it is possible to designate 2 main ultrasound patterns: scleroedematous and fibrosclerotic.[46]

Acute hypodermitis: scleroedematous pattern

There is an inflammatory edema manifested by thickening of the dermis, disappearance of PD and the D-HJ, and thickening and hyperechogenicity of the hypodermis (*Figure 8*).[46]

Chronic hypodermitis: fibrosclerotic pattern

The fibrosclerotic pattern of chronic hypodermitis is characterized by progressive dermal sclerosis with disappearance of the PD and D-HJ, and subcutaneous layer thinning and hyperechogenicity by progressive fibrous proliferation and disappearance of fat lobules (liposclerosis).[46] *Figure 9*.

A prospective study of 14 limbs with CEAP class C4-C6 CVD found on high-frequency ultrasound examination showed that dermis thickness and the dermis and subcutaneous layer echogenicity were higher in the areas of LDS than in normal thigh skin. Subcutaneous layer and venous wall calcification and fibrosis of the affected skin were also detected. Compression static elastography showed lower compliance of the subcutaneous layer than muscle.[47]

The retrospective case-control study published recently by Suehiro et al has shown differences in the dermal and subcutaneous ultrasound findings in patients diagnosed with acute LDS between patients that progressed to chronic LDS and those who did not.[28] These results may have opened a line of investigation on the prognosis of CVD.

Diagnosis: skin ultrasound

Normal skin

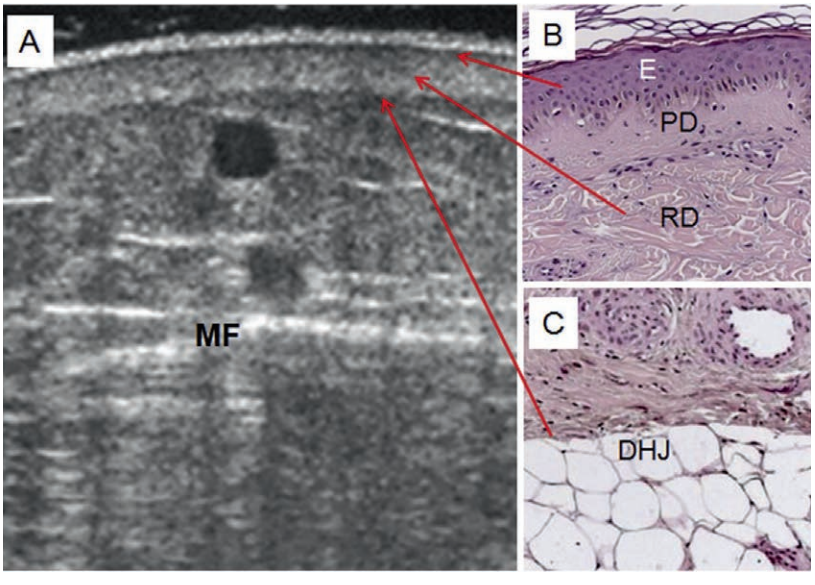


Figure 7. Normal skin ultrasound. Ultrasonography of skin changes in legs with chronic venous disease.

A) Normal skin, 12 MHz sonography. B,C) Light microscopy.

Abbreviations: DHJ, dermo-hypodermic junction; E, epidermis; MF, muscular fascia; PD, papillary dermis; RD, reticular dermis.

After reference 46: Caggiati. Eur J Vasc Endovasc Surg. 2016;52(4):534-542.

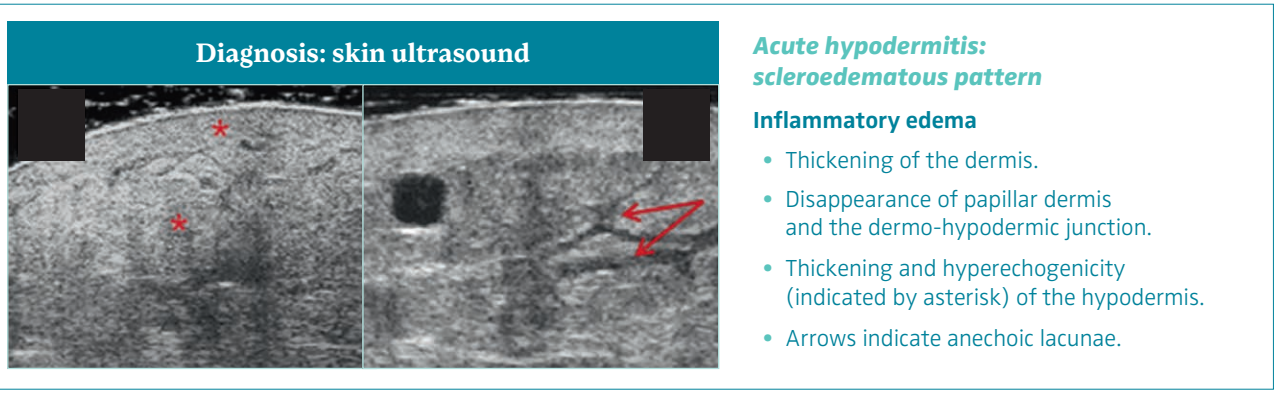


Figure 8. Skin ultrasound of acute hypodermitis: scleroedematous pattern. Ultrasonography of skin changes in legs with chronic venous disease.

After reference 46: Caggiati. *Eur J Vasc Endovasc Surg.* 2016;52(4):534-542. © 2016, European Society for Vascular Surgery. Published by Elsevier, Ltd.

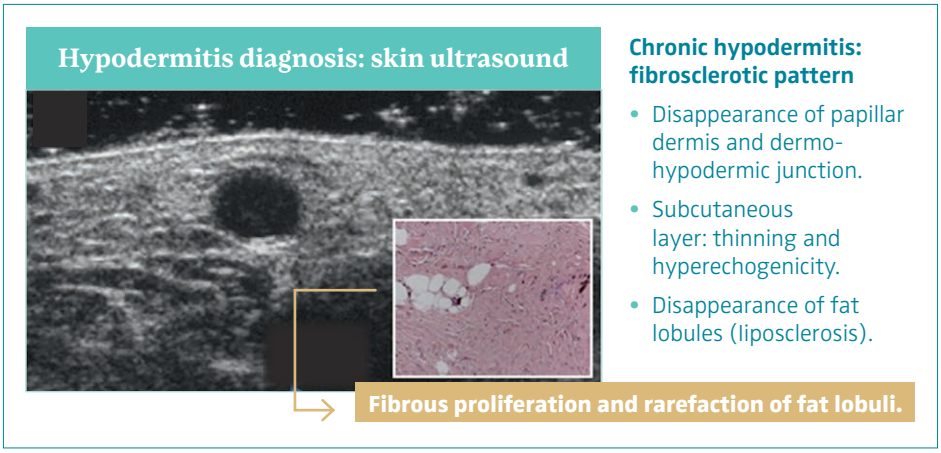


Figure 9. Skin ultrasound of chronic hypodermitis: fibrosclerotic pattern. Ultrasonography of skin changes in legs with chronic venous disease.

After reference 46: Caggiati. *Eur J Vasc Endovasc Surg.* 2016;52(4):534-542. © 2016, European Society for Vascular Surgery. Published by Elsevier, Ltd.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is another potentially useful alternative to skin biopsy that reveals thickening of the skin with typical distinct fibrous septa in the hypodermis with a ''honey-comb'' appearance, which is in concordance with the histopathologic features of LDS.[41]

Indication of investigations in CEAP C4b

The European Venous Forum (EVF), International Union of Phlebology (UIP), and International Union of Angiology (UIA) clinical guidelines recommend doing a lower-limb and abdominal echo-doppler examination. If venous obstruction is suspected, it is recommended to do a plethysmography, computed tomography venography (CTV), magnetic resonance venography (MRV), venography, pressure measures, and/or intravascular ultrasound (IVUS). If phlebolymphedema is suspected, it is recommended to do lower-limb isotopic lymphoscintigraphy (*Figure 10*).[48]

According to the European Society for Vascular Surgery (ESVS) clinical guidelines, if suprainguinal pathology is suspected, it is recommended to do an abdominal echo-doppler, abdominal CTV, abdominal MRV, or abdominal venography.[49]

Lower-limb echo-doppler

Lower-limb echo-doppler is the primary test of choice. One must evaluate the deep venous system, the superficial venous system, and the perforant veins in the vicinity of severe skin changes (*Figures 11 and 12*).

Indication of investigations in C4b CEAP
Lower-limb and abdominal echo-doppler exam.
If venous obstruction suspected: plethysmography, CT venogram, MRV, venography, pressure measures or IVUS.
If phlebolymphedema suspected: lower-limb isotopic lymphoscintigraphy.

Figure 10. Indication of investigations in class C4b of CEAP classification according to the guidelines of UIP, EVF, and UIA.

Abbreviations: CEAP, clinical, etiological, anatomical, pathophysiological classification system; CT, computed tomography; EVF, European Venous Forum; IVUS, intravascular ultrasound; MRV, magnetic resonance venography; UIA, International Union of Angiology; UIP, International Union of Phlebology.
Based on reference 48: Nicolaides et al. *Int Angiol.* 2018;37(3):181-232.

The definition of a perforant vein as being pathological when surpassing an outward flow >0.5 seconds and a diameter >3.5 mm in area of skin changes is controversial.[49-51]

Of patients with CVD, 40% to 70% have superficial venous reflux (SVR), associated or not with reflux of perforant veins or in the deep venous system.[52,53] This reflux can be eliminated through invasive procedures.[49-51,54]

Lower-limb echo-doppler

The primary test of choice

- Deep venous system
- Superficial venous system
- Perforant veins in the vicinity of severe skin changes

Pathological perforant vein criteria: outward flow >0.5 s and a diameter >3.5 mm in area of skin changes

"Controversial"

Figure 11. Lower-limb echo-doppler is the primary test of choice. Definition of pathological perforant veins remains controversial.

Figure 12. Lower limb echo-doppler examination of a patient with hypodermitis and incompetence of perforant tibial vein.
Images from: University Hospital Central Cruz Roja Collection.

Treatment

The objective of treatment should be to eliminate the chronic ambulatory venous hypertension and its secondary inflammatory process in the microcirculation. To achieve the first goal, one can eliminate the SVR and/or the deep venous reflux or obstruction by invasive procedures and conservative measures such as compression therapy, calf muscle activation, and elevation of the leg. Venoactive drugs (VADs) and compression therapy are indicated to counter the inflammatory process at the microcirculatory level.[48-51,55]

Treatment of lymphatic insufficiency associated with advanced stages of CVD

The treatment of the lymphatic insufficiency associated with advanced stages of CVD (phlebolymphedema) should not be forgotten. This objective will be gained by compression therapy through complex decongestive therapy with manual lymphatic drainage in acute and intensive care and in the maintenance phase, skin care, exercise, drugs, and nutraceuticals.[56,57]

Treatment of nonvascular factors that impact venous and lymphatic disease

An interdisciplinary medical pathway that approaches both diabetes and obesity is encouraged. This combined syndrome is a true pandemic worldwide, sharing its endothelial lesion with the venous and lymphatic disease.[32] The treatment strategy should approach the commonalities of these interconnected diseases.[58] Other therapeutic alternatives such as new drugs and nutraceuticals, measures to improve parasympathetic systems, gene treatment, stem cell treatment, and improvement of poor health habits are being investigated.[32,39]

Treatment for the acute phase

The acute phase requires rapid treatment. Oral analgesics are essential to reduce the pain. Compression therapy is the first-line treatment, preferably by multilayer bandaging (MLB) and adjustable compression garments (ACG). Using elastic compression stockings (ECS) may be difficult because of pain.[1,27,28,59]

Reich-Schupke et al observed in a case series a lower recurrence of acute episodes in those patients in which SVR was eliminated.[22]

Among other general measures are the nonsteroidal anti-inflammatory drugs, the topical/oral corticosteroids, and skin care with zinc oxide and emollients, although there is poor evidence to support them. Various treatments including nonsteroidal anti-inflammatory drugs, antibiotics, and topical/oral steroids were provided in 28 patients with acute-subacute LDS for 8 weeks (2-52 weeks) without improvement.[28]

Venoactive drugs (VADs)

The 2018 UIP, UIA, and EVF clinical guidelines scrutinized both old and new meta-analyses addressing the effect of individual VADs on individual symptoms and signs of CVD. The only drug that had been evaluated in placebo-controlled, double-blind, RCTs on its effect on leg redness and skin changes was the micronized purified flavonoid fraction (MPFF). The analyses showed improvement in these signs with a level of evidence B and A, respectively, the clinical guidelines giving a strong recommendation for this drug in this indication (*Tables IV and V*).[60,61] In a pooled analysis of 4 RCTs evaluating the effects of MPFF treatment on skin trophic disorders, the risk ratio (RR) of 0.87 (95% CI, 0.81-0.94) for persistence of the skin trophic disorder with MPFF treatment vs placebo indicated a statistically significant benefit with MPFF.[62,63]

Symptoms/ signs	MPFF	Ruscus HMC AA	OxerutIns	HCSE	Calcium dobe.
Pain	A	A	B	A	B
Heaviness	A	A	B		A
Feeling of swelling	A	A			B
Discomfort	A				B
Leg fatigue	NS	B			
Cramps	B	B/C	B		
Paresthesiae	B/C	A			B
Burning	B/C	NS			
Pruritus/itching		B/C	A		
Tightness	NS				
Restless legs	NS				
Leg redness	B				
Skin changes	A				
Ankle circumference	B	A	NS	A	
Foot or leg volume	NS	A	NS	A	A
QOL	A				NS

Table IV. Effect of venoactive drugs on symptoms and signs of chronic venous disease. Level of evidence.

Abbreviations: MPFF, micronized purified flavonoid fraction; Ruscus HMC AA, Ruscus aculeatus extract, hesperidin methyl chalcone and ascorbic acid; HCSE, horse chestnut extract; Calcium dobe, Calcium dobesilate; QOL, quality of life.

However, studies focusing on the use of MPFF-based conservative treatment in patients with CEAP class C4 CVD are scarce. Bogachev et al recently published a prospective, observational study with 365 patients with CEAP class C4 CVD treated with MPFF, associated with other conservative measures, such as compression for 6 months, and showed a significant improvement in subcutaneous adipose thickness assessed by ultrasound and a significant reduction in lesion area and skin density measured by curvimetry and durometry, respectively. The VCSS and symptoms typical of C4 class (itching, skin tightening, burning, pain) evaluated by a 10-cm visual analog scale (VAS) and the health-related quality of life (HRQoL) evaluated by the CIVIQ-14 scale (14-item ChronIc Venous Insufficiency Quality of Life Questionnaire) were also improved. No adverse reactions were reported.[25]

A 3-month treatment with sulodexide significantly improved objective signs of erythema, skin temperature and induration, and all subjective symptoms of CVD in an open, uncontrolled observational study in 450 CVD patients.[63,64]

The ESVS clinical guidelines have provided a single generic recommendation on VADs, recommending "For patients with symptomatic chronic venous disease, who are not undergoing interventional treatment, are awaiting intervention, or have persisting symptoms and/or oedema after intervention, medical treatment with venoactive drugs should be considered to reduce venous symptoms and oedema, based on the available evidence for each individual drug. Class IIa, Level A."[49,61,65,66]

Compression therapy

Compression therapy by ECS has been shown to reduce skin induration in patients with hypodermitis in 2 RCTs.[11,67]

Firstly, in a RCT with 77 patients treated with ECS and 81 patients that were not, Vandongen et al showed that below-knee 35-45-mm-Hg ECS reduced the area of LDS and ulcer recurrence in C5 CEAP.[11]

The second one is a pilot study of 17 patients with bilateral LDS,[67] where each leg was treated with a different stocking. One of the patient's legs was treated using a stocking permanently impregnated with copper oxide ions. Copper oxide has been shown to have biocidal and antimicrobial effects and is an essential element for normal skin function and is involved in several processes crucial for wound healing.

Symptoms/ signs	MPFF	Ruscus HMC AA	OxerutIns	HCSE	Calcium dobe.
Pain	Strong	Strong	Strong	Strong	
Heaviness	Strong	Strong	Strong	-	
Feeling of swelling	Strong	Strong	-	-	
Functional discomfort	Strong	-	-	-	
Cramps	Strong	Weak	Strong	-	
Leg redness	Strong	-	-	-	
Skin changes	Strong	-	-	-	Weak in view of the possibility of including agranulocytosis
Edema	Strong	Strong	Weak	Strong	
Quality of life	Strong	-	-	-	
Paresthesiae	Weak	Strong	-	-	
Burning	Weak	-	-	-	
Leg fatigue	-	Strong	-	-	
Pruritus	-	Weak	-	Strong	

Table V. Recommendation level for venoactive drug (VAD) treatment of symptoms and signs of chronic venous disease.

Abbreviations: MPFF, micronized purified flavonoid fraction; Ruscus HMC AA, Ruscus aculeatus extract, hesperidin methyl chalcone and ascorbic acid; HCSE, horse chestnut extract; Calcium dobe, Calcium dobesilate.
Based on reference 60: Nicolaides et al. *Int Angiol.* 2018;37(3):232-254.

The leg treated with nonimpregnated ECS was the control group. Below-knee 14-18-mm-Hg graduated ECS impregnated with copper reduced the area of LDS in C4b CEAP.[67]

The ESVS clinical guidelines recommend: ''For patients with chronic venous disease and lipodermatofibrosis and/or atrophie blanche (CEAP clinical class C4b), using below-knee ECS, exerting a pressure of 20-40 mm Hg at the ankle, is recommended to reduce skin induration. Class I, Level B.''[49]

Multilayer bandaging

MLB achieving an interface pressure of >40 mm Hg is a more suitable treatment for the acute-subacute phase of LDS than ECS or superimposed stockings, providing higher pressure and more effectiveness in relieving pain. Using ECS is difficult for patients with acute LDS because of pain.[1,4] In a case-report study, MLB eased the pain in 8 of 9 patients within 2 to 7 weeks of treatment with only occasional use of painkillers and no other treatment.[27] In another case-report study of 30 patients with acute LDS, in all cases, the symptoms subsided within 5 weeks (2-11 weeks) after treatment with MLB exerting an interface pressure >40 mm Hg. Patients did not require particular medications, except for the occasional use of analgesics. Six legs out of 30 patients had a recurrent acute LDS. The treatment with MLB controlled symptoms and prevented re-recurrence.[28] Nevertheless, MLB is sometimes neither possible nor tolerated; 1 of 9 patients in the study of Suehiro did not tolerate it.[27] It must be taken into account that LDS modifies the limb shape, therefore ECS and MLB may have limitations.[59] Moreover, compression therapy in patients with acute-subacute LDS is unlikely to prevent the progression to chronic LDS.[28]

Adjustable compression garments

ACGs are made of stiff material with self-adhesive straps, usually applied from the ankle to the knee. The more the straps are stretched around the leg, the higher the compression pressure. Inelastic compression devices are more effective than inelastic bandages because they can be readjusted. They are easy to apply after a short training, allowing for self-management (*Figures 13-15*).[68,69] ACGs allow for compression therapy in morbid obesity, for nonstandard legs, for skin that needs daily care, and allow the use of footwear (*Figure 16*).[70] ACG have been used to treat the very painful phase of acute LDS.[59] Similarly to the MLB, ACG can achieve higher pressure than ECS, helping to control pain more easily. In contrast to MLB, ACG can be adapted to limbs with chronic LDS and an inverted champagne-bottle shape.

Figure 13. Adjustable compression garments for the treatment of chronic lipodermatosclerosis.
Images from: University Hospital Central Cruz Roja Collection.

Supervised physical exercises and walking associated with compression therapy

Patients with advanced stages of CVD present significant limitations of ankle and foot-joint mobility. LDS often covers the structures of foot joints, particularly the ankle joints and the Achilles tendon. The stiffness of the ankle joint limits foot mobility and disturbs the proper biomechanics of walking.[71] As 2 RCTs have shown, patients should be encouraged to regularly exercise (standing on tiptoes, foot bending, using a training bike) and walk to increase foot and ankle joint mobility and to improve calf muscle pump function.[72,73] Compression increases the function of the calf muscle pump.[74]

Elimination of superficial venous reflux

Traditional surgery by stripping is unpopular or impossible in elderly patients with skin lesions or comorbidity.[54] Endovenous echo-guided techniques are less invasive, can be performed without anesthesia or local anesthesia, are less painful with a short return to daily activities, have less major complications, and prevent incision of the skin (*Figure 17*).[75] Therefore, they are preferred in patients with skin lesions (C4b), in the elderly with comorbidities, obesity, or lymphedema.

The UIP, UIA, and EVF clinical guidelines[55] give a strong recommendation based on high-quality evidence (A) for treatment of the great saphenous vein (GSV) with modern open echo-guided surgery (1A), thermal ablation with endolaser or radiofrequency (1A), and echo-guided sclerotherapy with foam (1A). Ablation with steam, cyanoacrylate, and mechanochemical ablation (MOCA) have a recommendation of 1B, awaiting long-term results. These clinical guidelines recommend the treatment of tributaries with sclerotherapy or phlebectomy at the same time or at a second stage.[55]

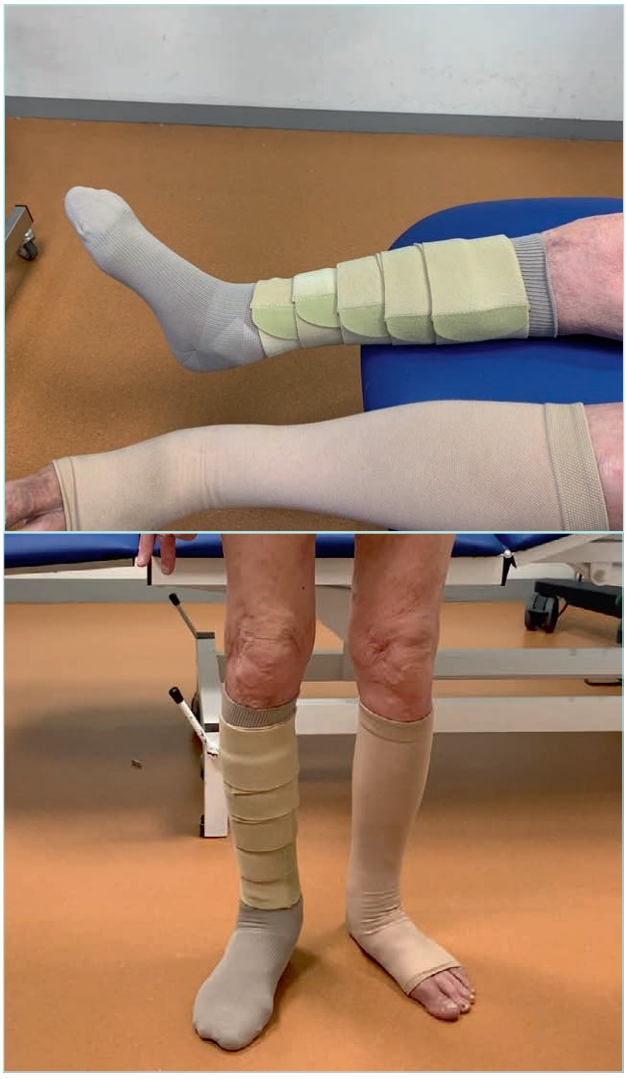


Figure 14. Elastic compression stockings (ECS) and adjustable compression garments (ACG) in bilateral lipodermatosclerosis.

Images from: University Hospital Central Cruz Roja Collection.

