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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.**

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Content

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Editorial

Dear Readers,

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

I. FORNER-CORDERO and **J. VAZQUEZ-DIEZ** ***(Spain)*** review the role of compression therapy in lipedema, a very frequent chronic disease that mostly affects women and is frequently underdiagnosed and misdiagnosed, and whose pathophysiology is still under research. Clinical guidelines and consensus documents state that compression therapy should be part of the conservative treatment for lipedema and that patients with lipedema should receive compression garments as part of their treatment.

E. CONDE MONTERO ***(Spain)*** and **A. VIVERO** ***(Argentina)*** review *atrophie blanche*, a distinctive dermatological finding characterized by stellate, porcelain-white, atrophic plaques, commonly located on the lower extremities, which can be caused by chronic venous insufficiency (CVI), livedoid vasculopathy, vasculitis, and medication-induced vascular damage. This article aims to clarify the clinical significance of *atrophie blanche*, emphasizing the importance of accurate diagnosis and etiology-based management.

Although foam sclerotherapy remains the gold standard for telangiectasias and reticular vein treatment, newer approaches have emerged aiming to optimize results and reduce complications. **A. RODRIGUES** ***(Brazil)*** describes the sequential use of transdermal long-pulsed 1064-nm Nd:YAG laser following sclerotherapy, enhanced by cryo-cooling and augmented-reality guidance in the form of cryo-laser cryo-sclerotherapy (CLaCS). Evidence shows higher clearance rates and fewer adverse effects when laser and sclerotherapy are used in tandem.

R. REACHI ***(Mexico)*** focuses on the challenge of management of chronic venous disease in an increasing number of elderly patients or patients that suffer associated comorbidities such as obesity or coagulopathies. The reviewed evidence shows how these associated diseases may contribute to the physiopathology and progression of chronic venous disease. Also, that elderly patients with superficial venous reflux can be safely treated with endovenous procedures.

The prevalence of neuropathy in chronic venous disease is poorly studied. **N. E. OROZCO MONTENEGRO, R. RIAL-HORCAJO**, **N. CORRALES,** and **A. DIAZ** ***(Guatemala)*** share the results of their transversal descriptive study on the prevalence of neuropathic pain in 370 patients with chronic venous insufficiency in Guatemala City, which affects around half of the studied patients, being more frequent in advanced stages of disease.

Enjoy reading this issue!

Co-Editor

Dr Lourdes Reina-Gutierrez

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Role of compression therapy in lipedema

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ABSTRACT

Lipedema is a very frequent chronic disease, frequently underdiagnosed and misdiagnosed and whose pathophysiology is still under research. Patients, most of them women, present with evident disproportion in the distribution of fat between the upper and lower part of the body, swelling, easy bruising, and pain in the lower limbs, and sometimes in the upper limbs.

The major aims of its management are to reduce symptoms such as heaviness and pain, reshape the affected limbs, control weight, improve mobility, and improve the quality of life. Setting realistic expectations is important for both patient and medical care providers. Depending on the stage, treatment includes physical therapies, compression garments, exercise, diet, psychological support, and surgical treatment in selected cases. The approach must be integrative and multidisciplinary, looking for a change in patients' habits.

Although there is no scientific evidence to support the additional value of using compression garments for managing lipedema, some reports do show benefits in reducing pain in lipedema patients. Clinical guidelines and consensus documents state that compression therapy should be part of the conservative treatment for lipedema, and that patients with lipedema should receive compression garments as part of their treatment. The lowest compression class that alleviates the patient's symptoms should be preferred. Further research is needed.

Keywords

compression | compression garments | inflammation | lipedema | liposuction | medical hosiery | pain | treatment

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What is lipedema?

Lipedema is a chronic disease that affects many women worldwide, causing swelling and abnormal fat deposition in the lower limbs, bruising, and pain.[1] There is an evident disproportion in the distribution of fat in the lower limbs and sometimes the upper limbs.[2] Due to the lack of awareness and knowledge among professionals, the real prevalence is underestimated due to misdiagnosis or failure to refer patients.[3-5] Etiopathogenic mechanisms have not yet been fully described; however, lipedema has been associated with lymphatic dysfunction, genetic background, and susceptibility to influence by hormonal changes.[6] The main complaint of the patients is the enlargement of the lower limbs, with pain or discomfort. As the disease progresses, leg heaviness may increase and cause impairments in mobility[7] and global capacity. Lipedema, even in early stages, has been associated with several health problems and a lower quality of life.[8]

Despite the increase in studies on lipedema and greater awareness among health care professionals, its recognition as a disease is recent. In 2018, following the request of the European Society of Lymphology, it was included in the International Classification of Diseases (ICD11) by the World Health Organization as EF02 noninflammatory alteration of subcutaneous fat.[9] It is necessary to promote knowledge of this disease to help patients obtain an early diagnosis and appropriate management.