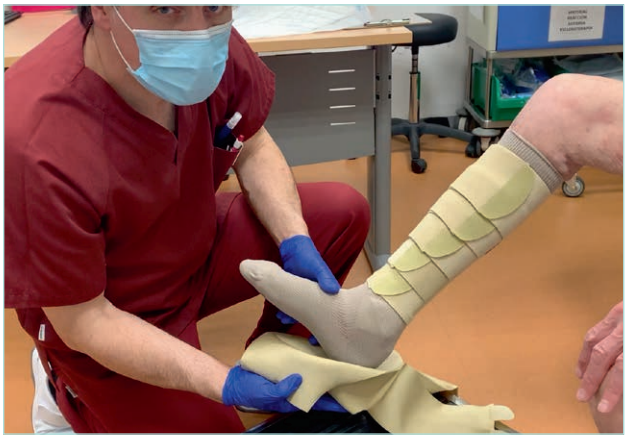


Figure 15. Adjustable compression garments (ACG) with the garment for the foot.

Images from: University Hospital Central Cruz Roja Collection.

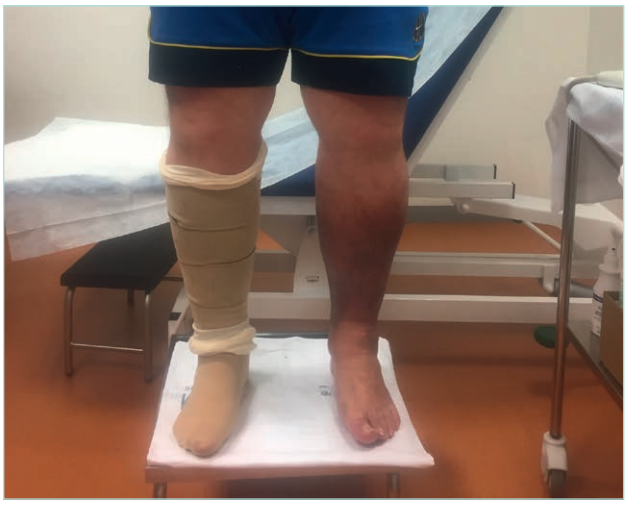


Figure 16. Adjustable compression garments (ACG) in a patient with morbid obesity and bilateral lipodermatosclerosis.

Images from: University Hospital Central Cruz Roja Collection.

Ultrasound-guided foam sclerotherapy (UGFS) is the most frequent procedure in the treatment of SVR. The advantages of UGFS compared with thermal ablation and phlebectomy is that LDS and lymphedema limit open surgery, thermal ablation, and tumescent anesthesia. Although the long-term anatomical effectiveness of UGFS is lower, it can be repeated. Sclerotherapy is the simplest and fastest and imposes no limitation on normal activity. *Figure 18*.

The ESVS clinical guidelines[49] recommend:

- ''For patients with saphenous trunk incompetence undergoing treatment, ultrasound guided foam sclerotherapy may be considered for treating saphenous trunk with a diameter less than 6 mm. Class IIb, Level B.'' "In patients with clinical class C4b, ultrasound guided foam sclerotherapy is a better alternative to phlebectomy for the treatment of tributaries. Phlebectomy may be complicated by delayed wound healing.''

- ''For patients with great saphenous vein incompetence requiring treatment, endovenous thermal ablation is recommended as first choice treatment, in preference to high ligation/stripping and ultrasound guided foam sclerotherapy. Class I Level A." *Figure 19*.

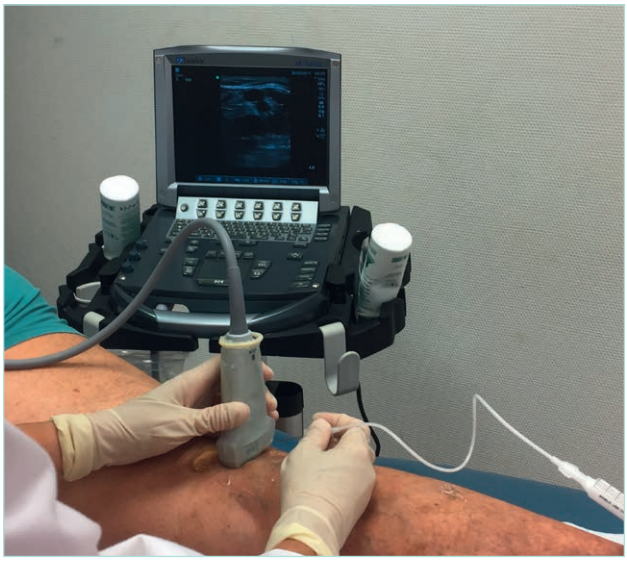


Figure 18. Echo-guided sclerotherapy of small saphenous vein in a patient with clinical class C4b of CEAP classification.
Images from: University Hospital Central Cruz Roja Collection.

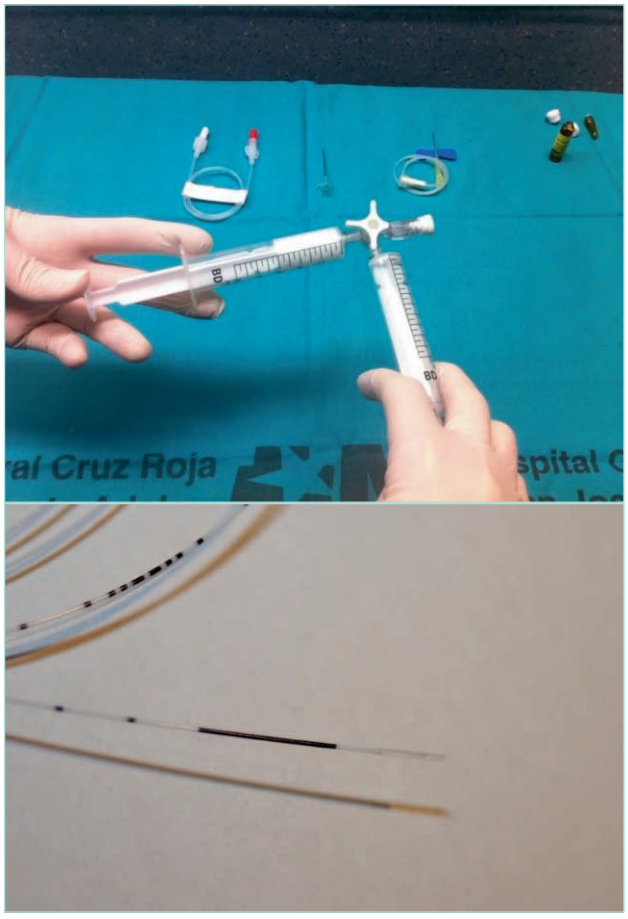


Figure 17. Echo-guided procedures in the ablation of the superficial venous reflux. *Up:* hand-made foam with Tessari technique. *Down:* endolaser fiber.
Images from: University Hospital Central Cruz Roja Collection.

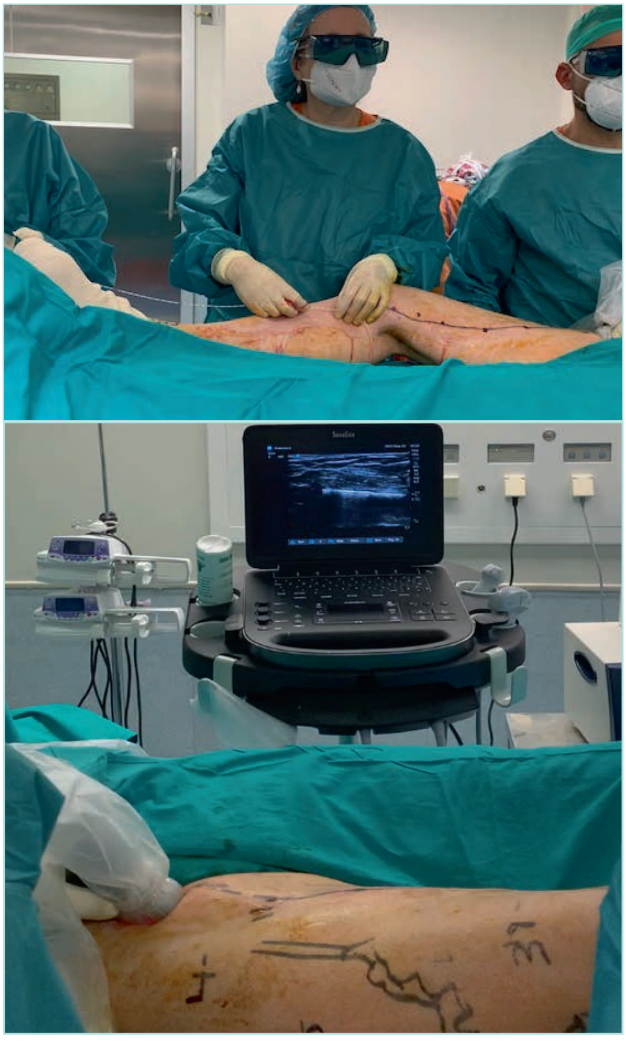


Figure 19. Thermal ablation of the great saphenous vein with endolaser. *Down:* ultrasound image of the thermal ablation of the vein.
Images from: University Hospital Central Cruz Roja Collection.

- ''For patients with great saphenous vein incompetence requiring treatment, cyanoacrylate adhesive closure should be considered when a non-thermal non-tumescent technique is preferred. Class IIa, Level A.'' *Figure 20*.
- ''For patients with great saphenous vein incompetence requiring treatment, mechanochemical ablation may be considered when a non-tumescent technique is preferred. Class IIb, Level A.'' *Figure 21*.
- ''For patients with small saphenous vein incompetence requiring treatment, endovenous thermal ablation is recommended in preference to surgery or foam sclerotherapy. Class I, Level A.''
- ''For patients with small saphenous vein incompetence requiring treatment, endovenous non-thermal non-tumescent ablation may be considered. Class IIb, Level B.''
- ''For patients with incompetence of the anterior accessory saphenous vein requiring treatment, endovenous thermal ablation should be considered. Class IIa, Level C.''
- ''For patients with incompetence of the anterior accessory saphenous vein requiring treatment, ultrasound guided foam sclerotherapy may be considered. Class IIb, Level C.''

Treatment of incompetent perforant veins

UGFS is the most commonly used technique (*Figure 22*).

No treatment is defined as superior because there are no randomized studies comparing the different techniques. In general, smaller incompetent perforant veins are treated with UGFS and larger ones with cyanoacrylate adhesive closure (CAC) or thermal ablation.[49-51]

The ESVS clinical guidelines recommend: ''For patients with CVD requiring treatment of incompetent perforating veins, endovenous ablation, division, or ligation should be considered. Class IIa, Level C.''[49]

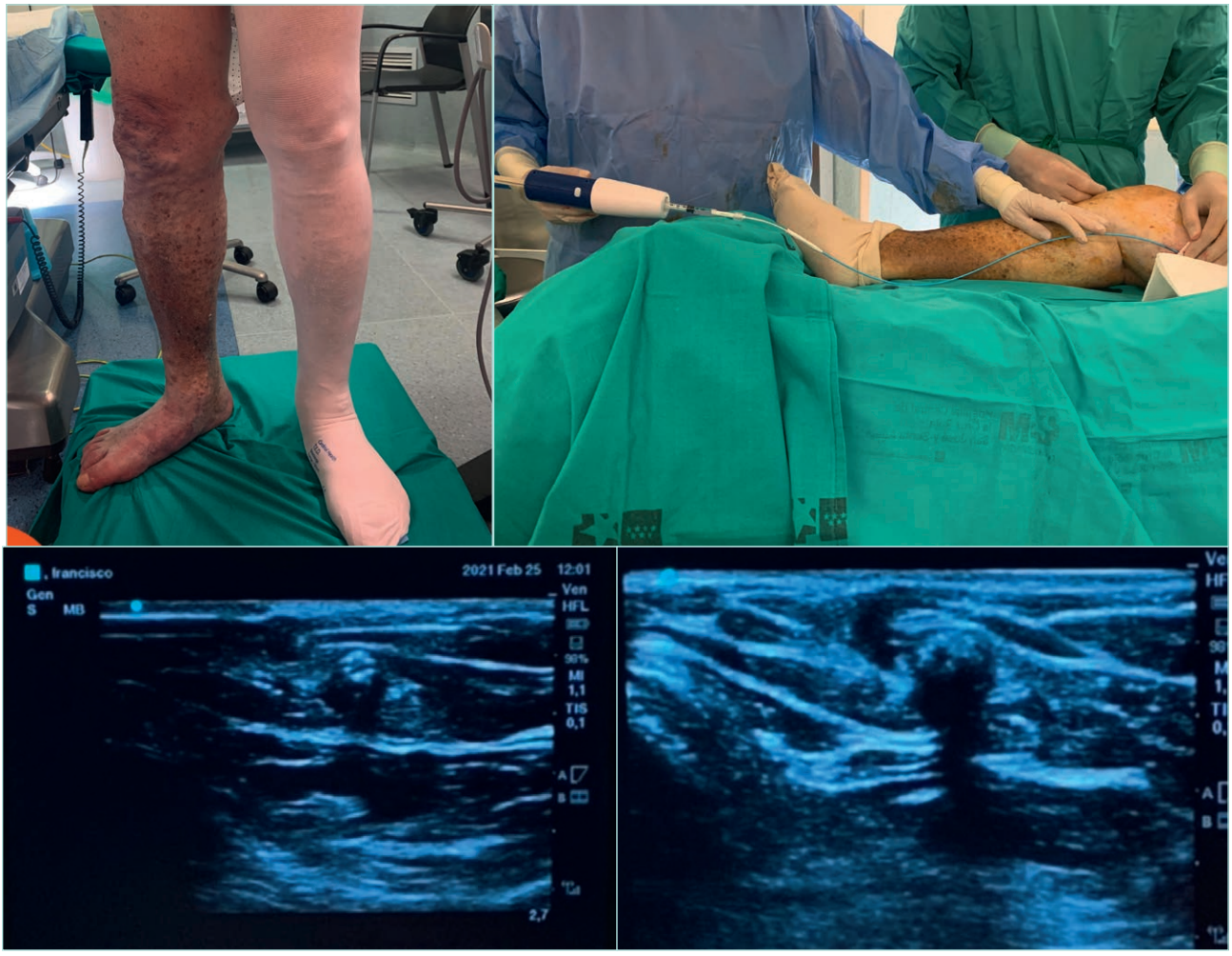


Figure 20. Endovenous closure of the great saphenous vein with cyanoacrylate adhesive with the VenaSeal technique. *Up:* VenaSeal Procedure. *Down left:* ultrasound images of the VenoSeal catheter inside the great saphenous vein. *Down right:* cyanoacrylate adhesive inside the great saphenous vein with acoustic shadow.

Images from: University Hospital Central Cruz Roja Collection.

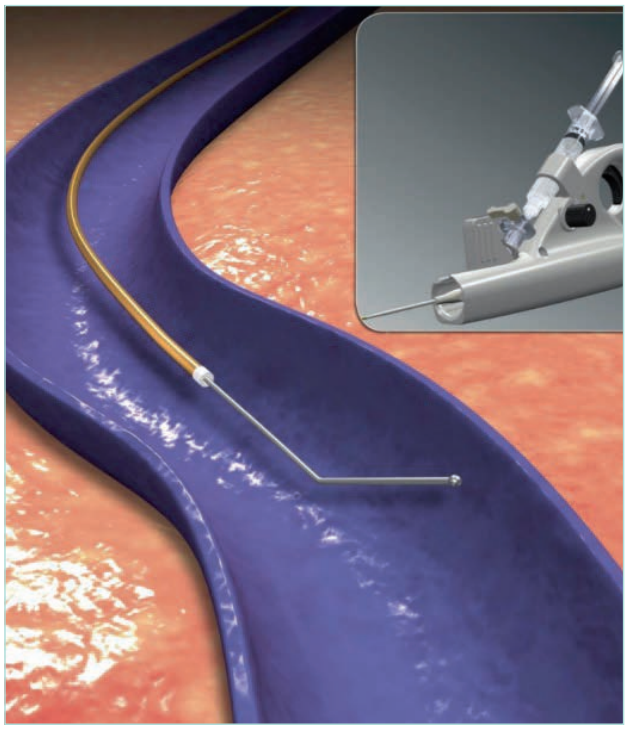


Figure 21. Mechanochemical ablation of the saphenous trunks with catheter ClariVein.

Based on reference 82: Reina and Solares. *Angiología*. 2018;70(1):25-32. https://doi.org/10.1016/j.angio.2017.10

Images from: University Hospital Central Cruz Roja Collection.

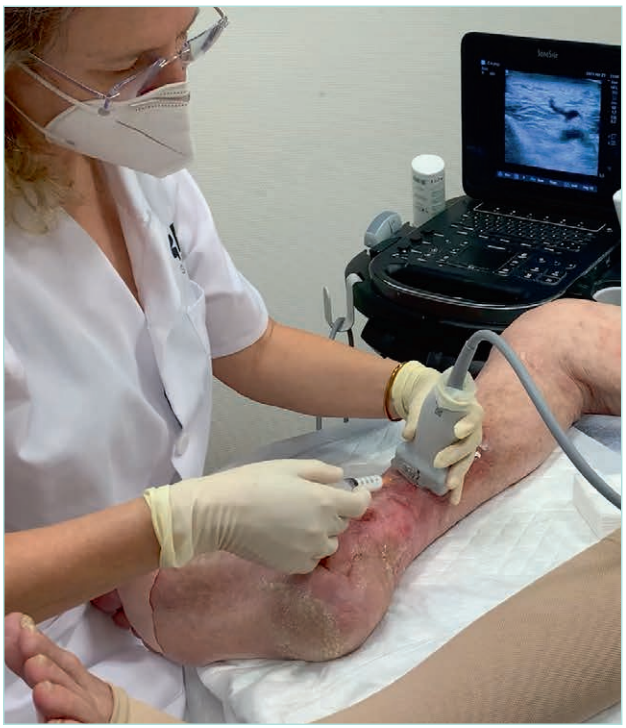


Figure 22. Echo-guided foam sclerotherapy of pathologic perforant vein in a patient with lipodermatosclerosis.

Images from: University Hospital Central Cruz Roja Collection.

Which technique do we choose?

We should take into account the following considerations: clinical guidelines recommendations and RCT results, local conditions determined by hospital or outpatient setting, refund and device availability, experience and preferences of the medical staff, and clinical condition and preferences of the patient.

What is the current trend?

The trend is to apply thermal ablation of the GSV in young patients with acceptable surgery risk, using UGFS of the tributaries.

In patients with lymphedema, obesity, advanced age, high risk for surgery or tumescent anesthesia, incompetence of SSV, and tributaries in the area of LDS, and taking into account the preference of the patient, the nonthermal, nontumescent techniques represented by UGFS, CAC, and MOCA are frequently performed.

Deep venous system and pelvic venous disorders

Interventional techniques to eliminate reflux or obstruction of the deep venous system in the lower limbs or abdominal veins or to treat pelvic venous disorders should be done in specialized centers in selected patients (*Figure 23-26*).[49-51]

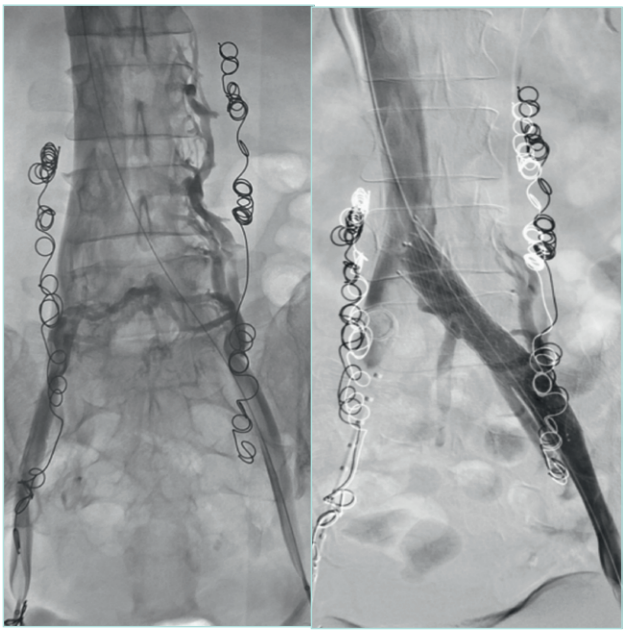


Figure 23. Stent in left iliac vein obstructed after a deep venous thrombosis.

Courtesy of: Dr Angel Sanchez and Dr Roberto Villar. Interventional Radiology Department. University Hospital 12 de Octubre, Madrid. University Hospital Central Cruz Roja Collection.

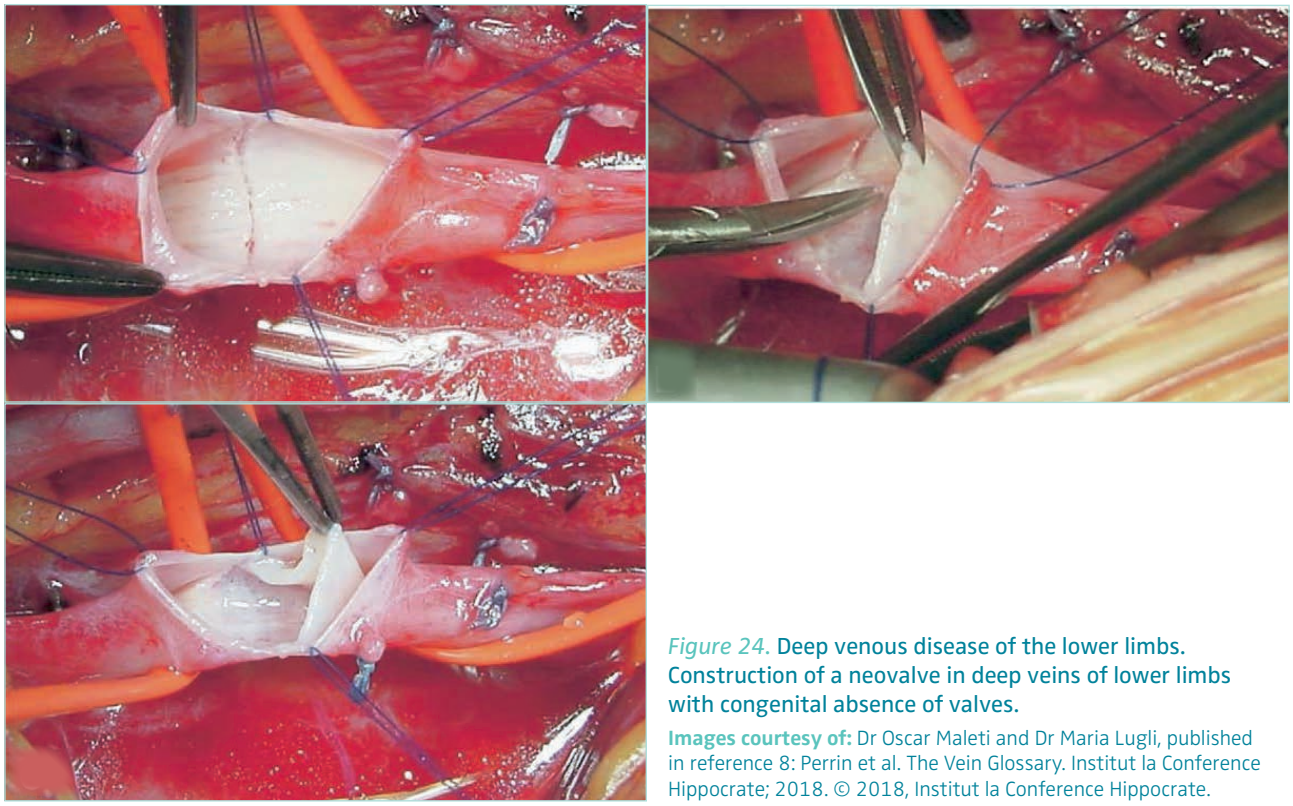


Figure 24. Deep venous disease of the lower limbs. Construction of a neovalve in deep veins of lower limbs with congenital absence of valves.

Images courtesy of: Dr Oscar Maleti and Dr Maria Lugli, published in reference 8: Perrin et al. The Vein Glossary. Institut la Conference Hippocrate; 2018. © 2018, Institut la Conference Hippocrate.

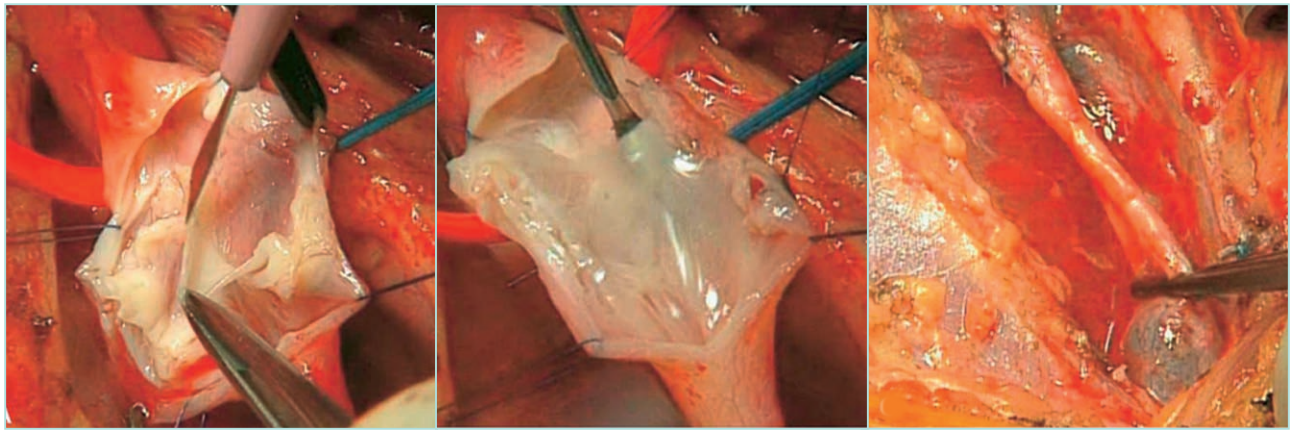


Figure 25. Deep venous disease of the lower limbs. Construction of a neovalve in deep veins of lower limbs after a deep venous thrombosis.

Images courtesy of: Dr Oscar Maleti and Dr Maria Lugli, published in reference 8: Perrin et al. The Vein Glossary. Institut la Conference Hippocrate; 2018. © 2018, Institut la Conference Hippocrate.

Other surgical approaches

The above-described invasive venous procedures can eliminate chronic venous hypertension, but the long-term accumulated liquefied fatty and necrotic subcutaneous tissue cannot be directly removed. Percutaneous drainage with multiple tiny incisions of the skin showing LDS and blunt dissection associated with saphenous vein stripping has been shown to relieve the tenderness, induration, redness, and swelling.[76,77] In a RCT of 60 patients with CEAP class C4-C6 CVD, this surgical drainage decreased the calf and ankle circumference, improved the subcutaneous thickness and Venous Clinical Severity Score (VCSS), inhibited the expression of adhesion molecules as well as the inflammatory response, improved the microcirculation of the lower extremities, reduced the mRNA expression of collagen type I alpha 1 chain 1, and improved QOL at 6 months after surgery.[78]

The excision of LDS tissue by radical surgery associated with saphenous vein stripping in the management of C5/C6 patients with LDS might be considered for very select patients who fail to respond to endovenous techniques, but evidence is lacking.[79-81]

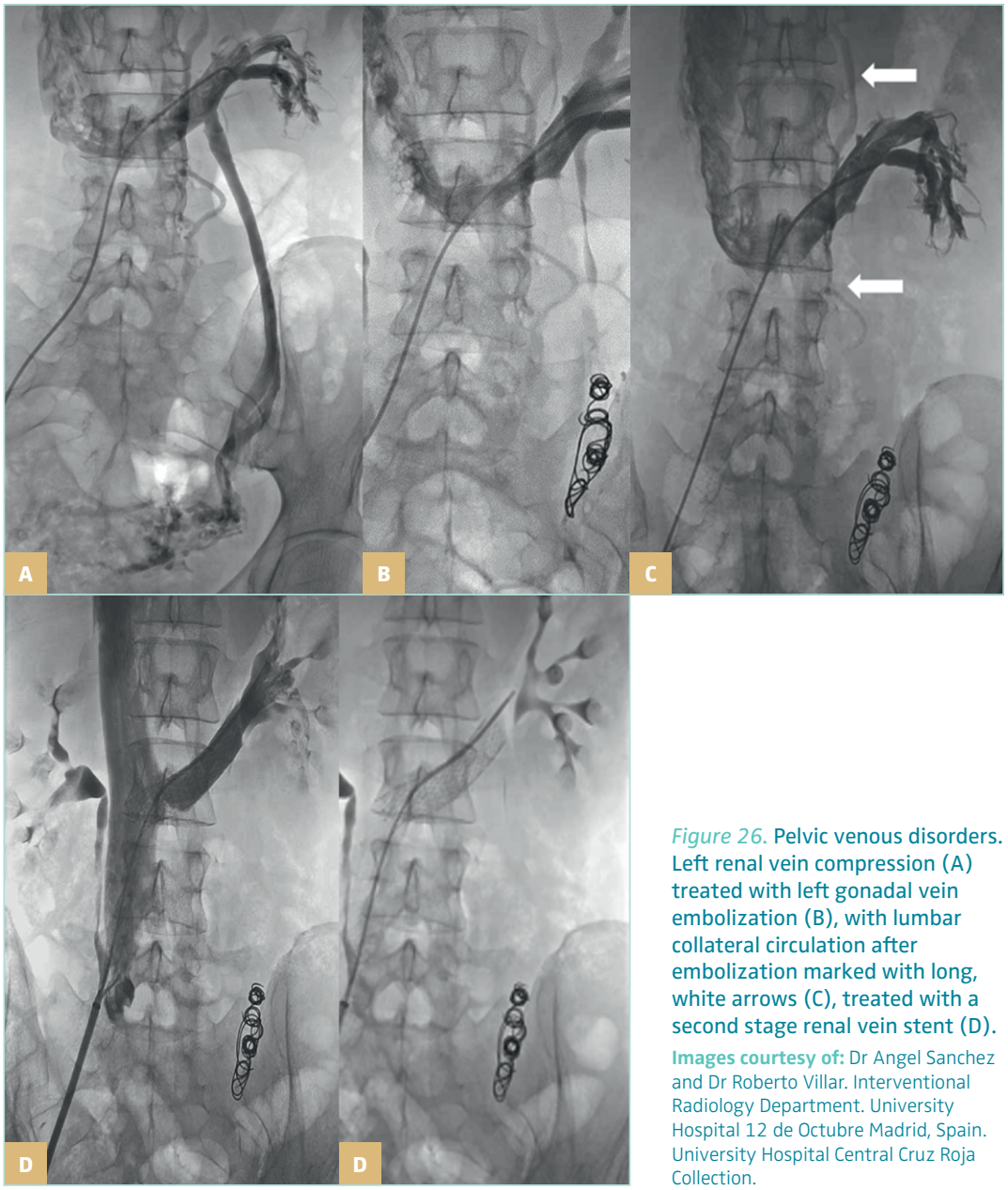


Figure 26. **Pelvic venous disorders. Left renal vein compression (A) treated with left gonadal vein embolization (B), with lumbar collateral circulation after embolization marked with long, white arrows (C), treated with a second stage renal vein stent (D).**

Images courtesy of: Dr Angel Sanchez and Dr Roberto Villar. Interventional Radiology Department. University Hospital 12 de Octubre Madrid, Spain. University Hospital Central Cruz Roja Collection.

Conclusion

The management of advanced-stage CVD is a challenge that begins with the understanding of its physiopathology, above all at the microcirculatory and molecular level. This seems to connect CVD with other common chronic disorders such as obesity and diabetes mellitus among others. The diagnosis of hypodermitis is based on clinical findings and may not be easy during the acute phase, being frequently misdiagnosed as cellulitis and other panniculitides, which delay optimal treatment. Ultrasound examination with probes used in the routine venous examination of lower limbs can easily identify the histopathologic changes that affect the dermis and subcutaneous layer in CEAP class C4b CVD. Treatment must focus on eliminating ambulatory chronic venous hypertension through conservative and invasive measures and controlling the factors that determine the onset or progression of CVD.

CORRESPONDING AUTHOR

Dr Lourdes Reina-Gutierrez

Avenida de la Reina Victoria 22-24, 28003 Madrid, Spain.

EMAIL: *lreina@salud.madrid.org*

References

1. Kirsner RS, Pardes JB, Eaglstein WH, Falanga V. The clinical spectrum of lipodermatosclerosis. *J Am Acad Dermatol*. 1993;28:623-627.
2. Bruce A, Bennett D, Lohse CM, Rooke TW, Davis MD. Lipodermatosclerosis: review of cases evaluated at Mayo Clinic. *J Am Acad Dermatol*. 2002;46:187-192.
3. Jorizzo JL, White WL, Zanolli MD, Greer KE, Solomon AR, Jetton RL. Sclerosing panniculitis: a clinicopathologic assessment. *Arch Dermatol*. 1991;127:554-558.
4. Miteva M, Romanelli P, Kirsner RS. Lipodermatosclerosis. *Dermatol Ther*. 2010;23:375-388.
5. Huriez C, Legache G, Desmons F, et al. Leg ulcers and trophic disorders of venous origin; data from the study of one thousand hospitalized patients with ulcers. Article in French. *Rev Prat*. 1955;5(26):2703-2721.
6. Sánchez-Saldaña L, Sáenz-Anduaga E, Thomas-Gavelan E. Paniculitis. Parte I: Paniculitis lobular. *Dermatol Peru*. 2006;16(3):36-61.
7. Bondi E, Margolis DJ, Lazarus GS. Paniculitis. In: Fitzpatrick TB ed. Dermatología en Medicina General. 5 ed. Éd. Medica Panamericana; 2001:1341-1356.
8. Perrin M, Eklof Bo, Maleti O. The Vein Glossary. Institut la Conference Hippocrate; 2018.
9. Lurie F, Passman M, Meisner M, et al. The 2020 classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord*. 2020;8:342-352.
10. Nemeth A, Eaglestein WH, Falanga V. Clinical parameters and transcutaneous oxygen measurements for the prognosis of venous ulcers. *J Am Acad Dermatol*. 1989;20:186-190.
11. Vandongen VK, Stacey MC. Graduated compression elastic stockings reduce lipodermatosclerosis and ulcer recurrence. *Phlebology*. 2000;15:33-37.
12. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. *Int Angiol*. 2018;37(3):191-192.
13. Salim S, Machin M, Patterson BO, Onida S, Davis AH. Global epidemiology of chronic venous disease: a systematic review with pooled prevalence analysis. *Ann Surg*. 2021;274:971-976.
14. Lee AJ, Evans CJ, Allan PL, et al. Lifestyle factors and the risk of varicose veins Edinburgh Vein Study. *J Clin Epidemiol*. 2003;56:171-179.
15. Pannier F, Rabe E. Progression in venous pathology. *Phlebology*. 2015;30(1 suppl):95-97.
16. Rabe E, Pannier F, Ko A, Berboth G, Hoffmann B, Hertel S. Incidence of varicose veins, chronic venous insufficiency, and progression of the disease in the Bonn vein study II. *J Vasc Surg*. 2010;51(3):791.
17. Naschitz J, Yeshurun D, Schwartz H, et al. Pathogenesis of lipodermatosclerosis of venous disease: the lesson learned from eosinophilic fasciitis. *Cardiovasc Surg*. 1993;1:524-529.
18. Buurnand KG, Whimsterm I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *Br Med J (Clin Res Ed)*. 1982;285:1071-1072.
19. Gniadecka M. Dermal oedema in lipodermatosclerosis distribution, effects on posture and compressive therapy evaluated by high frequency ultrasonography. *Acta Derm Venereol*. 1995;75:120-124.
20. Gross E, Wood CR, Lazarus GS, Margolis DJ. Venous leg ulcers: an analysis of the underlying venous disease. *Br J Dermatol*. 1993;129:270-274.
21. Snow J, Su WPD. Lipomembranous (membranocytic) fat necrosis: clinicopathologic correlation of 38 cases. *Am J Dermatophatol*. 1996;18:151-155.
22. Reich-Schupke S, Kreuter A, Altmeyer P, Stücker M. Wrong diagnosis erysipelas: hypodermitis-case series and review of literature. Article in German. *J Dtsch Dermatol Ges*. 2009;3:222-225.
23. Huang TM and Lee JYY. Lipodermatosclerosis: a clinicopathologic study of 17 cases and differential diagnosis from erythema nodosum. *J Cutan Pathol*. 2009;36:453-460.
24. Choonhakarn C, Chaowattanapanit S, Julanon N. Lipodermatosclerosis: a clinicopathologic correlation. *Int J Dermatol*. 2016;55:303-308.
25. Bogachev V, Boldin B, Turkin P, Samenkov A, Dzhenina O. Micronized purified flavonoid fraction-based conservative treatment of chronic venous disease in a real-world setting. *Future Cardiol*. 2022;18(10):777-785.
26. Arendsen LP, Vig S, Thakar R, Sultan AH. Impact of copper compression stockings on venous insufficiency and lipodermatosclerosis: a randomized controlled trial. *Phlebology*. 2019;34(4):224-230.
27. Suehiro K, Morikage N, Harada T, et al. Compression therapy using bandages succesfully manages acute or subacute lipodermatosclerosis. *Ann Vasc Dis*. 2019;12(1):77-79.
28. Suehiro K, Morikage N, Harada T, et al. Post-treatment course of acute lipodermatosclerosis. *Phlebology*. 2023;38(2):73-79.
29. van Rij AM, De Alwis CS, Jiang P, et al. Obesity and impaired venous function. *Eur J Vasc Endovasc Surg*. 2008;35(6):739-744.
30. Millen RN, Thomas KN, Versteeg MPT, van Rij AM. Popliteal vein compression, obesity, and chronic venous disease. *J Vasc Surg Venous Lymphat Disord*. 2022;10(1):200-208.
31. Lane RJ, Cuzzilla ML, Harris RA, Phillips MN. Popliteal vein compression syndrome: obesity, venous disease and the popliteal connection. *Phlebology*. 2009;24(5):201-207.
32. Cavezzi A. Medicine and phlebolymphology: time to change? *J Clin Med*. 2020;9:4091.
33. Labrapoulos N. How does chronic venous disease progress from the first symptoms to the advanced stages? A review. *Adv Ther*. 2019;36(suppl 1):13-19.
34. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation*. 2014;139:333-346.
35. Mansilha A, Sousa J. Pathophysiological mechanism of chronic venous disease and implications for venoactive drugs therapy. *Int J Mol Sci*. 2018;19:1669.
36. Castro-Ferreira R, Cardoso R, Leite-Moreira A, Mansilha A. The role of endothelial dysfunction and inflammation in chronic venous disease. *Ann Vasc Surg*. 2018;46:380-393.
37. Mannello F, Ligi D, Raffetto JD. Glycosaminoglycan sulodexide modulates inflammatory pathways in chronic venous disease. *Int Angiol*. 2014;33:236-242.
38. Prochaska JH, Arnold N, Falcke A, et al. Chronic venous insufficiency, cardiovascular disease, and mortality: a population study. *Eur Heart J*. 2021;42(40):4157-4165.
39. Cavezzi A et al. Lymphology and translational medicine. *Int Angiol*. 2020;39:422-432.
40. Lee BB, Andrade M, Antignani PL, et al. Diagnosis and treatment of primary lymphedema consensus document of the International Union of Phlebology (IUP)-2013. *Int Angiol*. 2013;32(6):541-574.
41. Chan CC, Yang CY, Chu CY. Magnetic resonance imaging as a diagnostic tool for extensive lipodermatosclerosis. *J Am Acad Dermatol*. 2008;58(3):525-527.
42. Ayele A, Tidman MJ, Biswas A. Pseudomembranous changes in the dermis: a novel observation and potential clue for evolving lipodermatosclerosis? *J Cutan Pathol*. 2017;44:1070-1074.
43. Caggiati A, Rosi C, Casini A, et al. Skin iron deposition characterizes lipodermatosclerosis and leg ulcer. *Eur J Vasc Endovasc Surg*. 2010;40:777-782.
44. Greenberg AS, Hasan A, Montalvo BM, et al. Acute lipodermatosclerosisis associated with venous insufficiency. *J Am Acad Dermatol*. 1996;35:566-568.
45. Hirschmann JV, Raugi GJ. Lower limbs cellulitis and its mimics. Part II. Conditions that simulate lower limb cellulitis. *J Am Acad Dermatol*. 2012;67:177-179.

46. Caggiati A. Ultrasonography of skin changes in legs with chronic venous disease. *Eur J Vasc Endovasc Surg.* 2016;52(4):534-542.

47. Wozniak W, Danowska A, Mlosek RK. The use of high-frequency skin ultrasound in the diagnosis of lipodermatosclerosis. *J Ultrason.* 2021;20(83):e284-e290.

48. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines according to scientific evidence. Part I. *Int Angiol.* 2018;37(3):181-232.

49. Maeseneer MG, Kakkos SK, Aherne T, et al. ESVS 2022 Clinical practice guidelines on the management of chronic venous disease of the lower limbs. *Eur J Vasc Endovasc Surg.* 2022;63:184-267.

50. O'Donnell TF, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2014;60:35-59.

51. Mosti G, Maeseneer M, Cavezzi A, et al. Society for Vascular Surgery and American Venous Forum guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology. *Int Angiol.* 2015;34(3):202-218.

52. Robertson LA, Evans CJ, Lee AJ, Allan PL, Ruckley CV, Fowkes FG. Incidence and risk factors for venous reflux in the general population: Edinburgh Vein Study. Eur *J Vasc Endovasc Surg.* 2014;48;208-214.

53. Myers KA, Ziegenbein RW, Zeng GH, Matthews PG. Duplex ultrasonography scanning for chronic venous disease: patterns of reflux. *J Vasc Surg.* 1995;21:605-612.

54. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet.* 2004;363(9424):1854-1859.

55. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines according to scientific evidence. Part II. Chapters 9-18. EVF and UIP. *Int Angiol.* 2020;39(3):175-240.

56. Mosti G, Cavezzi A. Compression therapy in lymphedema: between past and recent scientific data. *Phlebology.* 2019;34:515-522.

57. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. *Lymphology*. 2020;53:3-19.

58. Gastaldi G, Pannier F, Roztočil K, et al. Chronic venous disease and diabetic microangiopathy: pathophysiology and commonalities. *Int Angiol.* 2021;40(6):457-469.

59. Rastel D, Pichot O. Auto-adjustable medical compression device to treat acute lipodermatosclerosis in superficial chronic venous disease: a case report. *J Med Vasc.* 2022;47(3):141-144.

60. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines according to scientific evidence Part I. Chapter 8. Venoactive drugs. *Int Angiol.* 2018;37(3):232-254.

61. Kakkos SK, Nicolaides AN. Efficacy of micronized purified flavonoid fraction (Daflon) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. *Int Angiol.* 2018;37:143-154.

62. Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM, et al. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev.* 2016;4(4):CD003229.

63. Mansilha A, Sousa J. Pathophysiological mechanism of chronic venous disease and implications for venoactive drugs therapy. *Int J Mol Sci.* 2018;19:1669.

64. Elleuch N, Zidi H, Bellamine Z, Hamdane A, Guerchi M, Jezalli N. Sulodexide in patients with chronic venous disease of the lower limbs: clinical efficacy and impact on quality of life. *Adv Ther.* 2016;33:1536-1549.

65. Bignamini AA, Matuska J. Sulodexide for the symptoms and signs of chronic venous disease: a systematic review and meta-analysis. *Adv Ther.* 2020;37:1013-1033.

66. Kakkos SK, Allaert FA. Efficacy of ruscus estract, HMC and vitamin C, constituents of Cyclo 3 fort®, on improving individual venous symptoms and edema: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. *Int Angiol.* 2017;36:93-106.

67. Arendsen LP, Vig S, Thakar R, Sultan AH. Impact of copper compression stockings on venous insufficiency and lipodermatosclerosis: a randomised controlled trial. *Phlebology.* 2019;34(4):224-230.

68. Mosti G. Self-management by firm non-elastic adjustable compression wrap device. *Veins Lymphatics*. 2017;6:7003.

69. National Institute for Health and Care Excellence. The Juxtacures adjustable compression system for treating leg venous ulcers. Medtech innovation briefing [mib25]. Published March 25, 2015. https://www.nice.org.uk/advice/mib25

70. Blecken SR, Villavicencio JL, Kao TC. Comparison of elastic versus non-elastic compression in bilateral venous ulcer: a randomised trial. *J Vasc Surg.* 2005;42(6):1150-1155.

71. Orsted HL, Radke L, Gorst R. The impact of musculoskeletal changes on the dynamics of the calf muscle pump. *Ostomy Wound Manage.* 2001;47:18-24.

72. Padberg FT Jr, Jonhnston MV, Sisto SA. Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. *J Vasc Surg.* 2004;39:79-87.

73. Szewczyk MT, Jawien A, Cwajda-Biatasik J, Cierzniakowsk K, Moscicka P, Hancke E. Randomized study assessing the influence of supervised exercises on ankle joint mobility in patients with venous ulcerations. *Arch Med Sci.* 2010;6(6):956-963.

74. Hirai M. Changes in interface pressure under elastic and short-stretch bandages during posture changes and exercise. *Phlebology.* 1998;13:25-28.

75. Gohel M S, Heatley F, Liu X, Bradbury A, et al. A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med.* 2018;378:2105-2114.

76. Li Y, Zhou H, Ning Y, Wan B, Zhu Y. Efficacy of point-of-care drainage surgery in chronic venous insufficiency of the lower extremities with lipodystrophy. *China Clin Med.* 2015;22:218-221.

77. Sun H. Effectiveness of point-of-care drainage surgery in chronic venous insufficiency of the lower extremities with lipid scleroderma. *Biped Health Care.* 2018;27:90-92.

78. Zhou H, Ma Z, Lu G, Wan B. The effects of percutaneous drainage using tiny incisions on the inflammatory factors in chronic venous insufficiency combined with lipodermatosclerosis of the lower extremities. *Am J Transl Res.* 2021;13(4):2635-2643.

79. Martis G, Laczik R. The role of radical surgery in the management of CEAP C5/C6 and lipodermatosclerosis. *Phlebology.* 2016;31(10):753-768.

80. Whiteley M. Letter regarding the role of radical surgery in the management of CEAP C5/C6 and lipodermatosclerosis. *Phlebology.* 2016;31(10):769.

81. Martis G. Reply letter to the editor, regarding the role of radical surgery in the management of CEAP C5/C6 and lipodermatosclerosis. *Phlebology.* 2016;31(10):770-771.

82. Reina-Gutierrez L, Fernández Solares JI. Clarivein mechano-chemical ablation of the great saphenous vein: technique details and literature review. Article in Spanish. *Angiología.* 2018;70(1):25-32. https://doi.org/10.1016/j.angio.2017.10.002

Phlebolymphology Vol 30 | No.1 | 2023

Treatment of iliofemoral deep vein thrombosis: challenges, opportunities, and future perspectives

Marie Josee E. van Rijn, MD, PhD

Department of Vascular and Endovascular Surgery, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

Jay M. Bakas, MD

Department of Vascular and Endovascular Surgery, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

ABSTRACT

Acute iliofemoral deep vein thrombosis (DVT) is more symptomatic than a thrombosis distal to the common femoral vein and increases the risk of postthrombotic syndrome (PTS), which reduces quality of life, and increases medical costs. To provide the best possible medical care, it all starts with identifying iliofemoral DVT. This will be achievable when visualizing the most upper thrombus part becomes standard practice. Treatment should be done by a multidisciplinary team encompassing lifestyle changes to compression therapy and adequate anticoagulation. In addition, early clot removal may lower the risk of PTS. Knowing which patients will benefit most is still unpredictable. New thrombectomy devices aim to restore patency without the use of thrombolysis. This may lower the threshold to consider a patient for early clot removal but may increase overtreatment. That is why it is equally important to focus future research on establishment of an accurate definition of PTS, a reliable prediction model to identify those who benefit from endovenous treatment, and to standardize postinterventional anticoagulation. Intensive collaboration between medical disciplines must therefore be continued during the complete pathway, from referral to long-term follow-up. In an aging population with a rapid increase in obesity and sedentary lifestyle, prioritizing the need for appropriate care for iliofemoral DVT patients is key.