Pathophysiology

The etiology of lipedema is still under research, and various hypotheses have been suggested.[10] These include genetic predisposition,[11,12] with the epigenetic influence of hormonal changes, particularly estrogens, fat gain, and inflammation, leading to a dysfunction in adipocyte cells and differentiation[13,14] and microvascular dysfunction in lymphatic and blood vessels.[15]

The subcutaneous adipose tissue of lipedema is characterized by an increase in the quantity and structure of fat, which is resistant to weight loss and is therefore considered persistent fat.[16,17] Pathological studies show an increase in adipose tissue due to adipocyte hyperplasia or hypertrophy and cell death due to hypoxia,[18] capillary filtration that could overload a morphologically normal lymphatic system, and capillary fragility that can cause easy bruising.[2]

There is increasing evidence of the presence of a chronic low-grade inflammatory state that contributes to the development of obesity-related disorders, particularly metabolic dysfunction.[19,20]

The dysregulated expression of inflammatory factors, caused by excess adiposity and adipocyte dysfunction, has been linked to the pathogenesis of various pathological processes through altered immune responses. New factors secreted by adipose tissue have been identified that promote inflammatory responses and metabolic dysfunction or contribute to the resolution of inflammation and have obesity-related effects.[21,22] Inflammatory cytokines or adipokines could affect the phenotypic presentation of lipedema or cause disorders that can be confused with lipedema.

Clinical manifestations of lipedema

The patients present a symmetrical and abnormal increase in adipose tissue from the hips, including buttocks, thighs, and calves (for calves, only in lipedema type 3) *(Figures 1A, 2A, and 3A)*. Furthermore, they always present bilateral involvement of the legs, sparing the foot, causing the typical ''cuffing sign'' only in lipedema type 3, which is the abrupt end of the accumulation of fatty deposits that can appear in both the ankles and wrists *(Figure 2A)*.[23] There is an evident disproportion in the distribution of fat in these patients.[24] The presence of symptoms such as pain, heaviness, or discomfort in the legs is necessary for the diagnosis of lipedema.[25,26] Its absence in a patient with increased fat would indicate lipohypertrophy, not lipedema. It can also affect upper limbs.[23]

Patients report worsening leg edema throughout the day due to standing and heat. Furthermore, they report greater sensitivity to pain and the appearance of bruises, spontaneously or from light trauma *(Figure 2A)*.[23]

On the other hand, it has been described that in patients with lipedema, the prevalence of joint hypermobility is much higher than in the general population, which may suggest that it is a comorbidity and may be related to a collagenopathy involved in its condition.[27]

According to a previous study from our group, the differential diagnosis between lipedema and lymphedema can be made

by evaluating the presence of three clinical features: bruising, disproportion between the upper and lower part of the body, and spared feet.[28]

Progression of lipedema, described as a change in volume superior to 10%, was related to global fat increase.[29]

Figure 1. Case 1: 25-year-old patient with type 3 lipedema, stage 1, (A) presenting with easy bruising, pain, and swelling in lower limbs; (B) wearing a footless legging in circular fabric ccl2.

Figure 2. Case 2: 38-year-old patient with type 3 lipedema. (A) Front view and side view. (B) Front view and side view of flat-knit pantyhose worn by the patient.

Figure 3. Case 3: 48-year-old patient with type 2 lipedema (A) affecting hips to knees, sparing the lower part of the legs. (B) Side view of Bermuda pantyhose worn by the patient.

Complementary tests

A blood test with a complete blood count and biochemistry is recommended, with a study of thyroid hormones to rule out systemic causes of edema and to detect comorbidities that may appear.

Imaging tests such as lymphoscintigraphy, lymphofluoroscopy, magnetic resonance lymphography, and high-resolution Doppler ultrasound can provide structural and functional information about the lymphatic system, but do not show any pathognomonic signs of lipedema that could help us with the definitive diagnosis.[30,31]

The lack of a pathognomonic test for lipedema makes it impossible to have a certain diagnosis.

Lipedema definition framework

Through analysis of the literature and consensus among the authors, a definition framework for lipedema was reached based on clinical manifestations *(Table I)*.[32]

According to a recently proposed framework for research in lipedema, a patient should be eligible for studies if she is female, has pain and/or heightened sensitivity and one of the following:

1. All five agreed-upon characteristics are present.
2. Two more agreed-upon characteristics and at least two characteristics from the additional evidence column are present.
3. One more agreed-upon characteristics and at least four characteristics from the additional evidence column are present.

Lipedema definition framework	
Agreed-upon characteristics	***Additional evidence***
1. Female (*)	A. Wrist/ankle cuffing
2. Pain and/or heightened sensitivity (*)	B. Nonpitting edema + negative Kaposi-Stemmer sign
3. Disproportionate distribution of adipose tissue to limbs	C. Onset/exacerbation with hormonal flux
4. Skin and tissue changes	D. Family history
5. Unresponsive to diet	E. Easy bruising without trauma

(*) Must be present always.

Table I. Lipedema definition framework.
Based on reference 32: Keith et al. *Lymphat Res Biol*. 2024;22(2):93-105.

Classification

Based on inspection and palpation, lipedema can be classified in 4 clinical stages of severity.[3-5]

Stage 1: the skin surface is normal, and the subcutaneous fatty tissue has a soft consistency with multiple small nodules.

Stage 2: the skin surface becomes uneven and harder due to the increasing nodular structure (big nodules) of the subcutaneous fatty tissue (liposclerosis).

Stage 3: lobular deformation of the skin surface due to increased adipose tissue. The nodules vary in size and can be distinguished from the surrounding tissue on palpation. The phenomenon of "peau d'orange" can be seen by pressing the skin.

Stage 4: lipolymphedema.

Management of lipedema

Effective management of lipedema, ideally coordinated through a specialized Lymphedema Unit, is associated with improved pain control, limb contour, mobility, and overall quality of life.[5] A multidisciplinary, patient-centered approach

is essential, integrating psychosocial support, self-care education, dietary interventions, physical activity, and, where appropriate, surgical options.