Keywords

acute deep vein thrombosis
endovenous treatment
mechanical thrombectomy
postthrombotic syndrome
thrombolysis

Phlebolymphology. 2023;40(1):26-34.

www.phlebolymphology.org

Introduction

Approximately a quarter of deep venous thrombosis (DVT) is localized in the iliac and/or common femoral veins (CFV), also referred to as iliofemoral DVT.[1] Acute symptoms and signs of iliofemoral DVT often involve both the upper and lower part of the leg and are more severe compared with a DVT distal to the CFV. Also, the risk for developing chronic complaints related to postthrombotic syndrome (PTS) is increased.[2,3] Various symptoms and signs related to deep venous obstruction and/or reflux may arise, starting from months to even years after the initial DVT.[4] The incurability, chronicity, and severity of symptoms makes it one of the worst long-term complications. Therefore, adequate treatment of iliofemoral DVT involves PTS prevention, beside the acute symptom resolution.
Noninvasive treatment such as compression therapy and adequate anticoagulation, together with lifestyle changes like exercise and weight loss, should always be applied immediately after acute DVT and may also successfully relieve complaints of PTS.[5,6] European Society of Vascular Surgery (ESVS) guidelines recommend an endovenous treatment for symptomatic patients with acute iliofemoral DVT.[7] Beside resolution of acute symptoms and signs, it lowers the risk of PTS and improves quality of life (QOL) compared with noninvasive treatment.[8] However, the reality is that in most hospitals treatment is still only conservative.

The increased use of endovenous treatment has changed the field for acute iliofemoral DVT treatment over the past decades. This article provides an overview of the challenges, opportunities, and future perspectives for these patients.

Deep venous thrombosis

Incidence of acute DVT is approximately 1-2 per 1000 patients per year.[9] Hypercoagulability, stasis, and endothelial damage (Virchow's triad) are key elements in DVT pathophysiology. New insights show many more involving factors like altered flow around the valves generating hypoxia, leading to endothelial activation and triggering adhesion molecules. In turn, there is recruiting of blood cells such as monocytes, neutrophils, and platelets. Monocytes and neutrophils activate coagulation through the extrinsic and intrinsic pathways, favoring thrombus formation and growth, and trapping more cells.[10]

Various risk factors can provoke a DVT, such as hormone therapy, pregnancy, immobilization, thrombophilia, recent surgery, endovenous procedures or placement of central venous catheters, cancer, obesity, and advanced age.[10] An "unprovoked" DVT arises without any preceding risk factors. Distinction between "provoked" and "unprovoked" DVT is important in terms of prognostic and treatment implications.[11] Stopping anticoagulants might be considered after DVT with a transient risk factor, whereas life-long prescription is considered for persistent risk factors and unprovoked DVT.

Impaired blood flow in compression syndromes may also trigger DVT. Left iliac vein compression, caused by the May-Thurner syndrome (MTS), explains why most iliofemoral DVTs are left-sided.[12] The attributing risk of MTS to DVT, and whether it counts as a "provoking factor," is unclear.

Anatomical sites of a DVT are divided into the calf veins, popliteal vein, femoral vein, CFV, and iliac veins with or without the inferior vena cava (IVC).[13] An iliofemoral DVT without thrombus below the groin is uncommon. Therefore, the term "proximal" DVT can be misleading and should be avoided.[13]

Diagnostics

Management of suspected DVT starts with the assessment of patient history and physical examination. These factors are used to estimate the probability of acute DVT by using the Wells score. A D-dimer test and/or duplex ultrasound (DUS) can be added next.[14,15] The preferred imaging modality for suspected DVT is DUS, but its accuracy depends on the technique used and the ultrasonographers' experience. Combined color Doppler techniques have optimal sensitivity, whereas compression has optimal specificity for detecting DVT.[16] Ideally, both techniques should be applied. In addition, 2 ultrasound assessments are practiced: 2- or 3-point compression scanning, and whole-leg ultrasound scanning. Both techniques may miss iliofemoral DVT when the upper thrombus part is not visualized. If thrombus is present in the femoral vein or CFV, the iliac veins should be visualized as well, with additional computed-tomography venography (CTV) or magnetic resonance venography (MRV) if DUS is inconclusive.[17]

Intravascular ultrasound (IVUS) is an increasingly performed imaging modality to visualize the extent of venous lesions during intervention for both acute and chronic cases.[18] Because of its invasive nature, IVUS should not be used

purely as a diagnostic. Peri-interventional use of IVUS provides useful complementary information, as multiplanar venography might underestimate the amount of residual thrombus during performance of a clot removal technique (*Figure 1*), as well as residual obstruction.[19] Also, IVUS discriminates between acute and chronic clots, the latter being more echogenic, surrounded by a thickened vein wall.[20] However, the recommendation for IVUS use during endovenous treatment is weak because the uncertain clinical and economic benefits require validation from randomized controlled trials (RCTs).[21]

Recently, a risk score was developed to distinguish iliofemoral DVT from all other suspected DVTs, with 77% sensitivity and 82% specificity.[22] The model includes D-dimer levels, Wells score, age, and anticoagulation therapy, and may help to prioritize patients for immediate imaging to confirm or exclude iliofemoral DVT.

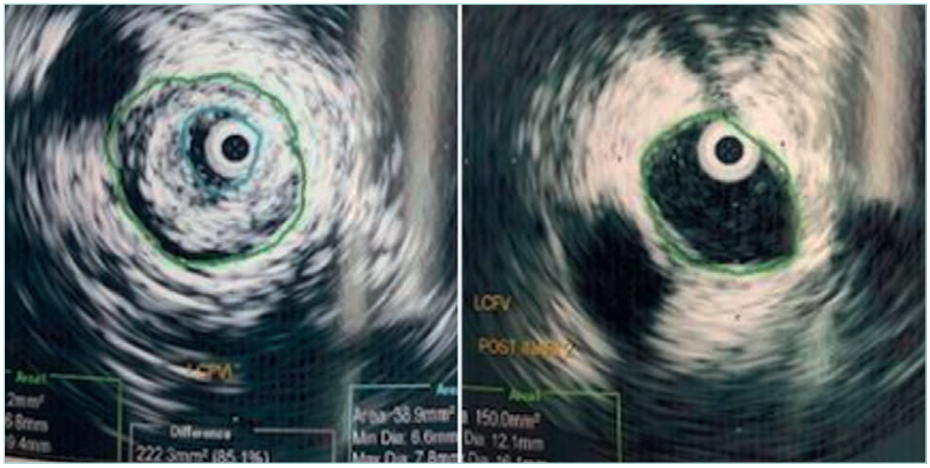


Figure 1. Peri-interventional intravascular ultrasound before and after thrombus removal at the level of the common femoral vein. *Left panel (within the green circle):* hyperechogenic, older age, clot. *Right panel (within the green circle):* a cleared vein without thrombus.

Postthrombotic syndrome

Localization of DVT is important because thrombus extending into the CFV, iliac veins, and/or the IVC, may be considered for early clot removal.[17] These DVTs are often more symptomatic than DVTs distal from the CFV and have an increased risk for PTS.[2] Various symptoms and signs of impaired venous outflow may arise in PTS, as a result of deep venous obstruction and/or reflux after DVT. It occurs in 20% to 50% of DVT, of which 5% to 10% result in severe PTS. Whereas PTS frequently arises within the first year, it may develop 10 to 20 years after the initial DVT.[4,23] Common symptoms include pain, cramps, heaviness, paresthesia, and pruritis of the leg; common signs are edema, skin changes, redness, and pain during calf compression, with venous ulceration as one of the worst clinical features.[23,24]
Preventing PTS, or reducing the severity, is important as PTS decreases QOL and imposes a burden on the health care system through high medical costs, lost workdays, and job loss.[23] Optimized anticoagulation, compression therapy, lifestyle changes (eg, exercise and weight loss), and early thrombus removal may restore vessel and valve patency, thereby preventing (recurrent) DVT and worsening of PTS.

Various PTS scoring systems are available. The Villalta score combined with a venous disease–specific QOL score is the recommended golden standard[25]; however, PTS definition and classification should be further optimized. The ideal scoring system is easy to use, reliable, and objective. It should take into account the broad spectrum of PTS manifestation, such as venous claudication,[26] and exercise intolerance,[27] which are both absent in current PTS scores.

Endovenous treatment

The ESVS guidelines on the management of venous thrombosis (2021) recommend considering early thrombus removal for selected patients with symptomatic iliofemoral DVT, a class IIa, level A recommendation.[7] The recommendation is based on reduced PTS risk after early clot removal for iliofemoral DVT. However, in most hospitals, treatment is still mainly conservative. Four randomized-controlled studies—TORPEDO (Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion), CaVenT (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis), ATTRACT (Acute venous Thrombosis Thrombus Removal with Adjunctive Cather-directed Thrombolysis),

and CAVA (Catheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT)—are randomized between i) oral anticoagulants only; and ii) early thrombus removal with catheter-directed thrombolysis (CDT), combined with (pharmaco)mechanical thrombectomy (PMT), and/or percutaneous transluminal angioplasty and stenting.[28-31] A meta-analysis showed that early thrombus removal was more effective than anticoagulation alone in preventing PTS (relative risk [RR] 0.67; 95% confidence interval [CI]: 0.45-1.00; *P*=0.05), but unfortunately with an increased major bleeding risk (RR: 5.68; 95% CI: 1.27–25.33; *P*=0.02).[17] An increased risk reduction for PTS after endovenous treatment was shown during long-term follow-up of the CaVenT and CAVA trials,[29,32] indicating the added impact of early clot removal over time.

Venous stenting in addition to clot removal is successful in terms of venous patency with primary, assisted-primary, and secondary patency rates between 74% and 95%, 90% and 95%, and 84% and 100%, respectively after 12 months.[33,34] Venous stenting should open up compression points or obstructed segments from earlier (asymptomatic) thrombotic events. Restoring venous patency is believed to lower the risk of re-thrombosis, although no RCT has been performed to confirm this. High patency and low migration rates suggest that there is little harm in performing additional stenting.[33,34] At the least, 12% of all DVTs would be eligible for early clot removal[13]; however, overtreatment should be avoided. Patients are frequently symptomatic in the acute phase, but only a portion develop PTS over time. A prediction system is therefore needed to optimize patient selection for endovenous treatment.

Less-invasive treatment methods, such as compression therapy and daily walking, should always be encouraged to prevent PTS, stimulate venous recanalization, and increase inflow in case venous intervention is indicated during follow-up.[35,36] Thrombectomy devices that are used without thrombolysis are dealing with the bleeding risks of endovenous treatment.[37] These devices are able to shorten hospitalization, as they aim to clear the veins in a single session (*Figure 2*). Patients can therefore be discharged the next day, preferably after confirming patency, but even same-day discharge might be possible.[38] The largest prospective series is the CLOUT registry (ClotTriever® Outcomes, Inari Medical, Irvine, CA). In 250 patients (82% iliofemoral and/or caval DVT), no thrombolytics were used and 99.6% were treated in a single session. At 6 months, 24% of patients had PTS and all clinical outcomes improved, including the Revised Venous Clinical Severity Score, the numeric pain rating scale, and the EuroQoL Group 5-Dimension Self-Report Questionnaire.[37] *Figure 3* shows a ClotTriever® device with extracted thrombus in it.

Early clot removal, using either PMT or CDT, is cost-effective and falls below the United Kingdom National institute threshold for cost-effectiveness.[39] An incremental cost-effective ratio of US $20 000 per quality-adjusted life year makes CDT a cost-effective alternative to conservative treatment of iliofemoral DVT.[40] However, the long-term cost-effectiveness is higher for PMT than CDT.[41] Lower costs for PMT compared with CDT are likely to be caused by shorter length of hospitalization and less invasive surveillance.[42]

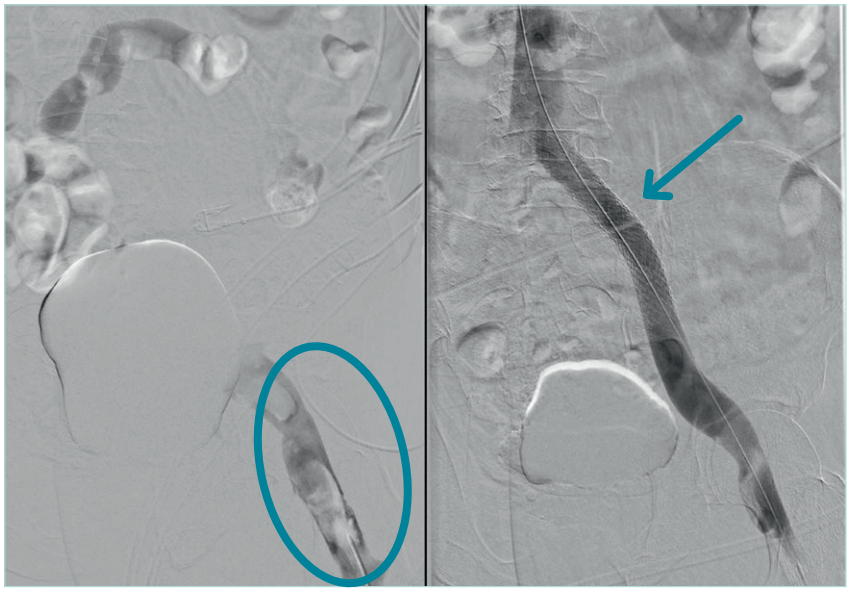


Figure 2. Venography in patient with acute deep vein thrombosis with complete occlusion of the iliac veins, before and after mechanical thrombectomy with ClotTriever® followed by venous stenting of the common iliac vein to overcome compression at the May Thurner point. *Left panel:* a stop of contrast/flow proximal from the common femoral vein (CFV), with visible thrombus (blue circle) in the CFV. *Right panel:* open common femoral and iliac veins and a stent (blue arrow) in the common iliac vein.

Figure 3. Mechanical thrombectomy device (ClotTriever®) with extracted thrombus.

Thrombus age

Thrombus age is critical for treatment success because older collagen-rich thrombi are less susceptible to lysis than younger fibrin-rich thrombi.[43] Mean thrombolysis duration for >90% thrombus resolution was 23 hours for acute, 43 hours for subacute, and 85 hours for old clots.[44] CDT was almost 11 times more successful for acute and subacute clots than for older thrombi (odds ratio [OR]: 10.7; 95% CI: 2.1-55.5). Thrombus age was defined using MRV. Acute DVT was defined as an enlarged dilated vein with hypointense signal intensity surrounded by a thin rim of contrast; subacute DVT, as an enlarged dilated vein with heterogeneous signal intensity surrounded by a thick rim of contrast; and older DVT, as a normalized caliber vein with heterogeneous and/or hypointense material without an evident rim of contrast and no apparent edema.[45]

The most reliable DVT-staging method before endovenous treatment is unknown. Both magnetic resonance imaging and ultrasound elastography were previously used to distinguish between acute and chronic DVT, but the optimal method in terms of accuracy, cost-effectiveness, and reproducibility is yet to be found.[46] The CLOUT registry showed that chronicity assessed using symptom duration alone mismatched morphology-based chronicity in 55.1% of limbs (P<0.0001), with 49.0% being more chronic than symptom duration suggested. Chronicity assessed using imaging mismatched the morphology chronicity in 17.5% of limbs (P<0.0001).[38] Mechanical thrombectomy might lower the need for pre-interventional clot staging because of its favorable effectiveness of thrombus removal at various stages.[37]

Technical aspects

Open thrombectomy is performed by venotomy in the CFV with a Fogarty embolectomy catheter to evacuate the thrombus proximally and manual massage of the entire leg to evacuate the thrombus distally, or over-the-wire catheterization in the direction of the foot, passing the valves, and then performing a thrombectomy. Open thrombectomy improves patency and reduces PTS compared with anticoagulant therapy alone.[47] Patency after 10 years was 83% compared with 41% after anticoagulant therapy only (P<0.05). However, the open technique has become less popular with percutaneous options readily available.

Percutaneous techniques can be divided into CDT, mechanical thrombectomy, and PMT. *Table I* provides an overview of devices used for early thrombus removal in the venous system.[48] Often, the popliteal vein is punctured for access under DUS guidance. However, depending on the technique used and the thrombus extent, veins distal from the popliteal vein can be used for access too (for PMT devices with a small sheath size or for CDT), as well as the internal jugular vein (in case of deep femoral vein catheterization), or the CFV (up and over to catheterize the deep femoral vein, or if only the iliac or IVC is thrombosed). When choosing the puncture site, physicians should always anticipate venous stenting. Determining the degree of clot removal can be estimated using multiplanar venography during all different

Company (alphabetical)	Product
Abbott®	• Jeti
AngioDynamics®	• AlphaVac System
BD Interventional®	• Aspirex Mechanical Aspiration Thrombectomy System
Boston Scientific Corporation®	• AngioJet Thrombectomy Catheter: Solent Omni, Proxi, ZelanteDVT, ClotHunter, and PE • Ekos and Ekos+
Control Medical Technology®	• Control Mechanical Thrombectomy System • Control Mechanical Aspirator
Inari Medical®	• ClotTriever System • FlowTriever System
Penumbra, Inc. (Peripheral Vascular)®	• Indigo System • Indigo System with Lightning Aspiration
Philips®	• QuickClear Mechanical Thrombectomy System
Thrombolex, Inc.®	• Bashir Endovascular Catheter and S- B Endovascular Catheter
Truvic, Inc.®	• Prodigy Thrombectomy System

Table I. Devices for early thrombus removal in the venous system.
Based on reference 48: Endovasc Today. https://evtoday.com/device-guide/us/mechanical-thrombectomythrombolysis

techniques, but IVUS might be more accurate. The same is true for determining whether postthrombotic obstruction and/or compression syndromes have contributed to DVT and should be considered for stenting.[19] Intravenous heparin is administered during intervention. Immediately after cessation of the procedure, low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOAC) should be prescribed to prevent re-thrombosis of cleared segments. Vitamin-K-antagonists (VKA) may be started as well, after bridging with LMWH. As soon as possible, patients should be encouraged to walk. Pneumatic compression devices stimulate venous return if patients are not mobilizing after the procedure. As long as the leg is swollen, compression therapy should be applied. After clots are completely removed and leg circumference is decreased, continuing compression therapy mainly depends on patient preference.

Surveillance

Iliofemoral DVT may cause valve destruction (reflux) or scarring of the vein (obstruction), leading to PTS. Monitoring symptoms and signs of PTS during surveillance is important because PTS might develop within months to even years.[4] Treatment of PTS focuses on improving symptoms and signs, in the absence of a curative treatment.[5] The incurability of PTS and severity of symptoms and signs emphasize the importance of preventing it from the start.

Optimal anticoagulation, immediate mobilization, and compression therapy are first-line strategies for PTS prevention, but evidence for its efficacy is weak.[6] Wearing elastic compression stockings (ECS) for at least 2 years was found to lower PTS incidence compared with patients who stopped wearing ECS.[49] However, wearing ECS for at least 6 months followed by individualized extension of treatment duration is noninferior to the standard 2 years in terms of PTS prevention, as shown by the IDEAL trial (Ideal Deep Venous Thrombosis Study).[50]

Venous (stent) patency, residual obstruction, and venous reflux are evaluated using DUS. Peak flow velocity is combined with flow pattern analysis to diagnose, or rule out, stent occlusion and stenosis.[51] If DUS is inconclusive, additional CTV should be considered, or even more invasive imaging like venography or IVUS with immediate intervention, when the suspicion of loss of patency is high. Stent patency could be referred to as primary patency, secondary patency, or permanent stent occlusion. Primary patency is the percentage of open stents without reintervention. Secondary patency is the percentage of open stents after reintervention. Permanent stent occlusions are occluded stents without further options to restore stent patency. Anticoagulant therapy compliance, thrombus burden, and poor venous flow are risk factors for reintervention.[52] Reinterventions should ideally be prevented, or performed before vessel occlusion.[52] Usually, follow-up is intensified in the first weeks after intervention, gradually diminishing (after uncomplicated procedures) over time until once a year or once every other year.

Anticoagulation therapy

Evidence-based guidelines providing optimal anticoagulant therapy after venous stenting are lacking.[53] Patients usually receive a DOAC, or LMWH switched to a VKA. Adjunctive use of antiplatelet agents does not seem useful, based on the underlying pathophysiology and clinical experience.[54] It did not affect outcomes after venous stenting for acute DVT, including recurrence of DVT, patency, incidence of PTS, and restenosis.[55]

Effectiveness and safety of postinterventional treatment with DOAC and VKA is similar for acute DVT patients[56]; however, treatment with VKA provides time within therapeutic range, providing information about compliance. Anticoagulation therapy is considered for at least 3 to 6 months after acute DVT in general. Extension of treatment duration with anticoagulants depends on the presence or absence of provoking DVT factors.[57] Anticoagulants might be stopped if a transient provoking factor is present. Hypothetically, the introduction of venous stenting has transformed MTS into a "transient" factor. The ESVS guidelines recommend that duration of anticoagulant therapy after early thrombus removal (with or without venous stenting) should be based on the primary indication for anticoagulation and judged by the treating physician.[17] Evidence supporting the optimal length of anticoagulant treatment after successful venous stenting is lacking.

Challenges, opportunities, and future perspectives

Iliofemoral DVT increases the risk for PTS, a devastating, lifelong syndrome that lowers QOL and burdens the health care system.[23] Optimal treatment is key in preventing PTS, but several hurdles still need to be overcome. First of all, patients with an iliofemoral DVT should be identified. Physicians involved in the diagnostic phase of DVT should therefore be trained to always visualize the upper thrombus part. Next, these patients need to get referred to expert centers to discuss all treatment options, including early clot removal. This requires better, more intensive collaboration between vascular surgeons, interventionalists, phlebologists, dermatologists, internal medicine doctors, and general practitioners. The reality, however, is that most hospitals still only consider a conservative treatment for these patients.

Fortunately, (deep) venous disease is getting increased interest at conferences around the world. Increased awareness is also achieved through social media, at the level of physicians and by patients themselves. Interests from different medical specialists brings the opportunity for optimized care in a multidisciplinary approach.

Next, an objective, reliable, and easy to use scoring system for definition and classification of PTS should be developed, taking into account ''typical'' signs and symptoms, but also complaints such as exercise intolerance and venous claudication.[17] Studies aiming to prove benefits of early clot removal should have a much longer follow-up than the typical first year, as PTS may take years to develop.[4] New studies should also overcome the flaws of previous RCTs like low technical success, low rate of stenting, the use of nondedicated venous stents, and the absence of DUS follow-up.

Another challenge is motivating healthy lifestyles in an aging population with a rapid increase in obesity and a sedentary lifestyle. Lifestyle education is a huge part of patient care. With increased popularity of activity-tracking devices, motivation for exercise may become more easily accessible, as well as more playful and fun.

Opportunities arise from the evolution of new devices, presumably lowering the threshold for considering endovenous treatment. Aspiration devices without thrombolysis should, ideally, shift endovenous treatment to a low-risk technique, which also seems feasible for management of older thrombi.[37,38] The DEFIANCE trial randomizes between mechanical thrombectomy with the ClotTriever® and anticoagulation only and will hopefully further reveal the impact of early clot removal on PTS prevention. Another exciting discovery is the involvement of inflammation and microRNAs in the pathophysiology of DVT, which might lead to therapeutic targets for drug development.[10]

Clinicians must aim to give (iliofemoral) DVT patients a clot- and PTS-free future, with joined forces from all medical specialties involved. Venous thrombosis patients deserve just as much attention as those with arterial occlusions. With so many new and exciting developments in the field of acute iliofemoral DVT, it is our strong belief that this can and will happen.

CORRESPONDING AUTHOR

M. J. E. van Rijn

Department of Vascular and Endovascular Surgery, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

EMAIL: *m.vanrijn@erasmusmc.nl*

References

1. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med*. 2008;149(10):698-707.
2. Tick LW, Kramer MH, Rosendaal FR, Faber WR, Doggen CJ. Risk factors for post-thrombotic syndrome in patients with a first deep venous thrombosis. *J Thromb Haemost*. 2008;6(12):2075-2081.
3. Bikdeli B, Caraballo C, Trujillo-Santos J, et al. Clinical presentation and short- and long-term outcomes in patients with isolated distal deep vein thrombosis vs proximal deep vein thrombosis in the RIETE registry. *JAMA Cardiol*. 2022;7(8):857-865.
4. Schulman S, Lindmarker P, Holmström M, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost*. 2006;4(4):734-742.
5. Schleimer K, Barbati ME, Gombert A, Wienert V, Grommes J, Jalaie H. The treatment of post-thrombotic syndrome. *Dtsch Arztebl Int*. 2016;113(50):863-870.
6. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med*. 2004;164(1):17-26.
7. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. *Eur J Vasc Endovasc Surg*. 2022;63(2):184-267.
8. Kahn SR, Julian JA, Kearon C, et al. Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2020;8(1):8-23.e18.
9. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;34(11):2363-2371.
10. Navarrete S, Solar C, Tapia R, Pereira J, Fuentes E, Palomo I. Pathophysiology of deep vein thrombosis. *Clin Exp Med*. 2022 Apr 26. Epub ahead of print. doi:10.1007/s10238-022-00829-w.
11. Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost*. 2016;14(7):1480-1483.
12. May R, Thurner J. The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. *Angiology*. 1957;8(5):419-427.
13. De Maeseneer MG, Bochanen N, van Rooijen G, Neglén P. Analysis of 1,338 patients with acute lower limb deep venous thrombosis (DVT) supports the inadequacy of the term "proximal DVT." *Eur J Vasc Endovasc Surg*. 2016;51(3):415-420.
14. Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb Haemost*. 2005;94(1):200-205.
15. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795-1798.
16. Goodacre S, Sampson F, Thomas S, van Beek E, Sutton A. Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. *BMC Med Imaging*. 2005;5:6.
17. Kakkos SK, Gohel M, Baekgaard N, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. *Eur J Vasc Endovasc Surg*. 2021;61(1):9-82.
18. Woods MA, Knavel Koepsel EM, et al. Intravascular US: applications in interventional radiology. *Radiographics*. 2022;42(6):1742-1757.
19. Murphy EH, Broker HS, Johnson EJ, Modrall JG, Valentine RJ, Arko FR 3rd. Device and imaging-specific volumetric analysis of clot lysis after percutaneous mechanical thrombectomy for iliofemoral DVT. *J Endovasc Ther*. 2010;17(3):423-433.
20. Anne S, Margarita VR, Jeffrey P, et al. Deep vein thrombosis: update on mechanical thrombectomy and intravascular US. *Radiographics*. 2022;42(6):E184-E185.
21. Vedantham S, Desai KR, Weinberg I, et al. Society of Interventional Radiology position statement on the endovascular management of acute iliofemoral deep vein thrombosis. *J Vasc Interv Radiol*. 2023;34(2):284-299.e7.
22. Shekarchian S, Notten P, Barbati ME, et al. A risk score for iliofemoral patients with deep vein thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2022;10(1):33-41.e2.
23. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2014;130(18):1636-1661.
24. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost*. 2009;7(5):879-883.
25. Soosainathan A, Moore HM, Gohel MS, Davies AH. Scoring systems for the post-thrombotic syndrome. *J Vasc Surg*. 2013;57(1):254-261.
26. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. *Ann Surg*. 2004;239(1):118-126.
27. Morris RI, Sobotka PA, Balmforth PK, et al. Iliocaval venous obstruction, cardiac preload reserve and exercise limitation. *J Cardiovasc Transl Res*. 2020;13(4):531-539.
28. Sharifi M, Bay C, Mehdipour M, Sharifi J, Investigators T. Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial: midterm results. *J Endovasc Ther*. 2012;19(2):273-280.
29. Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. *Lancet Haematol*. 2016;3(2):e64-e71.
30. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med*. 2017;377(23):2240-2252.
31. Notten P, Ten Cate-Hoek AJ, Arnoldussen C, et al. Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial. *Lancet Haematol*. 2020;7(1):e40-e49.
32. Notten P, de Smet A, Tick LW, et al. CAVA (Ultrasound-Accelerated Catheter-Directed Thrombolysis on Preventing Post-Thrombotic Syndrome) Trial: long-term follow-up results. *J Am Heart Assoc*. 2021;10(11):e018973.
33. Taha MA, Busuttil A, Bootun R, Davies AH. A systematic review on the use of deep venous stenting for acute venous thrombosis of the lower limb. *Phlebology*. 2019;34(2):115-127.
34. Badesha AS, Siddiqui MM, Bains BRS, Bains PRS, Khan T. A systematic review on the incidence of stent migration in the treatment of acute and chronic iliofemoral disease using dedicated venous stents. *Ann Vasc Surg*. 2022;83:328-348.
35. Amin EE, Bistervels IM, Meijer K, et al. Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. *Blood*. 2018;132(21):2298-2304.
36. Labas P, Ohrádka B, Vladimír J, Cambal M. The home treatment of deep vein thrombosis with low molecular weight heparin, forced mobilisation and compression. *Int Angiol*. 2000;19(4):303-307.

37. Dexter DJ, Kado H, Schor J, et al. Interim outcomes of mechanical thrombectomy for deep vein thrombosis from the All-Comer CLOUT Registry. *J Vasc Surg Venous Lymphat Disord.* 2022;10(4):832-840.e2.

38. Maldonado TS, Dexter DJ, Kado H, et al. Outcomes from the ClotTriever Outcomes Registry show symptom duration may underestimate deep vein thrombus chronicity. *J Vasc Surg Venous Lymphat Disord.* 2022;10(6):1251-1259.

39. Pouncey A, Babigumira J, Johnson O, Black S. Cost utility analysis of treatment modalities for iliofemoral deep venous thrombosis: oral anticoagulation vs. catheter directed thrombolysis and pharmacomechanical thrombectomy. *Eur J Vasc Endovasc Surg.* 2019;58(6):e700.

40. Enden T, Resch S, White C, Wik HS, Kløw NE, Sandset PM. Cost-effectiveness of additional catheter-directed thrombolysis for deep vein thrombosis. *J Thromb Haemost.* 2013;11(6):1032-1042.

41. Li G, Xu M, Xu Z, Sun Y, Zhang J, Zhang X. Cost-effectiveness analysis of AngioJet and CDT for lower extremity deep vein thrombosis among Chinese population. *Clin Appl Thromb Hemost.* 2021;27:10760296211061147.

42. Mahmoud O, Vikatmaa P, Räsänen J, et al. Catheter-directed thrombolysis versus pharmacomechanical thrombectomy for upper extremity deep venous thrombosis: a cost-effectiveness analysis. *Ann Vasc Surg.* 2018;51:246-253.

43. Saha P, Andia ME, Modarai B, et al. Magnetic resonance T1 relaxation time of venous thrombus is determined by iron processing and predicts susceptibility to lysis. *Circulation.* 2013;128(7):729-736.

44. Arnoldussen CWKP, Notten P, Brans R, et al. Clinical impact of assessing thrombus age using magnetic resonance venography prior to catheter-directed thrombolysis. *Eur Radiol.* 2022;32(7):4555-4564.

45. Arnoldussen C, Strijkers RHW, Lambregts DMJ, Lahaye MJ, de Graaf R, Wittens CHA. Feasibility of identifying deep vein thrombosis characteristics with contrast enhanced MR-Venography. *Phlebology.* 2014;29(1 suppl):119-124.

46. Dharmarajah B, Sounderajah V, Rowland SP, Leen EL, Davies AH. Aging techniques for deep vein thrombosis: a systematic review. *Phlebology.* 2015;30(2):77-84.

47. Plate G, Eklöf B, Norgren L, Ohlin P, Dahlström JA. Venous thrombectomy for Iliofemoral vein thrombosis — 10-year results of a prospective randomised study. *Eur J Vasc Endovasc Surg.* 1997;14(5):367-374.

48. Endovasc Today. US device guide/other devices: mechanical thrombectomy/thrombolysis (peripheral/venous). Accessed March 16, 2023. https://evtoday.com/device-guide/us/mechanical-thrombectomythrombolysis

49. Mol GC, van de Ree MA, Klok FA, et al. One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. *BMJ.* 2016;353:i2691.

50. Ten Cate-Hoek AJ, Amin EE, Bouman AC, et al. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. *Lancet Haematol.* 2018;5(1):e25-e33.

51. Sebastian T, Barco S, Engelberger RP, et al. Duplex ultrasound investigation for the detection of obstructed iliocaval venous stents. *Eur J Vasc Endovasc Surg.* 2020;60(3):443-450.

52. Pouncey AL, Kahn T, Morris RI, Saha P, Thulasidasan N, Black SA. Risk factors and classification of reintervention following deep venous stenting for acute iliofemoral deep vein thrombosis. *J Vasc Surg Venous Lymphat Disord.* 2022;10(5):1051-1058.e3.

53. Notten P, van Laanen JHH, Eijgenraam P, et al. Quality of anticoagulant therapy and the incidence of in-stent thrombosis after venous stenting. *Res Pract Thromb Haemost.* 2020;4(4):594-603.

54. Meissner MH. Indications for platelet aggregation inhibitors after venous stents. *Phlebology.* 2013;28(1 suppl):91-98.

55. Eijgenraam P, ten Cate H, Arina J. Venous stenting after deep venous thrombosis and antithrombotic therapy: a systematic review. *Rev Vasc Med.* 2014;2(3):88-97.

56. Sebastian T, Hakki LO, Spirk D, et al. Rivaroxaban or vitamin-K antagonists following early endovascular thrombus removal and stent placement for acute iliofemoral deep vein thrombosis. *Thromb Res.* 2018;172:86-93.

57. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020;4(19):4693-4738.

Phlebolymphology Vol 30 | No.1 | 2023

Cyanoacrylate ablation for chronic venous disease: a review and future applications

Kathleen Ozsvath, MD, FACS

Chief of Surgery, Samaritan Hospital, Troy, New York; Vascular Associates, St Peters Health Partners, Albany, New York; Professor of Surgery, Albany Medical Center, Albany, New York, USA

ABSTRACT

Many endovenous procedural modalities exist today, including endovenous thermal ablation (laser ablation, [EVLT] and radiofrequency ablation [RFA]), nonthermal nontumescent ablation, and ultrasound-guided sclerotherapy (UGS) and chemical ablation. Recently, cyanoacrylate has been used for the treatment of axial insufficiency. The most studied preparation of N-butyl-cyanoacrylate is VenaSeal (Medtronic), which has been compared with the other ablative techniques. These studies have shown excellent results with patient satisfaction, outcomes, and low complication rates. Other cyanoacrylate preparations are being used, including VariClose (Biolas), and VenaBlock (Kalyon) outside the United States, but there are less than a dozen studies to date reporting on these formulations.

There is significant data with VenaSeal showing that post procedural pain was found to be less in patients undergoing ablation with cyanoacrylate than with thermal techniques. VenaSeal has been shown in many studies to be safe, with similar occlusion rates to thermal techniques. In a handful of studies published using VariClose and VenaBlock, closure rates have been shown to be similar to those with thermal techniques as well. Complications unique to cyanoacrylate include hypersensitivity reactions (early and delayed), glue extension, granuloma formation, and phlebitis. These complications are encountered with all 3 preparations of cyanoacrylate.

Nevertheless, cyanoacrylate is considered safe, and excellent results may be expected. Whereas VenaSeal has been extensively studied, and VenaBlock and VariClose have also been compared with thermal techniques, there are no studies to date comparing these 3 preparations with one another. There may be future uses for these compounds that may effectively treat additional venous beds.

Keywords

ablation | cyanoacrylate | pelvic venous disease | varicose veins | varicocele | venous disease | venous ulcer

Phlebolymphology. 2023;40(1):35-39.

www.phlebolymphology.org

Introduction

Venous disorders are the most common vascular disease in developed countries. Up to 40% of women and 17% of men have been reported to have chronic venous insufficiency, and upwards of 70% of women and 56% of men have been estimated to have varicose veins. Patients range in signs and symptoms from aesthetic issues to venous ulceration. Symptoms can include leg pain, aching, itching, bleeding varicosities, and restless legs. The cost of treating patients with venous disease is significant, and the treatment of venous leg ulcers (VLU) is a burden to the health care system. Issues affecting patients include misdiagnosis, incomplete care, limited access, and socioeconomic barriers to care.

Vein stripping and high ligation was the standard of care until approximately 25 years ago with the advent of less-invasive methods, including thermal ablation techniques. In the United States, thermal treatment is now regarded as standard of care. Treatment modalities include radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). Ultrasound-guided foam sclerotherapy (UGFS) has also gained popularity among providers with slightly lower closure rates and higher risks of deep venous thrombosis (DVT) as compared with other modalities, including thermal ablation of the saphenous veins. Newer techniques evolved including pharmacomechanical treatment (also known as mechanochemical ablation [MOCA]) with ClariVein.

Cyanoacrylate closure (CAC) of refluxing veins was developed in Europe. Initially known as Sapheon, the proprietary glue is now commercially available from Medtronic under the name of VenaSeal. The product has been well studied in the United States and has shown great promise in the field of superficial venous treatment. VenaSeal has been used to treat saphenous axial reflux[1] and may have future uses in other veins and tributaries and other venous beds. It is the most viscous with the longest polymerization time. Other cyanoacrylate formulations have been developed in Turkey, including VenaBlock and VariClose. VenaBlock is designed to be administered for catheter-directed as well as percutaneous injection. It has a very rapid polymerization time. A lighted catheter tip purportedly allows for better visualization. VariClose is the least viscous with a faster polymerization time than VenaSeal. Currently, VenaBlock and VariClose are not approved for use in the United States. There is growing evidence that these newer compounds may be efficacious as well in the treatment of refluxing veins.

In this article, we review the literature on VenaSeal as well VenaBlock and VariClose—2 compounds manufactured in Turkey and that are not available in the United States. It also includes a literature review on possible additional uses of cyanoacrylate in other applications within the venous system.

Results

VenaSeal is the most studied cyanoacrylate in the literature. The Turkish compounds have much fewer studies available to date. Similar closure rates and patient satisfaction have been found with the available cyanoacrylate products. No studies have been done to compare VenaSeal with VenaBlock or VenaClose. Complications, including hypersensitivity reactions (HSR), exist for all 3 formulations. New applications on the horizon include the treatment of perforator veins. Other venous beds treated with cyanoacrylate include the treatment of varicocele, pelvic veins, and bleeding gastrointestinal varices.

Discussion

In 2019, Almeida et al treated 38 patients with VenaSeal. They found occlusion rates of 94.7% at 36-month follow-up. No adverse complications were noted.[2] The multicenter, prospective eSCOPE study (European Sapheon Closure System Observational ProspectivE) showed occlusion rates of 92.9% at 12 months. There was significant improvement in quality of life (QOL) and in venous clinical severity scores (VCSS) at 12 months. Of 70 patients treated, 1 patient had phlebitis and 1 had thrombus extension beyond the saphenofemoral junction.

In a meta-analysis of 4 studies that included 378 patients undergoing CAC and 590 patients undergoing RFA, the authors found that CAC was comparable to RFA regarding closure rates, pain, VCSS, and Aberdeen Varicose Vein Questionnaire (AVVQ) scores in patients with incompetent saphenous veins.[3] The CAC group had lower ecchymosis and paresthesias than the RFA group. In a systematic review by Farah et al, CAC was found to have better QOL and lower risk of recurrence and of complications than thermal ablation techniques.[4] The multicenter, randomized control trial VeClose (VenaSeal Sapheon Closure System Pivotal Study) confirmed the results of the eSCOPE trial[5,6]; both show CAC to not be inferior to RFA. Kolluri et al reported a network meta-analysis comparing VenaSeal with other therapies.[7] The authors compared CAC

with RFA, EVLA, sclerotherapy, MOCA, and surgery. VenaSeal was found to be superior to surgery and to other comparators. VenaSeal was found to have the least probability of a number of adverse events and to be superior to all the other therapies in pain reduction scores and QOL measures.

The use of VenaSeal was found to be safe and effective in 37 Asian patients undergoing ablation for venous ulceration. All of the ulcers healed after the procedure.[8] In another study, the authors retrospectively analyzed 170 small saphenous veins treated with VenaSeal in an Asian population with an occlusion rate of 96.3% and no noted complications.[9] O'Banyion et al retrospectively compared CAC (via VenaSeal) (N=51) with RFA (N=68) in patients with venous ulcers. They found the ulcers in the CAC arm had faster healing and longer ulcer-free intervals than the RFA arm.[10] These results suggest that ablation by CAC is as efficacious as RFA in the venous ulcer population.

Although VenaSeal and VariClose have similar properties, VariClose has a faster polymerization rate (*Table I*[11]). Additionally, there is a difference in delivery of these cyanoacrylate formulations—VariClose is a continuous delivery of the glue, whereas VenaSeal is segmental (*Table I*). In a single-center trial, 310 patients were treated with either CAC (via VariClose) or EVLT. They found the operative time to be shorter and the procedural pain to be less with CAC.[12] Delivery of VenaBlock is via a pulse-system endovenous application of the glue. In a retrospective review, Yavuz et al investigated use of the VenaBlock catheter for embolization of incompetent greater saphenous veins in 538 patients. They found an improved QOL after treatment and no significant complications.[13] Differences in viscosity among these 3 formulations is important to note as well (*Table I*). VenoSeal is more viscous than the other 2 formulations, with a longer polymerization rate, and the glue is administered segmentally, with manual compression between the segments treated. The Turkish formulations are less viscous, which runs the risk of glue potentially spilling into the deep system. However, these are faster in delivery, as the polymerization is much faster (*Table I*), and tout a faster treatment time, though this has not been directly studied. Unfortunately, VariClose and VeniBlock have been studied less than VenaSeal, and most of those studies compare the formulations with thermal ablation. Thus, for differentiation between these formulations, prospective randomized trials are lacking.

	VariClose	VenaBlock	VenaSeal
Country	**Turkey**	**Turkey**	**USA**
FDA approval	No	No	Yes
Consistency	Low viscosity	Low viscosity	High viscosity
Distance from SFJ	3 cm	3 cm	5 cm
Speed of polymerization	<5 seconds	<5 seconds	20 seconds
Delivery	Continuous	Pulsed system Has a red-lighted tip	Segmental

Table I. Cyanoacrylate formulations.
Based on reference 11: Bissaco et al. *Minim Invasive Ther Allied Technol*. 2019;28(1):6-14.

Complications

Hypersensitivity reaction

Type IV HSR is a delayed-type hypersensitivity that is a T-cell–mediated immune response occurring within 24-48 hours. Gibson et al reported a 6% frequency of hypersensitivity in patients treated with VenaSeal. They found 4.3% were mild, 1.3% were moderate, and 0.3% were severe. The patients with moderate HSR were treated with steroids; some had need for recurrent steroid treatment. The patient with the severe reaction had multiple recurrent reactions and ultimately had the vein removed surgically.[14] Phlebitis-like allergic reaction (PLAR) was described by Park et al.[15] They described PLAR as any skin condition that is sudden and presenting as erythema, itching, swelling, and pain over the treated veins. They recommend using antihistamines and steroids to manage this type IV HSR. As more papers are published regarding hypersensitivity to CAC, it is evident that those patients who are suspected to be at risk for hypersensitivity should avoid treatment with CAC. Allergic reactions will occur in a small subset of treated patients, no matter what formulation is used.

Granuloma

Sermsathanasawadi et al reported cyanoacrylate granuloma in 2.3% of great saphenous veins after CAC treatment.[16] All patients in that study underwent incision, drainage, and removal of the glue.[16] This led to a change in the instructions from Medtronic in regard to VenaSeal. Recapturing the tip of the catheter to minimize the extravasation of glue into the surrounding tissue is important. The thought is that the risk of granuloma formation is mitigated.

Other uses of cyanoacrylate

In lower-extremity venous disease, cyanoacrylate is a novel treatment for the treatment of pathologic perforator veins. In a study by Mordhorst et al, the authors treated 83 perforator veins in 62 patients with CAC injected directly into the perforator. They found no cases of DVT. More than half of the patients did receive additional sclerotherapy. The authors found 100% initial closure rate; however, in the second follow-up, they had an 86% closure rate.[17] In a study by Prasad et al, 191 perforators were treated in inpatients with ulceration. All healed within 3 months of treatment.[18] There may be concern that the application of direct pressure on the treated vein is sometimes difficult with these procedures, and technical success may be hindered. Given the thermal options for perforator treatment, CAC is certainly easier to use and less painful in a difficult anatomic area. Another concern is that glue could enter the deep system, leading to DVT. As practitioners improve their technique, this may be less of an issue.

There are reports of successful embolization of varicoceles using CAC as well. Urbano et al studied 41 patients with varicocele who were treated with cyanoacrylate as an embolic agent.[19] The authors surmise that there is less pain compared with patients treated with sclerosants.[19] There are no prospective randomized trials comparing cyanoacrylate with sclerosant with or without coil embolization, or open surgery, in the treatment of varicoceles.

Female pelvic venous disease is less understood and less treated, especially in the United States. Without published prospective, randomized studies, insurance companies deny treatment and consider it "experimental." If better techniques can be developed that can show alleviation of pelvic pain, regression of vaginal/labial varicosities, and improvement in lower-extremity pain, it is hoped that care would be more available. In a study by Lorenzo et al, 29 out of 30 women were treated with bilateral ovarian vein embolization for pelvic venous disease.[20] They reported no access-related complications, nontargeted embolization, or migration of the glue. At 1 year, pain upon standing, dyspareunia, and menstrual pain was greatly diminished. This study is a single-arm, nonblinded, nonrandomized trial. More research needs to be done to better evaluate the use of CAC in this patient population.

Cyanoacrylate has been used as an embolic agent in interventional radiology, interventional neuroradiology, and in the treatment of arteriovenous malformations, portal venous disease (gastric varices), and in aneurysms. Gastric varices have been treated with cyanoacrylate with some reported success. Treatment of the periprostatic venous plexus in patients with erectile dysfunction from venous leakage has been successful with CAC.[21]

Table II briefly summarizes treatment methods for venous pathologies mentioned in this section, for which cyanoacrylate may prove to be helpful. Future development of technique and further investigation will help guide treatment of venous disease for which present treatments do not deliver consistent outcomes.

	Injection of sclerosant	Thermal ablation	Cyanoacrylate	Open surgery
Pathological perforators	Ultrasound-guided sclerotherapy	Both laser and RFA	Few published studies	Mostly abandoned given morbidity
Pelvic venous disease	In combination with coil embolization	NA	Few studies available	Performed with specific indications only
Varicocele	In combination with coil embolization	NA	Few studies available	Traditionally performed

Table II. Treatment of venous pathology: cyanoacrylate may prove to be very helpful.
Abbreviations: NA, non applicable; RFA, radiofrequency ablation.

Conclusion

In choosing the best methods for treatment of axial reflux, physicians must also take into account the cost and reimbursement. In the United States, not all insurers will pay for CAC, stating it is experimental, despite growing research confirming its efficacy. A novel use for CAC in the future includes treatment of perforators, which may prove to be less cumbersome than other modalities of treatment. It would certainly be less painful as there is no need for tumescent anesthesia with injection of cyanoacrylate. There are small case studies and series reported in the literature to date. Treatment of pelvic venous disease in both men and women must be further studied. With the advent of standardized treatment options, venous specialists will be able to offer better treatments to their patients. Deciding upon the best technology is difficult as technology is evolving. Which glue formulations are better than others remains to be understood. Presently, there are no studies comparing VenaSeal with VariClose or VenaBlock; however, studies comparing VariClose and VenaBlock with thermal ablation have shown higher recanalization rates. Research is lacking presently, but as formulations and delivery systems improve and the techniques become standardized, patient care will continue to evolve.