Psychosocial and educational support

Educational interventions are critical to empower patients in long-term disease management. These include counseling on genetic factors, pregnancy, and weight control, as well as daily guidance on compression therapy, skin care, and pain management. Setting realistic, personalized goals fosters adherence and improves psychological outcomes.[5]

Diet and weight management

Dietary interventions should focus on sustainable weight control rather than rapid loss, which may lead to psychological distress and subsequent weight gain. To date, no diets have clearly demonstrated efficacy in lipedema. Diets showing promise include the Harvie and Howell diet,[33] ketogenic diet,[34-37] Rare Adipose Disorders diet,[38] anti-inflammatory and Mediterranean-based regimens,[39] with emerging evidence supporting their role in symptom relief and inflammation reduction. Most of them are still under investigation. Reducing carbohydrate intake and increasing the interval of fasting could also improve edema, inflammation, and fibrosis.

Physical activity

Physical exercise, though historically undervalued in lipedema care, offers notable benefits including improved lymphatic flow, reduced edema, and enhanced mobility.[4,5,40,41] Low-impact aerobic activities, particularly aquatic exercise and strength training, are well-tolerated and effective. High-intensity regimens should be avoided due to the risk of exacerbating pain and bruising. Various types of exercise, such as aquatic exercises and strength training, have been shown to alleviate symptoms and improve the quality of life of patients with lipedema.[42] However, standardized guidelines for prescription are lacking, highlighting the need for recommendations and further research.

Pharmacological treatment

Although various pharmacologic agents (eg, corticosteroids, diuretics, flavonoids) have been proposed, there is currently insufficient evidence to support their routine use in lipedema management.[43] Ongoing research is evaluating their potential in modulating inflammation and edema.

Lymphedema decongestive therapy

Manual lymphatic drainage and compression therapies may alleviate discomfort and enhance quality of life[2,44] but are not proven to significantly reduce volume or prevent progression in pure lipedema cases.[45] These therapies are generally not considered first-line treatment but can help in relieving pain by the means of modulation of C nerve fibers.

Surgical interventions

Bariatric surgery may be considered in patients with significant obesity (body mass index [BMI] >40, or >35 with comorbidities), though its effect on limb volume is limited. Liposuction, particularly power-assisted (PAL) and water-assisted (WAL) techniques, has emerged as a key option for patients with refractory symptoms and functional impairment.[46] Surgical planning must prioritize lymphatic preservation and is ideally pursued following weight optimization. After liposuction, subsequent surgeries to remove excess skin or provide thigh lifting, as well as laser lipolysis may be needed. However, despite surgery, the use of continuous compression will remain essential. A recent study reported a lower use of compression after liposuction without relapse.[47]

Role of compression in lipedema

How does compression work?

Compression therapy primarily exerts its effects by increasing tissue pressure, thereby counteracting capillary leakage—an essential mechanism in the prevention and management of edema. In addition to reducing capillary permeability, it enhances lymphatic absorption through the opening of anchoring filaments in lymphatic capillaries, facilitating the entry of interstitial fluid into the lymphatic system.[48] In cases where lymphatic capillaries exhibit reduced absorptive capacity or impaired lymph transport, compression therapy assists in directing interstitial fluid proximally or into subfascial pathways to promote adequate drainage and reabsorption.[49]

Compression also modulates cutaneous microcirculation, normalizing its function by increasing leukocyte adhesion and improving vasomotor activity, which collectively enhance skin nutrition.[50] Another significant effect is the elevation of tissue oxygen partial pressure, often diminished in advanced chronic venous insufficiency. This is achieved through the breakdown of fibrosclerotic tissue characteristic of advanced stages of venous disease and lymphedema, as well as through the downregulation of proinflammatory cytokines and growth factor receptors.[45]

Within the lymphatic system, compression induces a rise in skin temperature, which leads to the opening of

intercellular junctions between lymphatic endothelial cells and, consequently, an increase in fluid reabsorption. Additionally, it exerts a prolymphokinetic effect by stimulating the myocontractile activity of lymphangions.[51,52]

Available evidence

What do studies say about compression? The few existing studies suggest that compression is beneficial in lipedema patients.

A recently published pilot study with 29 patients with lipedema demonstrated that wearing circular fabric micromassage leggings for 3 hours a day while exercising helped reduce lower-limb volume and pain.[53]

The Spanish National Health Service does not cover compression garments for lipedema owing to the lack of evidence regarding their effectiveness. As a result, the Health Technology Agency conducted a systematic review to assess the safety and efficacy of these garments for the treatment of lipedema. Studies published up to April 2024 in various medical databases were reviewed, evaluating the efficacy and safety of compression garments for people with lipedema when used in conjunction with usual treatment (exercise and dietary measures) versus usual treatment alone. No scientific evidence was found to support the additional value of using compression garments in combination with usual treatment for managing lipedema.[54]

Research in this field has many limitations:

- No definitive diagnostic test for lipedema.
- Few studies.
- Few randomized clinical trials.
- Studies with multimodal therapies.
- Small sample sizes, pilot studies.
- Surveys with subjective outcome measures.
- Adherence to wearing of compression garments not objectively measured.

However, clinical guidelines state that the use of compression aims to reduce symptoms (pain and heaviness), edema, and optimize the contours of the limbs. [1] A recent meta-analysis reported the beneficial effect of compression in the reduction of pain.[55]

Compression can be administered through bandages, self-adjusting devices, or compression garments.[40] In cases of edema with pitting, it is essential to use multicomponent bandages before prescribing compression garments in the maintenance phase.[30]

Despite limited research, several clinical guidelines and consensus documents establish that compression therapy should be part of the conservative treatment for lipedema, and that patients with lipedema should receive compression garments as part of their treatment.[30,40]

Expected effects when using compression in lipedema

Since fat tissue cannot be reduced through compression, compression garments are primarily aimed at improving symptoms, reducing pain and heaviness.[3,5] It is known that they have an anti-inflammatory and oxygenating effect on tissues. Moreover, they can prevent fluid accumulation and the potential progression to lymphatic insufficiency. Patients should be informed that compression is not suitable for reducing adipose tissue.[45]

Recommendations

Currently, there are no guidelines for prescribing compression garments in lipedema.[56] No research studies are available on the type of stockings or the level of compression, so the prescription provided by the physician is essentially empirical. In our experience, a phlebologist is more likely to prescribe circular fabric garments, whereas a lymphologist will probably indicate flat-knit garments.

Compression needs vary depending on the patient's clinical manifestations, pain, and physical ability to don and doff compression garments or bandages; therefore, we recommend involving the patient, physician, therapist, and provider in this process to maximize adherence to compression therapy and effectiveness.

Type of fabric

When choosing and prescribing compression garments, the most suitable fabric should be considered individually, in addition to the required pressure, as the effect of compression treatment depends both on the pressure and the characteristics of the fabric. Compression garment types can be combined to cover the limbs affected by lipedema. Fabrics vary from lightweight and micromassage materials to circular and flat-knit fabrics, with the latter providing the strongest containment.

In some cases, multicomponent low-elasticity compression bandages or velcro devices may be required to reduce edema.[30]

Compression class

The rigidity of the garments or the compression class level is determined independently of the fabric type and based on the stage of lipedema. If pain increases with compression, the compression class can be reduced, or garments can be layered on top of each other. A higher compression class does not necessarily result in better outcomes. Furthermore, the lowest compression class that alleviates the patient's symptoms should be preferred.[40]

Compression in mild stages

In the milder stages of lipedema, it is recommended to prescribe standard circular fabric pantyhose with compression class 2 (ccL 2) for daytime and daily use, with which patients usually report immediate benefits in reducing

edema and heaviness sensation. Since pantyhose are not easy to tolerate and lipedema spares the feet, leggings can be a good alternative as long as the feet do not become edematous *(Figure 1B)*.

Impact of compression hosiery

Despite a high nonadherence rate of 34% among compression hosiery users[57] and 30% in lipedema patients specifically,[58] compression garments have a good impact on lipedema symptoms control.

The top 3 reasons reported for wearing compression garments were to feel supported (73%), for reduction in pain (67%), and for improvement in mobility (54%), according to a survey.[53]

On the other hand, the main complaints about wearing compression garments included the following: doff-and-donning (77.7%), too warm (72.1%), ugly (65.9%), popliteal pain (62.8%), discomfort (62.7%), bad personal image (45.3%), itchy (42.3%), irritations (37.9%), bad fitting (32.9%), bad toleration to compression (13.7%). Patients with a higher BMI complained more of doff-and-donning, discomfort, and bad toleration to compression than patients with a lower BMI.[59]

The patients felt that they had not been fully informed by the prescriptor, and practical information should be given to the patient about correct fitting, wear duration, and washing of the garment, as well as what aids they should buy.[60]

Doff-and-donning difficulty can reduce adherence to wearing of compression garments and limit the independence of the patient.

Case 1

A 25-year-old woman with lipedema type 3, in stage 1, presented easy bruising, pain, and swelling in her lower limbs since the age of 15 *(Figure 1A)*. We prescribed a footless legging in circular fabric ccl2 *(Figure 1B)*, which proved enough to improve her symptoms and was well tolerated during summer, as she was able to wear sandals.

Case 2

We present a 32-year-old woman complaining of lower-limb swelling since puberty. She was diagnosed with lymphedema and obesity and was referred to the Lymphedema Unit of our center. Whereas her BMI was 30.9, her waist-to-height ratio fell into the healthy range (0.46).

She had already tried circular fabric compression garments, but the wrinkles on the popliteal fossa made them uncomfortable to wear. The prescription of flat-knitted pantyhose significantly improved fitting, as shown in *Figure 2B*.

Case 3

This 48-year-old patient has type 2 lipedema (affects hips to knees, sparing the lower part of the legs) *(Figure 3)*. The differential diagnosis with lipohypertrophy must be done: lipedema presents pain and discomfort whereas lipohypertrophy does not. In this case, due to the limb deformity, achieving an adequate fit with circular-knit garments is challenging; therefore, flat-knit compression is recommended. As legs are unaffected and the garment must cover the affected body areas, a Bermuda pantyhose was prescribed. The patient reported satisfaction with the hosiery and exhibited improved adherence *(Figure 3B)*.

Conclusions

The use of compression in the management of lipedema should be recommended in all the patients, regardless of the conservative or surgical approach. The selection of fabric, class, and type of hosiery should be tailored to the individual's specific characteristics, with an emphasis on symptom alleviation.