References

1. Belramman A, Roshan Bootun R, Lane TRA, Davies AH. Endovenous management of varicose veins. *Angiology*. 2019;70(5):388-396.
2. Almeida JI, Javier JJ, Mackay E, Bautista C, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. *J Vasc Surg Venous Lymphat Disord*. 2013;1(2):174-180.
3. Chen MS, Shuangmeng Mou BS, Gengwu Dai BS, Jinliang Hu MS. Comparison between cyanoacrylate embolization and radiofrequency ablation for superficial venous incompetence: a systematic review and meta-analysis. *Dermatol Surg*. 2021;47(8):e214-e219.
4. Farah MH, Tarek Nayfeh MH, Urtecho M, et al. A systematic review supporting the Society for Vascular Surgery, the American Venous Forum, and the American Vein and Lymphatic Society guidelines on the management of varicose veins. *J Vasc Surg Venous Lymphat Disord*. 2022;10(5):1155-1171.
5. Morrison N, Kolluri R, Vasques M, Madsen M, Jones A, Gibson K. Comparison of cyanoacrylate closure and radiofrequency ablation for the treatment of incompetent great saphenous veins: 36 month outcomes of the VeClose randomized controlled trial. *Phlebology*. 2019;34(6):380-390.
6. Proebstle TM, Alm J, Dimitri S, et al. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2015;3(1):2-7.
7. Kolluri R, Chung J, Kim S, et al. Network meta-analysis to compare VenaSeal with other superficial venous therapies for chronic venous insufficiency. J *Vasc Surg Venous Lymphat Disord*. 2020;8(3):472-481.
8. Chan SSJ, Yap CJQ Tan SG, et al. The utility of endovenous cyanoacrylate glue ablation for incompetent saphenous veins in the setting of venous leg ulcers. *J Vasc Surg Venous Lymphat Disord*. 2020;8(6):1041-1048.
9. Cho J, Joh JH. Cyanoacrylate closure of small saphenous vein insufficiency. *DermatoL Surg.* 2021;47:(3):381-384.
10. O'Banyion LA, Reynolds KB, Kochubey M, et al. A comparison of cyanoacrylate glue and radiofrequency ablation techniques in the treatment of superficial venous reflux in CEAP 6 patients. *J Vasc Surg Venous Lymphat Disord.* 2022;9(5):1215-1221.
11. Bissacco D, Stegher S, Callian FM, Viani MP. Saphenous vein ablation with new cyanoacrylate glue device: a systematic review on 1000 cases. *Minim Invasive Ther Allied Technol.* 2019;28(1):6-14.
12. Bozkurt AK, Yilmaz MF. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. *Phlebology.* 2016;31:106-113.
13. Yavuz T, Acar AN, Aydın H, et al. A retrospective study of a new n-butyl-2-cyanoacrylate glue ablation catheter incorporated with application guiding light for the treatment of venous insufficiency: twelve-month results. *Vascular.* 2018;26:547-555.
14. Gibson K, Minjarez R, Rinehardr E, Ferris B. Frequency and severity of hypersensitivity reactions in patients after VenaSeal cyanoacrylate treatment of superficial venous insufficiency. *Phlebology.* 2020;35(5):337-344.
15. Park I, Jeong MH, Park CJ, Park W, Park DW, Joh JH. Clinical features and management of ''phlebitis-like abnormal reaction'' after cyanoacrylate closure for the treatment of incompetent saphenous veins. *Ann Vasc Surg.* 2018:1-7.
16. Sermsathanasawadi N, Pruekprasert K, Chinsakchai K, Wongwanit C, Ruangsetakit C. Cyanoacrylate granuloma after cyanoacrylate closure of incompetent saphenous veins. *Dermatol Surg.* 2021;47(10):1372-1375.
17. Mordhorst A, Yang GK, Chen JC, Lee S, Gagnon J. Ultrasound guided cyanoacrylate injection for the treatment of incompetent perforator veins. *Phlebology.* 2021;36(9):752-760.
18. Prasad K, Joy B, Toms A, Sleeba T. Treatment of incompetent perforators in recurrent venous insufficiency with adhesive embolization and sclerotherapy. *Phlebology.* 2018;33(4):242-250.
19. Urbano J, Cabrera M, Alonso-Burgos A. Sclerosis and varicocele embolization with N-butyl cyanoacrylate: experience in 41 patients. *Acta Radiol.* 2014;55(2):179-185.
20. Lorenzo JIL, Madueno GG, Peral AA, Rodriquez EP, Santos RC, Burgos AA. Bilateral ovarian vein embolization from a unilateral basilic approach with n-2-butyl cyanoacrylate and crossover technique for pelvic congestion syndrome. *Eur J Vasc Endovasc Surg.* 2021;63(1):163-164.
21. Rebonato A, Auci A, Sanguinetti F, et al. Embolization of the periprostatic venous plexus for erectile dysfunction resulting from venous leakage. *J Vasc Inter Radiol.* 2014;25(6):866-872.

CORRESPONDING AUTHOR

Kathleen Ozsvath, MD

St Peters Health Partners,
Vascular Associates, 2 New Hampshire,
Troy, New York 12180, USA

EMAIL: Kathleen.Ozsvath001@sphp.com

Phlebolymphology Vol 30 | No.1 | 2023

Chronic pelvic pain and pelvic venous disorders: the gynecologist's point of view

Aleksandra Jaworucka-Kaczorowska, MD, PhD

Center of Phlebology and Aesthetic Medicine, Center of General and Vascular Surgery, Gynecology and Obstetrics "Jaworuccy", Gorzów Wlkp, Poland

ABSTRACT

Chronic pelvic pain (CPP) is a very common symptom with multiple potential etiologies. Very often, it is the result of an overlap of several pain-generating disorders of the reproductive tract, gastrointestinal system, urological organs, musculoskeletal system, and psychoneurological system. Living with CPP carries a heavy economic and social burden. Due to the complex etiology of CPP, to achieve good treatment results, the approach should be multimodal and requires a cooperative interdisciplinary team of clinicians, including gynecologists, vascular surgeons or phlebologists, interventional radiologists, gastroenterologists, urologists, physiotherapists, and psychologists. All the potential etiologies should be checked and ruled out before establishing the treatment modality. Central pain sensitization should also be considered. Appropriate management from the first presentation can improve health-related quality of life, work productivity, and health care utilization and reduce an endless series of referrals, investigations, and inappropriate treatment. This article presents the potential etiologies of CPP with a primary focus on gynecological issues, including pelvic venous disorders (PeVDs), which are an entity on the borderline of gynecology and vascular surgery and are an increasingly recognizable pathology.

Keywords

chronic pelvic pain

pelvic venous disorders

Phlebolymphology. 2023;40(1):40-47.

www.phlebolymphology.org

Introduction

There is no consensus on the definition of chronic pelvic pain (CPP), but it generally refers to pain with duration of at least 6 months that occurs at the anatomical pelvis, anterior abdominal wall below umbilicus, lumbosacral region of the back, and buttocks, is severe enough to cause functional disability, and requires treatment. Pain can be constant, although it does not have to occur every day to be considered chronic. It may follow a regular cycle with occurrences during menstruation (dysmenorrhea), during or after intercourse (dyspareunia), before or after eating, or while urinating.[1]

Based on a systematic review by the World Health Organization (WHO), the prevalence rates of CPP range from 4.0% to 43.4% according to 18 studies including 299 740 women. Among the 3 high-quality studies with representative samples, the rate of CPP was 2.1% to 24%.[2] The prevalence of CPP is comparable to that of other common medical problems. A cross-sectional analysis using the UK Mediplus Primary Care database found its incidence to be similar to those of asthma, back pain, and migraine, but only approximately one-third of women with CPP seek medical care.[3]

Living with any chronic pain carries a heavy economic and social burden. Based on a systematic review of the cost of CPP in women, the total direct outpatient medical costs are $2.8 billion per year. Fifteen percent of women with CPP miss more than 1 hour of paid work per month, and the cost of work time lost for CPP is $555.3 million per year.[4] Accurate diagnosis and effective management from the first presentation could reduce the endless series of referrals, investigations, and inappropriate treatment and could improve health-related quality of life, work productivity, and health care utilization.

Etiologies of CPP

CPP is a symptom with multiple potential etiologies and very often results from overlapping disorders of the reproductive tract, gastrointestinal system, urological organs, musculoskeletal system, and psychoneurological system, which each contribute to pain. Therefore, the aim of assessment should be to identify contributory factors rather than assign causality to a single pathology. It is often impossible to identify the cause of the pain confidently at the initial assessment.[1] The Royal College of Obstetricians and Gynecologists (RCOG) has divided the etiological factors causing pain into gynecological and extra-gynecological factors (*Table I*). The 5 most common etiologies of CPP include irritable bowel syndrome, musculoskeletal pelvic floor pain, gynecological disorders known as chronic uterine pain disorders, painful bladder syndrome, and peripheral neuropathy.[1,5]

Causes of chronic pelvic pain			
Gynecological disorders	Extra-gynecological disorders		
	Gastrointestinal causes	Urologic causes	Neurologic and musculoskeletal causes
Endometriosis/adenomyosis	Irritable bowel syndrome	Interstitial cystitis/ bladder pain syndrome	Myofascial pelvic pain syndrome
Adhesions	Inflammatory bowel disease	Urethral syndrome	Nerve entrapment syndrome
Uterine fibroids	Celiac disease		Central sensitization
Pelvic inflammatory disease	Diverticulitis		Disc injuries
Residual ovarian syndrome	Colorectal carcinoma		Postural changes
Pelvic venous disorders			Being overweight

Table I. Causes of chronic pelvic pain.

Gynecological disorders

Gynecological disorders account for approximately 20% of cases of CPP.[3] Despite this, 40% of laparoscopies and 12% of hysterectomies are still performed annually for CPP.[6]

Endometriosis and adenomyosis

Endometriosis and adenomyosis are the most common gynecological causes of CPP (*Figure 1*). Studies report that 20% to 80% of women who undergo surgery because of CPP are diagnosed with endometriosis. Adenomyosis has been reported to be present in approximately 20% of women undergoing surgery for endometriosis; it is most commonly seen in women with deeply infiltrative endometriosis.[7] The symptoms associated with a hormonally driven condition such as endometriosis or adenomyosis include pain in the lower abdomen or pelvis, which varies markedly throughout the menstrual cycle and worsens during menstruation, hindering normal activities. It may also involve pain during or after intercourse, urination, or defecation, as well as nausea, constipation, diarrhea, and blood in urine or stool, especially during periods.

CPP in patients with endometriosis may result from significantly higher levels of antiendometrial antibodies

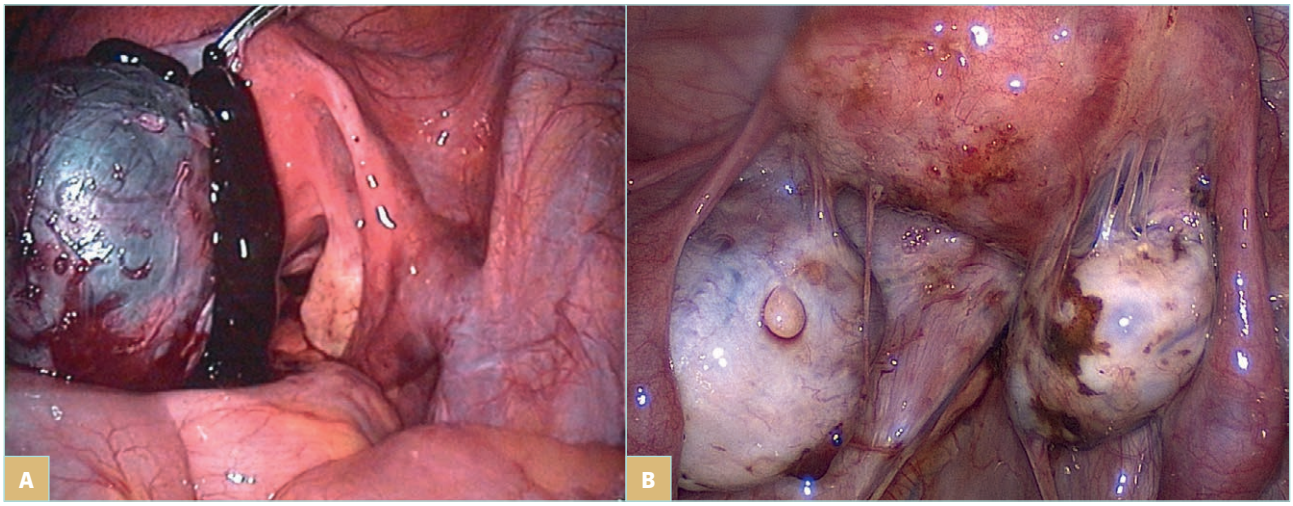


Figure 1. Laparoscopic view of endometriosis. A) An endometrial cyst of the ovary, known as "chocolate cyst." B) Endometrial lesions on the ovaries, uterus, and in the pelvic wall, and endometrial adhesions in the lower pelvis.

(AEAs), regulatory T lymphocytes (Tregs), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF) in the area affected by endometriosis, causing the ingrowth of nerve fibers toward the endometrial ectopic foci and neoangiogenesis in nerves.[8,9] Moreover, findings demonstrate that women with endometriosis have higher levels of inflammatory factors in the peritoneal fluid and blood serum, which may also affect the severity of pain sensation.[9] Pain may be due to nociceptive, neuropathic, or inflammatory mechanisms, and all 3 of these mechanisms are probably relevant to endometriosis-associated pelvic pain. However, it should be highlighted that there is no correlation between the location of disease and the location of pain. Moreover, the presence and severity of endometriosis do not consistently correlate with the severity of symptoms.[9,10]

Endometriosis was also found in almost 10% of asymptomatic women, whereas adenomyosis was found in 47% of hysterectomized specimens from women undergoing perimenopausal transition. However, it was defined as an incidental finding and not the source of the symptomatology.[11] The coexistence of other pain-generating disorders in women with endometriosis is higher than in the general population, so it is important to treat endometriosis in symptomatic patients, as well as to diligently identify and treat all other possible sources of pain, regardless of the presence of endometriosis. Other gynecological disorders that should be taken into consideration in the differential diagnosis of CPP include adhesions, uterine fibroids, pelvic inflammatory disease (PID), residual ovary syndrome, and ovarian tumors, although CPP is not a basic or characteristic symptom of these disorders.[1]

Adhesions

The mechanisms of adhesiogenesis are not well understood but probably involve mesothelial surface disruption with subsequent fibrinocoagulative and inflammatory signaling processes. Etiologically, adhesions can generally be classified as post-operative, post-inflammatory, and post-radiation adhesions.[12] Post-operative peritoneal adhesions have been reported to develop after more than 90% of abdominal surgeries (general, vascular, gynecological, and urological).[13] As adhesions can limit organ mobility, they may cause visceral pain, particularly upon organ distension or stretching. However, adhesions may also be asymptomatic.

Uterine fibroids / uterine myoma

Uterine fibroids are a common disease in women of child-bearing age. A population-based cross-sectional study including 635 participants found uterine fibroids in 15% of women (*Figure 2*). Women with fibroids were more likely to report moderate or severe noncyclic CPP (adjusted odds ratio [OR], 2.6; 95% confidence interval [CI], 0.9-7.6; statistically significant trend) and moderate or severe dyspareunia (adjusted OR, 2.8; 95% CI, 0.9-8.3; statistically significant trend) than women without fibroids. The number and total volume of fibroids were not related to pain.[14]

An international internet-based survey of 21 746 women also found that women with diagnosed uterine fibroids had the following pain symptoms significantly more often than women without uterine fibroids: CPP (14.5% vs 2.9%), painful sexual intercourse (23.5% vs 9.1%), pain occurring mid cycle, after, and during menstrual bleeding (31.3%, 16.7%, 59.7%, vs 17.1%, 6.4%, 52.0%), and pressure on the bladder (32.6% vs 15.0%). Of the women diagnosed with uterine fibroids, 53.7% reported that their symptoms had a negative impact on their life in the last 12 months, influencing their sexual life (42.9%), performance at work (27.7%), and relationship with family (27.2%).[15] However, these data were based on self-report, and it is unknown whether other causes of pain were also present.

Pelvic inflammatory disease

PID refers to acute and subclinical infection of the upper genital tract in women. The prevalence rates of PID range from approximately 3% to 10%. Around 30% of women with PID subsequently develop CPP as a long-term sequela of infection or as a result of chronic subclinical infection.

Patients with severe adhesive disease and tubal damage and/or persistent pelvic tenderness 30 days after diagnosis and pharmacological treatment of PID have a significantly higher risk for developing CPP.[16]

Residual ovarian syndrome

Residual ovarian syndrome (ROS) is a less common cause of CPP. It is a complication that occurs after hysterectomy in which one or both ovaries have been preserved and cause CPP (71%–77%) or dyspareunia (67%). The incidence of ROS is 2% to 3%, and almost 50% of patients with ROS require surgery for treatment of CPP due to ROS within the first 5 years after hysterectomy, whereas 75% require it within 10 years.[17]

Pelvic venous disorders

Pelvic venous disorders (PeVDs) are an entity on the borderline of gynecology and vascular surgery and are an increasingly recognizable pathology. It has been reported as a possible cause of pain in 16% to as much as 31% of women with CPP.[1,2] PeVDs result from pelvic venous incompetence (PVI), which originates from the left or right gonadal vein, the left or right internal iliac vein (IIV), or a combination of these veins. PVI may be a primary incompetence or secondary to extrinsic compression or intraluminal changes (post-thrombotic iliac obstruction). The most common compression syndromes include compression of the left common iliac vein (CIV) by the right common iliac artery, known as May-Thurner syndrome; and the compression of the left renal vein (LRV) between the aorta and the superior mesenteric artery, known as Nutcracker syndrome. Extrinsic compression may also be caused by endometriosis or a tumor mass.[18] Pelvic venous reflux may cause pelvic venous hypertension and subsequently varicose veins (VVs) in 3 reservoirs: the renal hilum, the venous plexuses of the pelvis (*Figure 3*), and the pelvic origin extra-pelvic veins when the reflux is transmitted through the pelvic escape points to the veins of vulva or lower limb.[18] It is worth mentioning that the presence of hypogastric vein tributaries is not necessarily correlated with pelvic reflux.

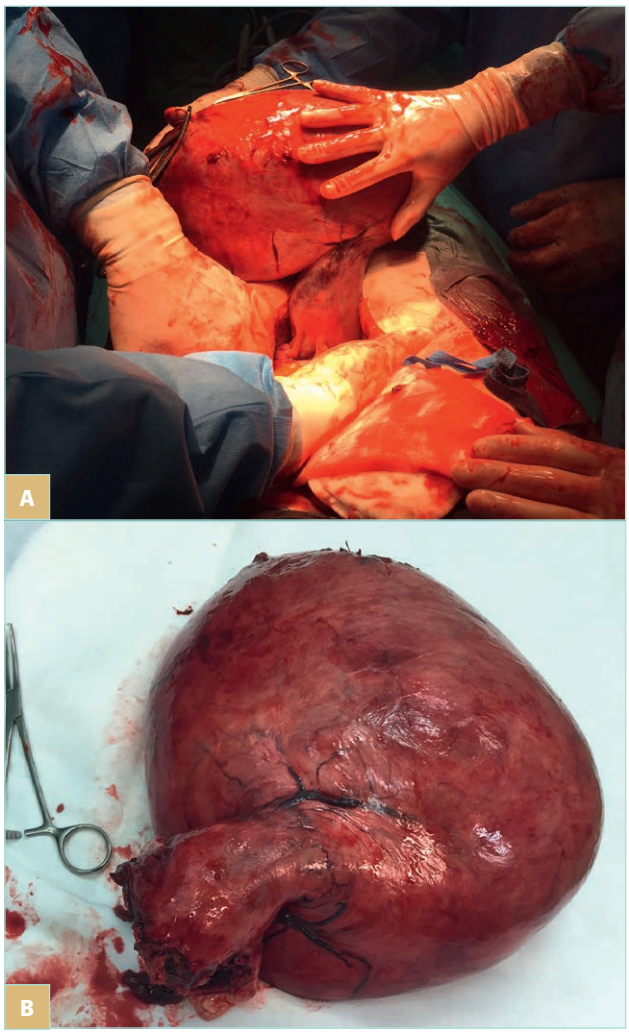


Figure 2. Myomatous uterus during hysterectomy (A, B).

It should be highlighted that most patients with PVI are asymptomatic and do not require any diagnostic and treatment at all.[18,19] Some patients may develop the following symptoms related to either VVs or increased venous pressure: CPP, including dyspareunia or prolonged post-coital pain, leg edema, and/or venous claudication, venous leg ulcer (in cases of CIV compression), left flank pain, and/or hematuria (in cases of LRV compression).[18] It is still unknown which patients will develop symptoms and why, whether the symptoms of the patient are related to PVI, or whether PVI is only an asymptomatic comorbidity.