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Atrophie blanche: a diagnostic and therapeutic challenge

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ABSTRACT

Atrophie blanche (AB) is a distinctive dermatological finding characterized by stellate, porcelain-white, atrophic plaques, commonly located on the lower extremities. Although traditionally regarded as a permanent sequela of chronic venous insufficiency (CVI), AB may also arise from diverse etiologies including livedoid vasculopathy, vasculitis, and medication-induced vascular damage. This review aims to clarify the clinical significance of AB, emphasizing the importance of accurate diagnosis and etiology-based management. AB is not a diagnosis itself but a marker of underlying vascular pathology; thus, a thorough clinical assessment—including duplex ultrasound and, in some cases, histopathological and immunological studies—is essential. Management strategies differ depending on the cause: compression therapy and venous interventions for CVI; anticoagulation for livedoid vasculopathy; and drug cessation in cases of hydroxyurea-induced ulcers. Adjunctive treatments such as punch grafting and advanced wound care can enhance healing and reduce pain of ulcerated AB. Multidisciplinary care is critical for optimal outcomes. Although AB is often associated with difficult-to-heal ulcers, emerging evidence suggests that, with targeted treatment, reversal of lesions might be possible. Further research is needed to better understand the pathophysiology and to establish standardized therapeutic protocols.

Keywords

atrophie blanche | chronic venous insufficiency | hydroxyurea | livedoid vasculopathy | thrombophilia | ulcerated *atrophie blanche* | vasculitis

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Introduction

Among practitioners, there is significant confusion regarding the concept of *atrophie blanche*, which frequently results in misdiagnosis and, consequently, therapeutic failure. For many professionals, due to a lack of awareness, it is erroneously regarded as synonymous with livedoid vasculopathy.

Atrophie blanche (AB) is the clinical term used to describe stellate, ivory-white atrophic plaques with central punctate erythema representing dilated capillaries *(Figure 1)*. These lesions typically occur on the lower extremities, particularly the legs and feet, and may result from various underlying etiologies. It is a descriptive dermatological finding rather than a pathognomonic feature of a specific condition, as it can be associated with multiple clinical scenarios, including chronic venous insufficiency (CVI), livedoid vasculopathy, and vasculitis. As such, a thorough clinical history and examination are essential upon identification.[1] An early adequate diagnosis is essential considering that AB lesions are often painful, and the presence of ulcers within these areas is associated with impaired wound healing and a chronic course. Understanding the link between the characteristic scar-like lesions and their potential to ulcerate is crucial for timely diagnosis and effective management.

Due to the limited number of studies available, this review does not follow a systematic approach and, to enhance its applicability in daily clinical practice, incorporates the authors' own observations.

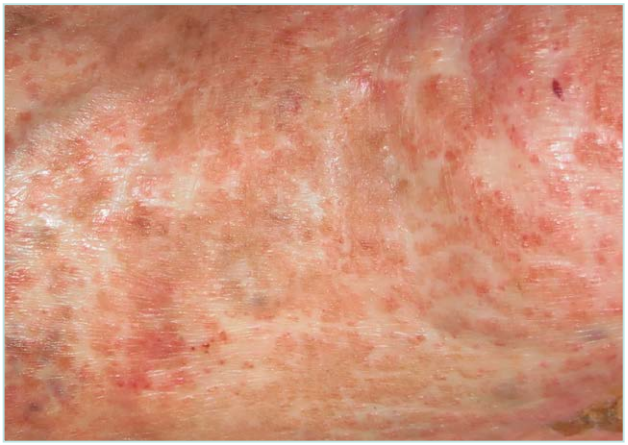

Figure 1. Typical clinical appearance of *atrophie blanche*.

Historical background

AB was initially identified in 1929 by Milian,[2] who described it as a unique type of skin atrophy known as "atrophie blanche en plaque." This first description highlighted that it typically presents as smooth, porcelain-white patches or plaques located on the lower limbs, often surrounded by a pigmented border and visible dilated capillaries (telangiectasias).[2,3] Milian originally associated these lesions with infectious diseases such as syphilis and tuberculosis. However, further research by Gonin[4] demonstrated that approximately 70% of cases were more accurately linked to vascular disorders.

Later, Gougerot and Hamburger proposed that these lesions resulted from chronic capillaritis and categorized AB as a variant of stasis dermatitis.[5] In 1950, Nelson[6] contributed a histological perspective, describing the presence of fibrin occlusions within small blood vessels, reinforcing the idea of an underlying microvascular pathology.

Pathogenesis

The development of AB is primarily attributed to microvascular injury, particularly thrombosis of the capillaries within the subpapillary vascular plexus. This occlusion leads to localized ischemia, resulting in the characteristic ivory-white patches seen in affected skin. As a compensatory response, dilated capillaries or megacapillaries—often observed as red dots—may emerge within these hypoxic areas as part of a dysfunctional repair mechanism. Consequently, any disorder that produces microcirculatory flow diminution can cause tissue infarction and these consecutive scar areas.[7]

Several underlying conditions can contribute to or exacerbate this vascular damage. CVI is one of the most common associated disorders, where persistent venous hypertension leads to endothelial dysfunction, leukocyte trapping, and microthrombi formation.[1] Moreover, a scar from a previous venous leg ulcer can also be considered AB.[1]

It is not uncommon to find erythematous-purpuric or brownish macules adjacent to areas of AB. These may evolve into papules or plaques, which can become verrucous

and eventually ulcerate. Such lesions are referred to as acroangiodermatitis secondary to CVI *(Figure 2)*. They represent a reactive proliferation of small blood vessels in response to longstanding vascular dysfunction, most commonly poorly controlled venous hypertension.[8]

It is essential to provide a more in-depth analysis to understand the role of microangiopathy secondary to CVI in the pathogenesis of AB. The severity of microangiopathy in patients with CVI determines the extent of the trophic disturbances of the skin. In the initial stages of CVI, the microangiopathy is characterized by dilatation of the blood capillaries. In more severe stages of CVI, microthrombosis of capillaries can be found contributing to the locally reduced capillary density. Most likely, these microthromboses are the consequence of interactions between leukocytes and other blood cells with the vessel wall of postcapillary venules. The capillaries are stuffed with red blood cell aggregates, which would not be the case if thrombosis were to start in the terminal arterioles or at the arterial side of the capillary loop.[9] In such cases, the capillaries are void of corpuscular blood elements. At the border zones of AB spots, which are potential sites for venous ulcer formation, the capillary density is significantly reduced, and the capillaries are even more tortuous than in the mild stages of the disease. In these cases, the increase in capillary size is most likely necessary to increase the exchange area between intra- and extravascular compartments for fluids and soluble substances. Similar changes in capillary morphology are observed at cutaneous scar sites after injuries.[9]

In the center of AB, avascular fields are present, which result in enlarged diffusion distances and in significantly prolonged diffusion times.[10]

A condition that often comes to mind—and, as previously mentioned, is sometimes mistakenly used synonymously with AB—is livedoid vasculopathy, a rare thrombo-occlusive disorder primarily affecting the superficial dermal vasculature. Livedoid vasculopathy has been given multiple names in the literature including livedo vasculitis, segmental hyalinizing vasculitis, livedo reticularis with summer ulceration, Milian white atrophy, AB en plaque, and PURPLE (painful Purpuric Ulcers with Reticular Pattern of Lower Extremities), among others.[1]

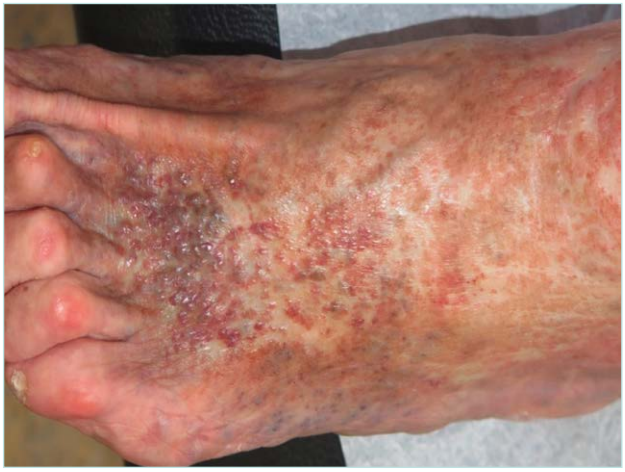

Figure 2. Clinical picture of acroangiodermatitis associated with *atrophie blanche* in patients with chronic venous insufficiency.

It typically presents with recurrent, painful ulcerations on the lower extremities that eventually heal into ivory-white, atrophic scars resembling those seen in AB. Although the clinical appearances can be similar, the underlying pathophysiology of livedoid vasculopathy is more strongly associated with hypercoagulable states and primary vascular occlusion, rather than venous insufficiency.[7]

The occlusion of blood vessels by fibrin thrombi is a primary event in livedoid vasculopathy. There is evidence for a decrease in fibrinolytic activity and an increase in thrombogenic activity. Several cases have been reported in association with other thrombophilias, such as with the lupus-type anticoagulant, hyperhomocysteinemia, increased levels of anticardiolipin, protein C deficiency, cryoglobulinemia, factor V Leiden mutation, plasminogen activator inhibitor 1 promoter mutation, and antithrombin III deficiency.[11]

Additionally, certain medications, such as hydroxyurea, have been implicated in the pathogenesis of AB. The underlying mechanisms behind the development of ulcerated AB in patients treated with hydroxyurea remain unclear. However, this antineoplastic agent, commonly used in myeloproliferative syndromes, also inhibits epidermal cell turnover and may induce microvascular alterations.

Clinical features of ulcerated *atrophie blanche*

Discussing AB inevitably involves addressing skin ulcers, as these lesions not only represent the possible sequelae of previous ulceration—as observed in livedoid vasculopathy—but also constitute a clinical context in which new ulcers may develop. This is particularly evident in CVI, where AB often precedes the onset of ulcers that are typically very painful and resistant to treatment *(Figure 3)*.

Although ochre dermatitis, due to its dark coloration, may appear more severe than AB, the opposite is actually true. The appearance of AB indicates a more advanced stage of venous insufficiency, and the ulcers that develop in this context tend to be more painful and resistant to treatment than those on legs with ochre dermatitis.

In the context of CVI, ulcerated AB typically presents as a superficial wound with a sclerotic, whitish-yellow base, often punctuated by small, highly vascularized areas.