Vein dilation and venous reflux are not enough to lead to both the symptoms and the diagnosis of PeVDs. There are no validated criteria or cutoff points to diagnose this disorder. Incompetent and dilated ovarian veins can be found in almost 50% of asymptomatic women, as can pelvic VVs, especially after a second pregnancy. Additionally, 90% of patients do not have valves in IIV. Asymptomatic compression of the CIV and the LRV causing ≥50% area reduction may be present in 25% to 33% and 51% to 72% of the general population, respectively.[18]

Hormonal factors may play a critical role in the patho-physiology and symptomatology of PeVDs. The suggestion that endogenous hormone levels matter arose from the worsening of symptoms during menstruation, an increased prevalence of PeVDs in multiparous and premenopausal women, the resolution of symptoms after menopause, and the positive therapeutic effects of hormonal substitution.[20] Due to congestion and the resulting ovary overstimulation, there is an increased level of estrogen. In combination with insufficient levels of progesterone-like hormones, these conditions can cause some changes in women's physiology and impact CPP related to PVI.[20]

Patients with PVI have been found to have significantly higher levels of estradiol in blood refluxing from the pelvis to the groin than in the upper extremities.[21] Higher levels of estrogen may be the reason for the significantly larger uterus and thicker endometrium in patients with congestion than in healthy women.[22] The mean endometrial thickness was found to be 9.9±1.8 mm in a group with pelvic VVs and was significantly higher (P=0.048) than in the healthy

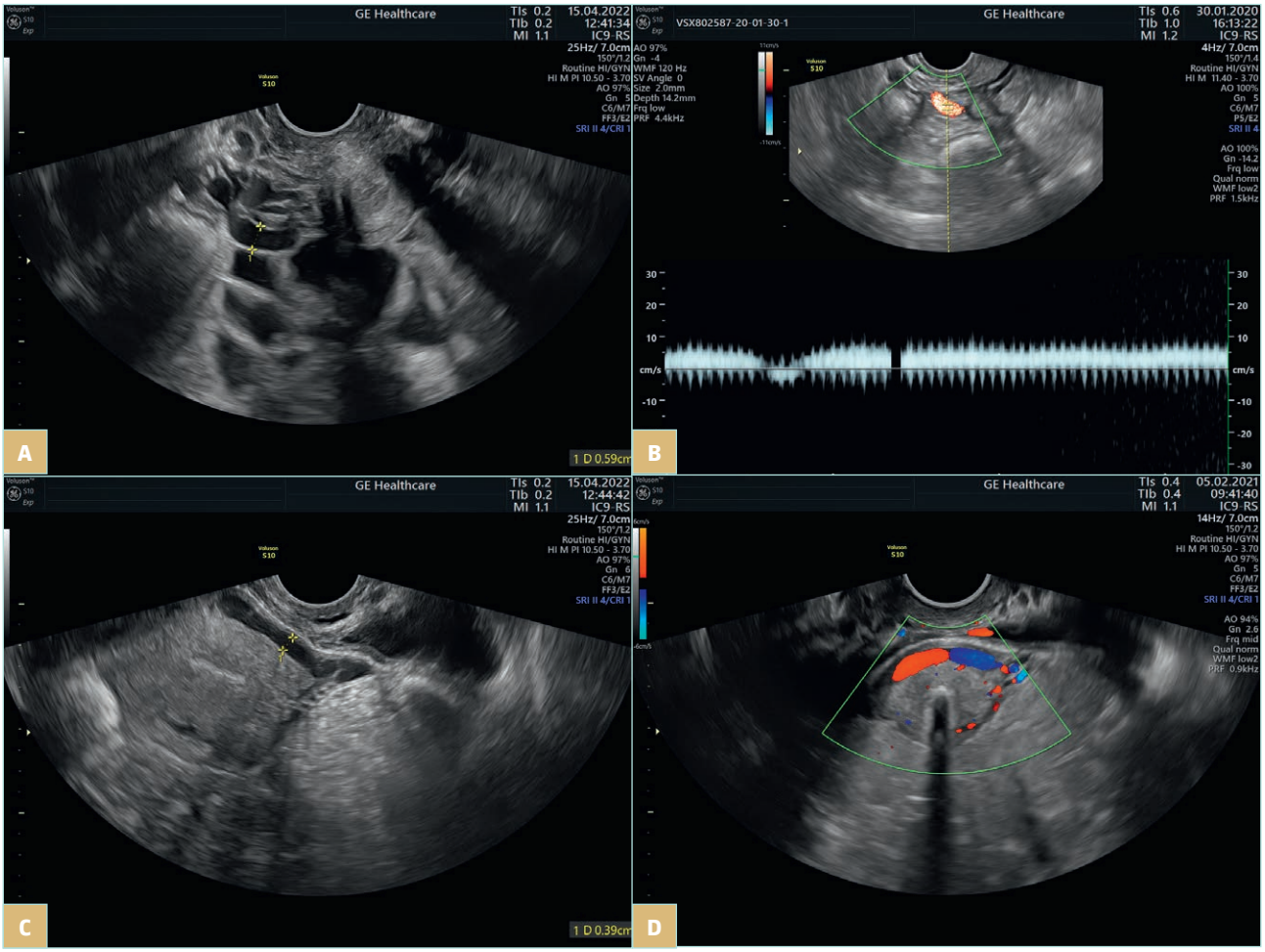


Figure 3. Transvaginal ultrasonography of a patient with a pelvic venous disorder. A) Pelvic varicocele. B) Venous reflux in periuterine venous plexus. C-D) An arcuate vein crossing the uterine body.

group, where the endometrial thickness was measured to be 6.2±2 mm.[23] Hormonal imbalance may also be responsible for polycystic ovary changes in as much as 56% of women with PVI.[20] According to Park et al, polycystic ovaries were found in 40.6% of patients with pelvic congestion and in 11.4% of a control group during ultrasound examination.[24]

Although the pathophysiology of CPP in patients with PeVDs is not fully understood, it is thought to be caused by a few estrogen-related mechanisms. Estrogen is a potent vasodilator, and its receptors are present on human vascular cells. Elevated estrogen can increase levels and activity of matrix metalloproteinases (MMPs), which cause degradation of extracellular matrix (ECM) proteins such as collagen and elastin, further decrease vein contraction, increase venous dilation, and consequently accelerate VV formation.

MMP-induced ECM degradation may also cause valve degeneration, leading to further increases in venous pressure. Increased MMPs leads to nitric oxide production, which not only weakens and dilates the uterine vessels, but also causes pelvic pain.[25] Fluctuations in estradiol levels also have an effect on nociceptive sensitivity.[26] Other likely mechanisms for pain in patients with PeVDs include stasis of engorged pelvic veins, which activates nociceptors within the venous wall, release of neurotransmitters from dilated pelvic veins, and compression from contiguous anatomical structures to nearby nerves.[27]

CPP of venous origin is often characterized as dull unilateral or bilateral pain with occasional sharp flares. Bimanual examination demonstrates more diffuse tenderness of the uterus, adnexa, parametrium, and ovarian point (the junction of the upper and middle thirds of a line drawn from the umbilicus to the anterior superior iliac spine), with no pelvic floor tenderness. Uterine and adnexal palpation usually leads to deep genital pain, whereas palpation of the ovarian point leads to pelvic pain. Symptoms are often worse with activities such as walking and prolonged standing and improve when lying down.

Although deep dyspareunia is common among women with pelvic pain from a variety of causes, pain of venous origin is more likely to be associated with prolonged postcoital ache. The combination of postcoital ache and tenderness over the ovarian point has been reported to be 94% sensitive and 77% specific for distinguishing a venous origin from other causes of pelvic pain.[28] Due to the high prevalence of PVI, which is usually asymptomatic and frequently coexists with other pain-generating diseases, all possible causes of CPP need to be ruled out before deciding to treat PVI.

Extra-gynecological disorders

Extra-gynecological disorders are a common cause of CPP. In a cohort analysis of a primary care database, irritable bowel syndrome (IBS) and interstitial cystitis (IC) were the most common diagnoses of women with CPP across all age groups.[3] These conditions may be primary causes of CPP, components of CPP, or secondary effects caused by efferent neurological dysfunction in the presence of chronic pain.

Irritable bowel syndrome

IBS is a gastrointestinal pain syndrome characterized by chronic or intermittent abdominal pain with variable intensity and periodic exacerbations associated with altered bowel function in the absence of any organic cause. Approximately 10% to 15% of the general population has symptoms compatible with IBS. It is diagnosed more than twice as often in women than in men. Based on a survey of 798 new referrals to a gynecological clinic, the prevalence of IBS was 37.3% compared with 27.7% among controls who visited an ear, nose, and throat (ENT) or dermatological clinic (P=0.003). Approximately 50% of women referred with CPP, dyspareunia, and dysmenorrhea had symptoms compatible with IBS (P<0.005).[29]

Another survey of 2304 patients found that half the women with CPP also had genitourinary symptoms, IBS, or both. IBS and stress were the most common diagnoses received by patients with CPP.[3] Unfortunately, approximately 40% to 50% of individuals who meet the diagnostic criteria for IBS do not have a formal diagnosis and appropriate treatment.[30] IBS is also very often a comorbidity and has high prevalence in women with endometriosis and other CPP-generating disorders, which may have a negative impact on diagnostic and treatment processes.

Interstitial cystitis/ bladder pain syndrome

IC is a diagnosis that applies to patients with chronic bladder and urinary urgency in the absence of an identifiable etiology. Little is known about the pathogenesis of IC. There is no clear evidence that inflammation or abnormalities in the interstitium of the bladder are involved.[1] Recent data suggest that IC is probably one of the most common causes of CPP. IC was diagnosed in 38% to 84% of women with CPP receiving secondary care.[31,32]

The most common symptom of IC is pain localized in the suprapubic, pubic, vaginal, and genital areas. Some patients report unilateral lower abdominal pain or low back pain with bladder filling. Pain is usually described as intermittent, regardless of the pain site, with moderate intensity.[33] Other symptoms of IC include urinary urgency, daytime frequency, dysuria, and nocturia.[34] Symptoms may be triggered or exacerbated by vaginal intercourse, exercise, prolonged sitting, intake of certain foods or drinks, stress, or the luteal phase of the menstrual cycle.[35,36] IC often coexists with other CPP syndromes, especially IBS, fibromyalgia, and vulvodynia.

Myofascial pelvic pain syndrome

Myofascial pelvic pain syndrome (MPPS) results from dysfunction, spasticity, or hypersensitivity of the muscles, fascia, or joints in the abdominal wall, pelvic floor, or lower back. It is an extremely common but underrecognized cause of CPP in women.[37] MPPS originates at the myofascial trigger points (MTrPts), which are hyperirritable spots, usually within a taut band of skeletal muscle, that are painful upon compression and can give rise to characteristic referred pain. Trigger points can be active, causing spontaneous or latent pain. It may remain asymptomatic for years and may be activated by physical trauma, a painful event in the area, or emotional stress.[38]

Pain can also involve the vulva, perineum, rectum, bladder, and more distant areas such as the thighs, buttocks, or lower abdomen. It may influence urinary, bowel, and sexual function. Irritative symptoms, including vulvar or vaginal burning or itching, pain during or after intercourse, urinary urgency, frequency, and dysuria, can be reported even more frequently than CPP.[39] The estimates of the prevalence of MPPS in the general population vary from 14% to 78%. It often coexists with other causes of pelvic pain. MTrPts have been identified in as much as 85% of patients suffering from urological, colorectal, and gynecological pelvic pain syndromes and can be responsible for some, if not all, symptoms related to these syndromes.[40] A routine assessment for MPPS should be considered for all patients presenting for evaluation of CPP.

Nerve injury or entrapment

Surgical injury or entrapment of abdominal or pelvic nerves, such as iliohypogastric, ilioinguinal, genitofemoral, lateral femoral cutaneous, or pudendal nerves, may cause subsequent CPP in the anatomic distribution of this nerve. The incidence of nerve injury following pelvic surgery is approximately 2%. Longitudinal incisions are associated with a low risk of nerve injury. Analysis of 690 patients after low transverse Pfannenstiel incision for cesarean delivery or abdominal hysterectomy showed that moderate or severe CPP associated with nerve injury or entrapment was reported by 7% and 8.9% of women, respectively.[41] This cause of CPP should especially be taken into consideration in patients with previous surgical treatment.

Central sensitization

Centralization of pain occurs when sensory pain information is abnormally processed in the central nervous system, causing central pain sensitization. This causes pain that is perpetuated by the central nervous system. It is described as a dysfunctional pain syndrome and is recognized as a systemic disease.[42] There is evidence that women with CPP have decreased thresholds to pain and that CPP is often present without an obvious cause according to imaging studies, laboratory values, or physical exams. Furthermore, it may persist despite treatment of the presumed etiologies.

Women with CPP often present with several seemingly unrelated symptoms. This can be explained by coexisting CPP syndromes occurring in the same patient. Central sensitization (CS) has been demonstrated in all of these syndromes, so it provides one possible explanation for CPP. In an observational cross-sectional study, CS was found in 75% of 111 women with CPP. Patients with CS were more likely to experience pain for more than 2 years (OR, 4.98; 95% CI, 1.94-12.82; *P*=0.001) and other pain symptoms involving the bladder (OR, 9.87; 95% CI, 2.52-38.67; *P*=0.001), bowel (OR, 3.13; 95% CI, 1.31-7.48; *P*=0.01), back (OR, 4.17; 95% CI, 1.66-10.51; *P*=0.002), and vulva (OR, 3.61; 95% CI, 1.21-10.82; *P*=0.02). They also had higher previous diagnoses of a mental health disorder (OR, 3.5; 95% CI, 1.5-8.4; *P*=0.005) or IBS (OR, 8.9; 95% CI, 1.6-49.1; *P*=0.01).[43] Patients with CS experience more prolonged and complex pain, which may have a negative impact on the treatment outcome.

Conclusions

Due to the complex etiology of CPP and the common coexistence of several pain-generating disorders, there is a necessity for more precise diagnosis by a specially trained team of experts. The approach to CPP patients should be multimodal and requires the cooperation of gynecologists, vascular surgeons or phlebologists, interventional radiologists, gastroenterologists, urologists, physiotherapists, and psychologists. It is recommended that a diagnostic protocol be established to check and rule out all the potential etiologies before treatment is determined. Patient involvement, shared decision-making, and discussion of expectations for long-term care are important parts of the evaluation process. Such an approach gives the most beneficial effects.

CORRESPONDING AUTHOR

Aleksandra Jaworucka-Kaczorowska, MD, PhD

Center of Phlebology and Aesthetic Medicine, Center of General and Vascular Surgery, Gynecology and Obstetrics "Jaworuccy," Plac Jana Pawła II 76 cd, 66-400 Gorzów Wlkp, Poland

EMAIL: *ajaworucka@gmail.com*

References

1. As-Sanie S. Chronic pelvic pain in non-pregnant adult females: causes. UpToDate. Updated Feb 07, 2023. Accessed February 11, 2023. https://www.uptodate.com/contents/chronic-pelvic-pain-in-nonpregnant-adult-females-causes
2. Latthe P, Latthe M, Say L, et al. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. *BMC Public Health.* 2006;6:177.
3. Zondervan KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH. Patterns of diagnosis and referral in women consulting for chronic pelvic pain in UK primary care. *Br J Obstet Gynaecol.* 1999;106(11):1156-1161.
4. Huang G, Le AL, Goddard Y, et al. A systematic review of the cost of chronic pelvic pain in women. *J Obstet Gynaecol Can.* 2022;44(3):286-293.e3.
5. Royal College of Obstetricians and Gynecologists. The Initial Management of Chronic Pelvic Pain: Green-top Guideline No. 41. 2012. Published May 2012. Accessed February 11, 2023. https://www.rcog.org.uk/media/muab2gj2/gtg_41.pdf
6. Lamvu G, Carrillo J, Ouyang C, Rapkin A. Chronic pelvic pain in women: a review. *JAMA.* 2021;325(23):2381-2391.
7. Leyendecker G, Bilgicyildirim A, Inacker M, et al. Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study. *Arch Gynecol Obstet.* 2015;291(4): 917-932.
8. Randall GW, Gantt PA, Poe-Zeigler RL, et al. Serum antiendometrial antibodies and diagnosis of endometriosis. *Am J Reprod Immunol.* 2007;58: 374-382.
9. Triolo O, Laganà AS, Sturlese E. Chronic pelvic pain in endometriosis: an overview. *J Clin Med Res.* 2013;5(3):153-163.
10. Kor E, Mostafavi SRS, Mazhin ZA, et al. Relationship between the severity of endometriosis symptoms (dyspareunia, dysmenorrhea and chronic pelvic pain) and the spread of the disease on ultrasound. *BMC Res Notes.* 2020;13(1):546.
11. Weiss G, Maseelall P, Schott LL, Brockwell SE, Schocken M, Johnston JM. Adenomyosis a variant, not a disease? Evidence from hysterectomized menopausal women in the Study of Women's Health Across the Nation (SWAN). *Fertil Steril.* 2009;91(1):201-206.
12. Tabibian N, Swehli E, Boyd A, Umbreen A, Tabibian JH. Abdominal adhesions: a practical review of an often overlooked entity. *Ann Med Surg (Lond).* 2017;15:9-13.
13. ten Broek RP, Strik C, Issa Y, Bleichrodt RP, van Goor H. Adhesiolysis-related morbidity in abdominal surgery. *Ann Surg.* 2013;258(1):98-106.

14. Lippman SA, Warner M, Samuels S, Olive D, Vercellini P, Eskenazi B. Uterine fibroids and gynecologic pain symptoms in a population-based study. *Fertil Steril.* 2003;80(6):1488-1494.

15. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC Womens Health.* 2012;12:6.

16. Trautmann GM, Kip KE, Richter HE, et al. Do short-term markers of treatment efficacy predict long-term sequelae of pelvic inflammatory disease? *Am J Obstet Gynecol.* 2008;198(1):30.e1-e7.

17. Dekel A, Efrat Z, Orvieto R, et al. The residual ovary syndrome: a 20-year experience. *Eur J Obstet Gynecol Reprod Biol.* 1996;68(1-2):159-164.

18. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. *Eur J Vasc Endovasc Surg.* 2022;63(2):184-267.

19. Khilnani NM, Meissner MH, Learman LA, et al. Research priorities in pelvic venous disorders in women: recommendations from a multidisciplinary research consensus panel. *J Vasc Interv Radiol.* 2019;30:781-789.

20. Jaworucka-Kaczorowska A. Conservative treatment of pelvic venous disease. *Turk J Vasc Surg.* 2021;30(1):S37-S43.

21. Asciutto G, Mumme A, Asciutto KC, Geier B. Oestradiol levels in varicose vein blood of patients with and without pelvic vein incompetence (PVI): diagnostic implications. *Eur J Vasc Endovasc Surg.* 2010;40:117-121.

22. Adams J, Reginald PW, Franks S, Wadsworth J, Beard RW. Uterine size and endometrial thickness and the significance of cystic ovaries in women with pelvic pain due to congestion. *Br J Obstet Gynaecol.* 1990;97(7):583-587.

23. Bora A, Avcu S, Arslan H, Adali E, Bulut MD. The relation between pelvic varicose veins and lower extremity venous insufficiency in women with chronic pelvic pain. *JBR–BTR.* 2012;95:215-221.

24. Park SJ, Lim JW, Ko YT, et al. Diagnosis of pelvic congestion syndrome using transabdominal and transvaginal sonography. *AJR Am J Roentgenol.* 2004;182:683-688.

25. MacColl E, Khalil RA. Matrix metalloproteinases as regulators of vein structure and function: implications in chronic venous disease. *J Pharmacol Exp Ther.* 2015;355(3):410-428.

26. Hassan S, Muere A, Einstein G. Ovarian hormones and chronic pain: a comprehensive review. *Pain.* 2014;155(12):2448-2460.

27. Phillips D, Deipolyi AR, Hesketh RL, Midia M, Oklu R. Pelvic congestion syndrome: etiology of pain, diagnosis, and clinical management. *J Vasc Interv Radiol.* 2014;25(5):725-733.

28. Meissner MH, Khilnani NM, Labropoulos N, et al. The symptoms-varices-pathophysiology classification of pelvic venous disorders: a report of the American Vein & Lymphatic Society International Working Group on Pelvic Venous Disorders. *J Vasc Surg Venous Lymphat Disord.* 2021;9(3):568-584.

29. Prior A, Wilson K, Whorwell PJ, Faragher EB. Irritable bowel syndrome in the gynecological clinic. Survey of 798 new referrals. *Dig Dis Sci.* 1989;34:1820-1824.

30. Sayuk GS, Wolf R, Chang L. Comparison of symptoms, healthcare utilization, and treatment in diagnosed and undiagnosed individuals with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol.* 2017;112(6):892-899.

31. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. *Obstet Gynecol.* 2002;100(2):337-341.

32. Parsons CL, Dell J, Stanford EJ, Bullen M, Kahn BS, Willems JJ. The prevalence of interstitial cystitis in gynecologic patients with pelvic pain, as detected by intravesical potassium sensitivity. *Am J Obstet Gynecol.* 2002;187(5):1395-1400.

33. FitzGerald MP, Brensinger C, Brubaker L, Propert K. What is the pain of interstitial cystitis like? *Int Urogynecol J Pelvic Floor Dysfunct.* 2006;17(1):69-72.

34. Teichman JM, Parsons CL. Contemporary clinical presentation of interstitial cystitis. *Urology.* 2007;69(4):41-47.

35. Friedlander JI, Shorter B, Moldwin RM. Diet and its role in interstitial cystitis/bladder pain syndrome (IC/BPS) and comorbid conditions. *BJU Int.* 2012;109(11):1584-1591.

36. Powell-Boone T, Ness TJ, Cannon R, Lloyd LK, Weigent DA, Fillingim RB. Menstrual cycle affects bladder pain sensation in subjects with interstitial cystitis. *J Urol.* 2005;174(5):1832-1836.

37. Billecocq S, Bo K, Dumoulin C, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and non-pharmacological management of female pelvic floor dysfunction. Article in French. *Prog Urol.* 2019;29(4):183-208.

38. Shah JP, Thaker N, Heimur J, Aredo JV, Sikdar S, Gerber L. Myofascial trigger points then and now: a historical and scientific perspective. *PM R.* 2015;7(7):746-761.

39. Meister MR, Sutcliffe S, Badu A, Ghetti C, Lowder JL. Pelvic floor myofascial pain severity and pelvic floor disorder symptom bother: is there a correlation? *Am J Obstet Gynecol.* 2019;221(3):235.e1-235.e15.

40. Moldwin RM, Fariello JY. Myofascial trigger points of the pelvic floor: associations with urological pain syndromes and treatment strategies including injection therapy. *Curr Urol Rep*. 2013;14(5):409-417.

41. Loos MJ, Scheltinga MR, Mulders LG, Roumen RM. The Pfannenstiel incision as a source of chronic pain. *Obstet Gynecol.* 2008;111(4):839-846.

42. Hoffman D. Central and peripheral pain generators in women with chronic pelvic pain: patient centered assessment and treatment. *Curr Rheumatol Rev.* 2015;11(2):146-166.

43. Ryan A, Healey M, Cheng C, Dior U, Reddington C. Central sensitisation in pelvic pain: a cohort study. *Aust N Z J Obstet Gynaecol*. 2022;62(6):868-874.

Phlebolymphology Vol 30 | No.1 | 2023

Varicose veins during pregnancy: risk factors and impact on quality of life

Sena Dilek Aksoy, PhD, RN

Department of Midwifery, Faculty of Health Science, Kocaeli University, Kocaeli, Turkey

Derya Kanza Gul, MD

School of Medicine Health, Medipol University, Istanbul, Turkey

Ayça Solt Kirca, PhD, RM

Department of Midwifery, School of Health, Kirklareli University, Kirklareli, Turkey

ABSTRACT

Objective: This study was carried out to examine the risk factors for varicose veins during pregnancy and their impact on quality of life.

Material and methods: This was a prospective, cross-sectional observational study in pregnant women in their second and third trimesters. In addition to the collection of sociodemographic and lifestyle data, the presence of varicose veins was assessed using the clinical, etiological, anatomical, and pathophysiological (CEAP) questionnaire, and the quality of life was assessed using the Chronic Venous Insufficiency Questionnaire (CIVIQ-20). Logistic regression analysis was conducted to identify independent risk factors for varicose veins.

Results: A total of 658 women were included. Considering all types of varicose veins, prevalence of varicose veins was 29% (191 women). Varicose veins presence was found to be significantly associated with gestational week (odd ratio [OR], 1.047; 95% CI, 1.013-1.083; *P*=0.03), thyroid diseases (OR, 2.474; 95% CI, 1.109-5.522; *P*=0.019), smoking status during pregnancy (OR, 7.294; 95% CI, 2.408-22.093; *P*<0.001), and positive family varix history (OR, 213.437; 95% CI, 87.248-522.138; *P*<0.001). As regards the quality-of-life evaluation, scores in all CIVIQ-20 dimensions—physical (mean deviation [MD], -4.30; 95% CI, -4.76 to 3.83; *P*<0.001), psychological (MD, -8.67; 95% CI, -9.60 to 7.73; *P*<0.001), social (MD, -3.13; 95% CI, -3.48 to 2.79; *P*<0.001), pain (MD, -3.94; 95% CI, -4.37 to 3.51; *P*<0.001)—and the global index score (MD, 25.06; 95% CI, 22.50 to 27.62; *P*<0.001) were significantly higher in patients with varicose veins than in those without (*P*<0.001).

Conclusions: In this prospective, observational study in pregnant women, gestational week, thyroid diseases, smoking status during pregnancy, and positive family history were identified as risk factors for varicose veins, and the presence of varicose veins was found to negatively impact quality of life in this setting.

Keywords

pregnancy | quality of life | risk factor | varicose vein

Phlebolymphology. 2023;40(1):48-55.

www.phlebolymphology.org

Introduction

Approximately half of the world's populations suffer from varicose veins (VV).[1] It is thought that both valve dysfunction and venous pressure play a key role in the onset and progression of the disease.[2] In addition, sexual hormones are implicated in venous pathology.[3] Pregnancy-related dilatation that occurs in various parts of the body triggers lower extremity VV formation.[4] In pregnancy, the total blood, serum, and erythrocyte volumes show an increase. Especially the total blood volume, which is around 4000 mL, reaching 5300 mL in the 36th gestational week. Moreover, the decrease in the tension of the blood vessels leads to slowed blood flow and swollen legs. As a result of this, VV formation occurs in women who are predisposed.[5] Whereas some studies have shown that the blood flow rate was significantly lower in pregnant women with venous deficiency, a significant reduction was observed in the blood flow rate especially in the last 3 months of pregnancy. This rate is especially at its lowest level in the 36th gestational week of pregnancy.[5,6] A reduction in blood flow rate may lead to substantial pain, night cramps, numbness, tingling sensation, and itching.[7] Although VV observed in pregnancy is a distressing experience during pregnancy, it may decrease or disappear after birth.[4] Only limited data are available on the prevalence of VV and on risk factors for VV during pregnancy.[4,8] This is an observational study conducted to estimate the prevalence of VV, to identify risk factors for VV, and to assess the impact on quality of life (QOL) of VV presence in pregnancy.