Regarding livedoid vasculopathy, the typical clinical presentation consists of painful purpuric reticular lesions, most commonly affecting middle-aged women. These lesions typically appear on the dorsum of the feet and the inframalleolar region, and often progress to ulceration and the formation of AB.[1] Since livedoid vasculopathy progresses in flare-ups, it is typical to find small pinpoint-crusted ulcers mixed with areas of AB patches in the periwound areas with associated telangiectasia *(Figure 4)*. The clinical appearance of livedo reticularis may relate to dilated or contracted blood vessels in addition to hyalinizing disorders.[1]

Considering patients receiving hydroxyurea treatment, resulting ulcers are typically very painful, tend to appear after several years of treatment, and may sometimes be triggered by minor trauma.[12] They are often multiple and bilateral, typically developing in the perimalleolar region. They are generally well-defined and shallow with an adherent, yellow, fibrinous base *(Figure 5)*.

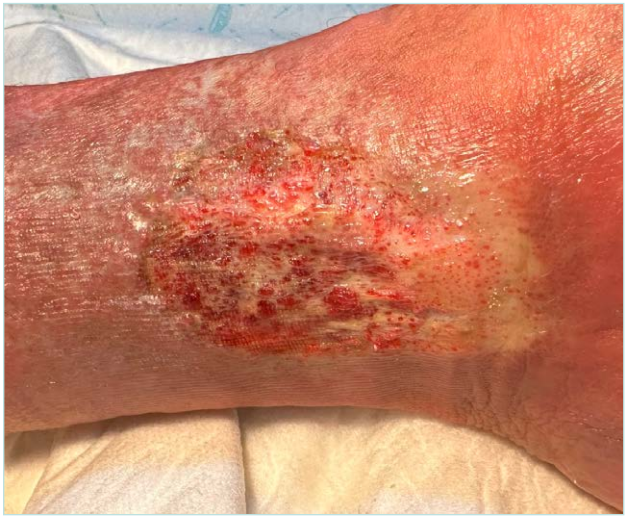

Figure 3. Ulcerated *atrophie blanche* in the context of chronic venous insufficiency.

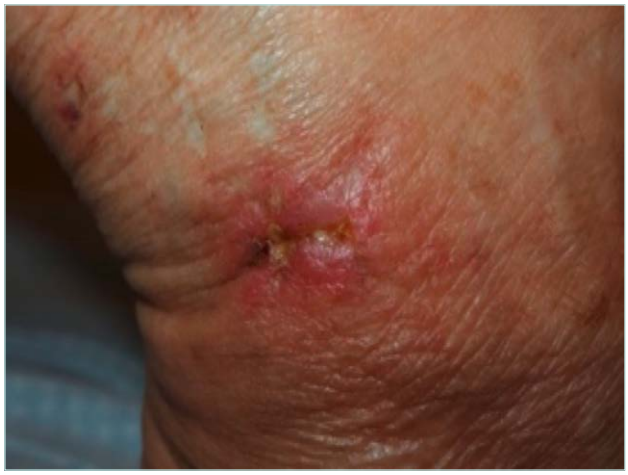

Figure 4. Pinpoint ulcer and *atrophie blanche* due to livedoid vasculopathy.

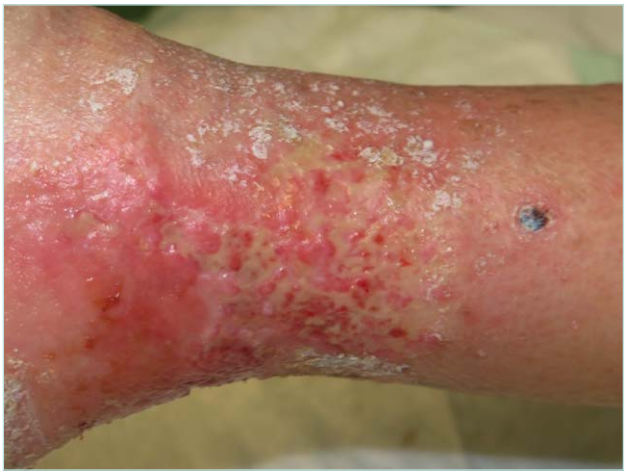

Figure 5. Hydroxyurea-induced leg ulcer.

Diagnosis of ulcerated *atrophie blanche* and its underlying conditions

The diagnosis of ulcerated AB requires a comprehensive approach. Whereas the patient's medical history—including current and past medications—is important, the cornerstone of diagnosis is clinical examination. The presence of clinical signs of venous insufficiency typically suggests an underlying venous etiology, which is the most common cause of AB. Clinically, these patients fall under stage C4b of the CEAP (clinical, etiological, anatomical, pathophysiological) classification, which includes skin changes such as AB.[13] In this context, a venous duplex ultrasound (Doppler ultrasound) is strongly recommended to assess for underlying chronic venous disease and guide further management. A skin biopsy is not necessary for diagnosis, but it would typically reveal dermal fibrosis, dilated and proliferated capillaries in the upper dermis, and hyperpigmentation of the basal layer of the epidermis or melanin-laden melanophages in the dermal papillae.[1]

However, in middle-aged women, when AB appears following previous ulcers located in the distal third of the lower extremities, livedoid vasculopathy should be strongly considered *(Figure 6)*. This condition can mimic other forms of chronic ulceration and warrants a more specific diagnostic approach.[7]

Consequently, in patients presenting with AB in the absence of CVI, a comprehensive diagnostic work-up is essential to identify potential underlying conditions and guide appropriate treatment.[14] A skin biopsy remains the gold standard for confirming the diagnosis, typically revealing intraluminal fibrin deposition, thrombosis, segmental hyalinization, and endothelial proliferation.[7,14] Given the thrombotic nature of livedoid vasculopathy, thrombophilia screening is recommended and should include assessment of protein C and S, antithrombin III, Factor V Leiden mutation, prothrombin gene mutation, antiphospholipid antibodies (including anticardiolipin antibodies and lupus anticoagulant), and homocysteine levels. Di Giacomo et al demonstrated procoagulable laboratory abnormalities in 52% of their study population.[15]