Methods

Study design and participants

This observational study was carried out between July 21, 2020 and October 31, 2020 at the gynecology and obstetrics polyclinics of a private hospital in Istanbul, which is the largest province of Turkey. The number of pregnant women who visited the gynecology polyclinics between January 1 and December 31, 2019 was approximately 2500. In the study, the sample size was calculated by using the method of known population sampling. The minimum number of individuals to be included in the sampling was calculated with a 95% confidence interval (CI) (α=0.05), *P*=0.050, and N=2500 population numbers and determined to be 334. Considering the possibility of loss of participants to no follow-up and/or data loss, a design effect of 2 was accepted, and approximately 600 patients were considered sufficient for the sample size (*Figure 1*).

Inclusion criteria

To fulfill inclusion criteria, participants needed to be in the second or third trimester of pregnancy, having a singleton pregnancy.

Exclusion criteria

Participants were excluded if they were unable to understand the research (eg, could not speak or understand Turkish).

Data collection instruments and data collection procedure

Information about sociodemographic and obstetric characteristics was collected and the Chronic Venous Insufficiency Questionnaire (CIVIQ-20)[8-11] and clinical, etiological, anatomical, and pathophysiological (CEAP)

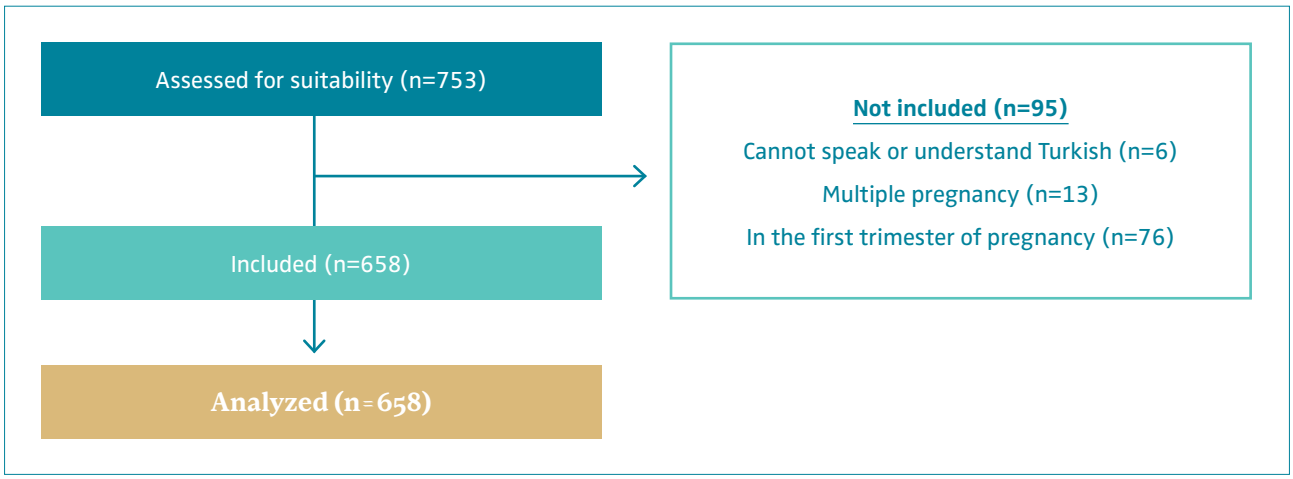


Figure 1. Diagram of the research process.

classification questionnaire were completed by one of the investigators during a face-to-face interview with each participant. In addition, a second investigator (a gynecologist) filled out the CEAP scoring instrument by observation.

Disease diagnoses were recorded not according to the statements of the participants but within the framework of the examinations in the hospital's pregnancy follow-up system.

The CEAP classification questionnaire is a well-established tool to aid in the diagnosis and classification of chronic venous disease. Women with CEAP >C1 are considered to have VV.[9]

The CIVIQ-20 is a QOL questionnaire that consists of 20 questions and covers 4 QOL fields regarding chronic venous insufficiency: physical, psychological, social disorders, and severity of pain. The total CIVIQ-20 score is obtained by summing the scores of 20 items for all subscales. The lower the score, the higher the QOL. The global index score is reached via a special calculation technique. The higher the global index score, the higher the QOL.[10,11]

Statistical methods

The data were analyzed by using IBM SPSS V23. Compatibility with normal distribution was examined by the Kolmogorov-Smirnov test. Chi-squared and Fisher's exact tests were used to compare the categorical variables based on the groups. The Mann-Whitney U test was used to compare the non-normally distributed data between 2 groups. Binary logistic regression analysis and the Hosmer and Lemeshow Test were used to identify independent risk factors for VV. The results of the analyses are presented as mean ± standard deviation and median (minimum - maximum) for the quantitative data and as frequencies (percentages) for the categorical dWata. *P* values less than 0.05 were accepted as statistically significant.

Ethics committee approval

Ethics committee approval was received for this study from the Ethics Committee of Kirklareli University (Protocol No. 69456409-199-E.10627). The study was carried out in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments. The author(s) can provide copies of the appropriate documentation if requested.

Patient consent

All participants were informed about the study and signed a consent form, knowing that they could withdraw from the study whenever they wanted.

Results

The study included a total of 658 pregnant women, whose mean age was 29.14±4.59 (min:18; max:45) years. Their sociodemographic, obstetric, and CEAP classification features are shown in *Table I*. Considering all types of VV, prevalence of VV was 29% (191 pregnant women) (*Table I*).

On average, patients with VV had a higher body mass index (*P*=0.008) and had a more advanced pregnancy (*P*=0.030). They were also more frequently smokers (during pregnancy) (*P*<0.001) than those without VV. Additionally, patients with VV were significantly more likely to have diseases accompanying pregnancy (*P*=0.019) and to have a family history of varices (*P*<0.001). On the other hand, these 2 groups were not significantly different in terms of age, gravida, and parity.

As regards the QOL evaluation, the physical disorder scores, psychological disorder scores, social disorder scores, pain scores, and global index score median values were significantly higher in patients with VV than in those without (*P*<0.001) (*Table II*).

The independent risk factors affecting VV presence were examined by binary logistic regression analysis. According to our analysis, gestational week, disease accompanying pregnancy (thyroid diseases), smoking status (during pregnancy), and family history of VV are significantly associated with VV presence. Each gestational week led to a 1.047-increased risk for VV (OR, 1.047; 95% CI, 1.013-1.083; *P*=0.006). The presence of thyroid disease increased by approximately 2.5 the chances of having VV (OR, 2.474; 95% CI, 1.109-5.522; *P*=0.027). We found a 7-fold increased risk for VV in women smoking during pregnancy (OR, 7.294; 95% CI, 2.408-22.093; *P*<0.001) and a 213-fold increased risk in those with a family history of VV (OR, 213.437; 95% CI, 87.248-522.138; *P*<0.001) (*Table III*).

Discussion

Pregnancy plays an important role in the onset and progression of VV in women. Changes that occur in the venous system during pregnancy are associated with not only hormonal secretions but also compression of the iliac veins by the uterus.[1] In this study, the independent risk factors affecting VV presence were examined by a binary logistic regression analysis, and the effect of VV on QOL in pregnant women was investigated.

Sociodemographic characteristics	Mean-SD	Min-max
Age	29.14±4.59	18-45
BMI	27.12±4.28	18-48
Educational status	n (658)	%
Illiterate or Primary school	157	23.9
Secondary or High school	501	76.1
Working status		
Working	179	27.2
Not working	479	72.8
Economic status		
Income less than expenses	24	3.6
Income equal to expenses	593	90.1
Income more than expenses	41	6.2
Obstetric and other characteristics	**Mean-SD**	**Min-max**
Gravida	1.65±0.81	1-6
Parity	1.35±0.63	0-5
Gestational week	24.89±9.08	12-40
Disease accompanying pregnancy	n	%
Thyroid diseases	64	9.7
Cardiovascular diseases	21	3.2
Diabetes mellitus	17	2.6
Other diseases	4	0.6
No disease	552	83.9
Smoking (during pregnancy)		
Yes	36	5.5
No	622	94.5
Positive family varix history		
Yes	144	21.9
No	514	78.1
CEAP Classification	**n**	**%**
C0=No visible or palpable varicose veins	467	71.0
C1=Telangiectasia (Thread veins / Spider veins / Broken veins	147	22.3
C2= Varicose veins, asymptomatic and symptomatic	31	4.7
C3= Swollen ankle (edema) due to varicose veins or hidden varicose veins (venous reflux)	13	2.0
Pregnant with varicose veins according to CEAP classification	**n**	**%**
Yes	191	29.0
No	467	71.0
Total	658	100

Table I. Sociodemographic and clinical characteristics of included women (n=658).

Abbreviations: BMI, body mass index; CEAP, clinical, etiological, anatomical and pathophysiological classification; SD, standard deviation.

	Varicose vein (n=191)	Not varicose vein (n=467)	Total (n=658)	*P*
	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	
Age	29.56 ± 4.77 29 (18 – 42)	28.97 ± 4.51 29 (19 – 45)	29.14 ± 4.5 29 (18 – 45)	0.107
BMI	27.73 ± 4.38 27 (18-44)	26.87 ± 4.21 26 (18-48)	27.12 ± 4.28 26 (18-48)	**0.008**
Gravida	1.78±0.96 2 (1 - 6)	1.6 ± 0.74 1 (1 - 4)	1.65 ± 0.81 1 (1 - 6)	0.058
Parity	1.43±0.79 1 (1- 5)	1.31±0.53 1 (0 - 3)	1.35 ± 0.63 1 (0 - 5)	0.462
Gestational week	26.24±8.72 28 (12-40)	24.34±9.18 24 (12-40)	24.89 ± 9.08 24 (12-40)	**0.030**
Disease accompanying pregnancy	n (%)	n (%)	n (%)	
Thyroid diseases	29 (4.4)	35 (5.3)	64 (9.7)	**0.019**
Cardiovascular diseases	7 (1.1)	14 (2.1)	25 (3.8)	
Diabetes mellitus	7 (1.1)	10 (1.5)	17 (2.6)	
Other diseases	1 (0.2)	3 (0.5)	4 (0.6)	
No disease	147 (22.3)	405 (61.6)	552 (83.9)	
Smoking (during pregnancy)				
Yes	27 (4.1)	9 (1.4)	36 (5.5)	**<0.001**
No	164 (24.9)	458 (69.6)	622 (94.5)	
Positive family varix history				
Yes	138 (21)	6 (0.9)	144 (21.9)	**<0.001**
No	53 (8.1)	461 (70.1)	514 (78.1)	
CIVIQ-20	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	
Physical score	9.48 ± 3.09 8 (4 - 19)	5.18 ± 1.59 4 (4 - 12)	6.43 ± 2.89 5.5 (4 - 19)	**<0.001**
Psychological score	20.31 ± 6.25 19 (9 - 40)	11.64 ± 3.02 11 (9 - 27)	14.16 ± 5.77 12 (9 - 40)	**<0.001**
Social score	6.86 ± 2.33 6 (3 - 14)	3.72 ± 1.02 3 (3 - 9)	4.63 ± 2.08 4 (3 - 14)	**<0.001**
Pain score	8.92 ± 2.85 8 (4 - 16)	4.98 ± 1.39 4 (4 - 11)	6.12 ± 2.63 5 (4 - 16)	**<0.001**
CIVIQ-20 total score	4.59 ± 13.75 43 (20 - 88)	25.54 ± 6.51 24 (20 - 57)	31.36 ± 12.95 27 (20 - 88)	**<0.001**
GIS	68.00 ± 17.19 71.2 (15 - 100)	93.07 ± 8.14 95 (53 - 100)	85.79 ± 16.19 91.2 (15 - 100)	**<0.001**

Table II. Comparison of variables based on varicose vein presence (n=658).

Abbreviations: BMI, body mass index; CIVIQ-20, Chronic Venous Insufficiency Questionnaire; GIS, global index score; SD, standard deviation; VV, varicose veins.
P<0.05, bold values are statistically significant; mean ± standard deviation, median (min-max).

			Odds ratio	95% Confidence interval	
Risk factors	**B (SE)**	***P***	**Exp (B)**	**Lower**	**Upper**
BMI	-0.013 (0.037)	0.937	0.997	0.927	1.072
Gestational week	0.046 (0.017)	**0.006**	1.047	1.013	1.083
Disease accompanying pregnancy					
Thyroid diseases	0.906 (0.410)	**0.027**	2.474	1.109	5.522
Cardiovascular diseases	0.013 (0.846)	0.988	1.013	0.193	5.313
Diabetes mellitus	0.137 (0.905)	0.880	0.872	0.148	5.136
Other diseases	0.948 (1.272)	0.456	2.579	0.213	31.226
Smoking (during pregnancy)	1.987 (0.565)	**<0.001**	7.294	2.408	22.093
Positive family varix history	5.363 (0.456)	**<0.001**	213.437	87.248	522.138

Table III. Risk factors associated with varicose vein presence (n=658).

Abbreviations: B, regression coefficient; BMI, body mass index; SE, standard error.
Classification table: Overall percentage: 71.0; Model Chi-Squared: 424.977; df:8; *P*<0.001; Hosmer–Lemeshow Test: 4.605; df: 8; *P*=0.799; *P*<0.05, bold values are statistically significant.

The prevalence of VV in this study was 29% (191 women). In a study conducted in Brazil in 2010, VV prevalence was found to be 72%.[4] In the study conducted in Iran, the prevalence was 18%.[8] There is a very substantial heterogeneity in the prevalence results.

Pregnancy is a significant risk factor in VV formation.[8] It has been reported in the literature that hormones such as estrogen and progesterone have an important role in the emergence of varices in most women in pregnancy.[3,12] In our study, it was found that the risk of VV increased as the gestational week increased. On the contrary, an epidemiological study conducted on 566 adults in Budapest determined that hormonal factors did not have an effect on VV formation.[13] Our finding that the risk of VV increased with the gestational week could be due to the fact that we only included women in their second and third trimesters of pregnancy. Considering the effect of progesterone hormone on smooth muscles during pregnancy, such a result is likely. In the literature, it was reported that varix complaints in pregnancy emerge at the beginning of the second trimester.[14]

In our study, it was determined that thyroid diseases can be a risk factor for VV during pregnancy. Dominguez et al (2018) determined that those with venous disease had a higher prevalence of hypothyroidism (17%) than the general population (2%-5%).[15] Kılınç et al (2021) emphasized that hypothyroidism may be a risk factor for the development of chronic venous insufficiency by impairing endothelial function.[16] The possibility of thyroid disease to be associated with negative pregnancy and birth outcomes is a significant result that has emerged especially in recent years. For this reason, the American Thyroid Association drew attention to the guidelines on the diagnosis and management of thyroid diseases during pregnancy and in the postpartum period.[17] VV can also be evaluated within this framework when thyroid screening is performed in pregnant women.

Smoking is an important risk factor in many chronic venous diseases including VV.[18] In their study in 1806 patients, Gourgou et al (2002) reported that smoking 10 to 20 cigarettes a day increased the risk of venous disease 1.7 times, whereas smoking more than 20 cigarettes a day increased this risk 2.4 times.[19] In our study, the VV risk of those who smoked was 7 times higher than those who did not smoke during their pregnancy.

It has been proven in various studies that family history plays a significant role in the emergence of VV.[4,20] In contrast, a population-based cohort study of 4903 people in Finland found that results regarding the effects of family history on VV were biased, reducing the credibility of reports suggesting a strong genetic component.[21] In this study, it was determined that family history increased the risk of having VV by 213 times.

Studies have shown that the QOL of those with VV is negatively affected.[22,23] In the study by Wik et al (2011), which used the VEINES (Venous Insufficiency Epidemiological and Economic Study)-QOL/Sym questionnaire, it was seen that disruption of venous circulation in pregnancy affected QOL negatively.[23] In our study, we found that the presence of VV had a negative impact on pregnant women's physical disorder, psychological disorder, social disorder, and pain

scores, as well as their CIVIQ-20 total scores and global index score. Overall, it has been determined that VV may negatively affect the QOL in pregnant women. Vuylsteke et al (2015) demonstrated that factors like being a woman, advanced age, and family history of varices were associated with higher CEAP scores, and this was correlated with poorer QOL and global index score.[22] In a recent study conducted with people with cardiovascular diseases in Romania, it was observed that the physical, psychological, and social functionality components of QOL were negatively affected in people with VV.[24]

Limitations

The strengths of the study are that it focuses on a topic that has been ignored in recent years and that it was performed in a large population. As the data were collected from a single center, the results of the study may not be generalized to the entire population. As the presence of varices was assessed visually based on CEAP scores, this may not provide as strong evidence as data obtained by measurement instruments such as Doppler ultrasonography.

Conclusions

This study we conducted regarding venous disease in pregnancy helped identify various risk factors and impact on QOL.

In the study, gestational week, disease accompanying pregnancy (thyroid diseases), smoking status (during pregnancy), and family varix history were determined as significant risk factors in VV presence in pregnancy. It was also found that the QOL of the pregnant women experiencing varix problems was negatively affected. The data we obtained may provide humble support for prevention of VV formation during pregnancy and for controlling the progression of the disease in the presence of risk factors. There is a need for broad-scoped prevalence and incidence studies that examine VV formation and effects in pregnancy.

CORRESPONDING AUTHOR

Assistant Professor
Sena Dilek Aksoy

Department of Midwifery,
Faculty of Health Science,
Kocaeli University,
Kocaeli, Turkey

EMAIL: *senadilek2010@gmail.com*

References

1. Cornu-thenard A, Boivin P. Chronic venous disease during pregnancy. *Phlebolymphology.* 2014;21(3):138-144.
2. Lim CS, Kiriakidis S, Paleolog EM, Davies AH. Increased activation of the hypoxia-inducible factor pathway in varicose veins. *J Vasc Surg.* 2012;55(5):1427-1439. doi:10.1016/j.jvs.2011.10.111.
3. Ortega MA, Asúnsolo Á, Álvarez-rocha MJ, et al. Remodelling of collagen fibres in the placentas of women with venous insufficiency during pregnancy. *Histol Histopathol.* 2018;33(6):567-576. doi:10.14670/HH-11-948.
4. JE de, Junior FM. Pregnancy and lower limb varicose veins: prevalence and risk factors. *J Vasc Bras.* 2010;9(2):29-35.
5. Gimunová M, Zvonař M, Kolářová K, et al. Changes in lower extremity blood flow during advancing phases of pregnancy and the effects of special footwear. *J Vasc Bras.* 2017;16(3):214-219. doi:10.1590/1677-5449.002617.
6. Ropacka-Lesiak M, Jarosław K, Bręborowicz G. Pregnancy-dependent blood flow velocity changes in lower extremities veins in venous insufficiency. *Ginekol Pol.* 2015;86(9):659-665. doi:10.17772/gp/59224.
7. Smyth RM, Aflaifel N, Bamigboye AA. Interventions for varicose veins and leg oedema in pregnancy. *Cochrane Database Syst Rev.* 2015;2015(10):CD001066. doi:10.1002/14651858.CD001066.pub3.
8. Dara A, Mahrokh A, Mehdi KG. Prevalence of pregnancy varicose and its effective factors in women referred to gynecology hospitals in Tabriz. *Iran J Obstet Gynecol Infertil.* 2019;22(9):1-7.
9. Lurie F, Passman M, Meisner M, et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord.* 2020;8(3):342-352. doi:10.1016/j.jvsv.2019.12.075.
10. Launois R, Mansilha A, Jantet G. International Psychometric Validation of the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20). *Eur J Vasc Endovasc Surg.* 2010;40(6):783-789. doi:10.1016/j.ejvs.2010.03.034.
11. Launois R. A quality of life tool kit in chronic venous disorders. *Phlebolymphology.* 2014;21(3):152-160.
12. Lenković M, Cabrijan L, Gruber F, et al. Effect of progesterone and pregnancy on the development of varicose veins. *Acta Dermatovenerol Croat.* 2009;17(4):263-267.
13. Bihari I, Tornoci L, Bihari P. Epidemiological study on varicose veins in Budapest. *Phlebology.* 2012;22(2):77-81. doi:10.1258/phleb.2011.010063.
14. Rabe E, Breu FX, Cavezzi A, et al. European guidelines for sclerotherapy in chronic venous disorders. *Phlebology.* 2013;29(6):338-354. doi:10.1177/0268355513483280.
15. Dominguez JU, Lopez PF, Ulloa JH, Salazar J, Penagos A. Prevalence of hypothyroidism in adults with chronic venous insufficiency. *Acta Phlebol.* 2018;19(3):112-114. doi:10.23736/S1593-232X.18.00430-7.
16. Kılınç F, Akbaş A, Şener S, Hayran Y, Aktaş A. Cutaneous findings in patients with chronic venous insufficiency. *J Cosmet Dermatol.* 2022;21(5):2106-2112. doi:10.1111/jocd.14337.
17. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid.* 2017;27(3):315-389. doi:10.1089/thy.2016.0457.
18. Piazza G. Varicose Veins. *Circulation.* 2014;130(7):582-587. doi:10.1161/*CIRCULATIONAHA*.113.008331.
19. Gourgou S, Dedieu F, Sancho-Garnier H. Lower limb venous insufficiency and tobacco smoking: a case-control study. *Am J Epidemiol.* 2002;155(11):1007-1015. doi:10.1093/aje/155.11.1007.
20. Sharma S, Vashist M, Vashist MG. Family history as major predisposing factor in varicose veins disorder. *Eur J Biomed Pharm Sci.* 2017;4(12):392-396.
21. Ahti TM, Makivaara LA, Luukkaala T, Hakama M, Laurikka JO. Effect of family history on the risk of varicose veins is affected by differential misclassification. *J Clin Epidemiol.* 2010;63:686-690. doi:10.1016/j.jclinepi.2009.10.003.
22. Vuylsteke ME, Thomis S, Guillaume G, Modliszewski ML, Weides N, Staelens I. Epidemiological study on chronic venous disease in Belgium and Luxembourg: prevalence, risk factors, and symptomatology. *Eur J Vasc Endovasc Surg.* 2015;49(4):432-439. doi:10.1016/j.ejvs.2014.12.031.
23. Wik HS, Enden TR, Jacobsen AF, Sandset PM. Long-term quality of life after pregnancy-related deep vein thrombosis and the influence of socioeconomic factors and comorbidity. *J Thromb Haemost.* 2011;9(10):1931-1936. doi:10.1111/j.1538-7836.2011.04468.x.
24. Branisteanu D-E, Feodor T, Baila S, Mitea I-A, Vittos O. Impact of chronic venous disease on quality of life: results of vein alarm study. *Exp Ther Med.* 2019;17:1091-1096. doi:10.3892/etm.2018.7054.

Discover the website on venous diseases by SERVIER

Vein academy

- One point of access to evidence-based medical education in Phlebology and Proctology.
- Recent scientific news, interviews, and podcasts on hot topics by international experts.
- Library with videos, books, slide sets on anatomy, epidemiology, and pathophysiology, treatments, and surgical techniques.
- Links to a selection of articles, practical applications, and relevant websites on venous diseases.

… go to

vein-academy.servier.com

SERVIER
moved by you

Correspondent

Servier Affaires Médicales - 35, rue de Verdun - 92284 Suresnes Cedex - France

www.servier.com

23DN0353BA