Autoimmune markers such as antinuclear antibodies (ANA), anti-SSA/SSB antibodies, and rheumatoid factor should be considered due to potential overlap with autoimmune diseases. Direct immunofluorescence (DIF) may also assist in distinguishing livedoid vasculopathy from other vasculopathies, with findings including vascular deposition of immunoreactants such as C3 and immunoglobulin M (IgM). Collectively, these investigations support a thorough and targeted approach to the diagnosis and management of livedoid vasculopathy.[14-16]

Deep and multiple biopsies may be necessary to exclude other entities such as medium-vessel vasculitis, particularly polyarteritis nodosa (PAN), which may present with similar features. A study by Mimouni et al highlighted that medium-sized vasculitides, such as PAN, can present with ulceration leading to AB-like scarring. In their cohort, 6 out of 29 patients with AB had underlying PAN, emphasizing the importance of considering vasculitis in the differential diagnosis, especially in the absence of venous insufficiency.[17]

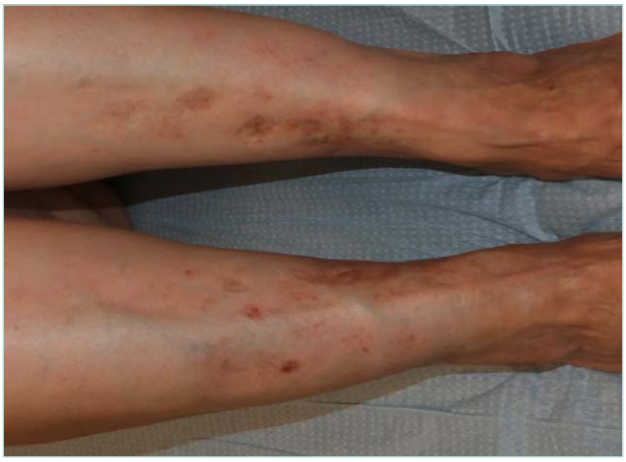

Figure 6. Typical involvement of the distal aspect of lower limbs in livedoid vasculopathy.

Dermoscopy can also aid in the diagnostic process. Common dermoscopic findings include centrally located crusted ulcers or ivory-white areas, often surrounded by reticular pigmentation and increased vascular structures. These features correlate histopathologically with dermal fibrosis, epidermal basal layer hyperpigmentation, and capillary proliferation.[18]

Treatment strategies for ulcerated *atrophie blanche*

The management of AB and ulcerated AB depends on its underlying cause. Strategies differ significantly due to their distinct pathophysiological mechanisms.

The treatment of AB secondary to CVI focuses on reducing venous hypertension and promoting wound healing. Compression therapy must be adjusted to the patient's tolerance, as these lesions are usually very painful. Pharmacological interventions, including venoactive agents such as micronized purified flavonoid fraction (MPFF), pentoxifylline, and sulodexide, can help reduce inflammation and improve microcirculation; combining these with compression may enhance healing.[19]

Lifestyle modifications, such as leg elevation, regular physical activity, and weight management, are also recommended to reduce venous hyperpressure. In case of superficial venous system insufficiency, interventional or surgical options like endovenous ablation are indicated.[19]

Although AB has traditionally been considered a permanent skin change associated with CVI, appropriate targeted treatments, such as endovenous procedures, may lead to its reversal, as has been published in a case after radiofrequency ablation and phlebectomies, followed by additional foam sclerotherapy.[20]

Despite an extensive review during which no previously published cases were identified, in our clinical practice we have observed reversal of the perilesional AB 6 weeks after punch grafting, as shown in this case depicted in *Figures 7 and 8*.

The treatment for livedoid vasculopathy involves a multifaceted approach aimed at managing pain, promoting ulcer healing, and preventing recurrence. There is a need for randomized clinical trials to better establish these treatments in clinical practice due to the current reliance on low levels of evidence, primarily from case reports and case series.[21]

Anticoagulants are the cornerstone of livedoid vasculopathy therapy, with rivaroxaban—a direct oral anticoagulant—demonstrating significant efficacy in reducing pain and facilitating ulcer healing.[22] Low molecular weight heparin is also commonly used and associated with favorable outcomes.[23]

Antiplatelet agents such as aspirin and clopidogrel are frequently employed to inhibit platelet aggregation and thrombus formation, often in combination with anticoagulants. Corticosteroids have also been used to reduce inflammation.[21] In refractory cases, intravenous immunoglobulins (IVIg) have proven effective, leading to rapid and notable improvement in both pain and ulceration.[24,25] Although the mode of action of IVIg is not completely understood, it induces modulation of cytokine production, neutralization of pathogens, and inhibition of complement-mediated damage. Multiple case studies have demonstrated the response of patients with livedoid vasculopathy to IVIg with minimal complications. Cessation of smoking may also be beneficial.[26]

A novel combination regimen referred to as "CHAP" has been recently described and consists of cilostazol, hydroxychloroquine, aspirin, and pentoxifylline.[27] This combination aims to address the thrombotic and inflammatory components of the disease, leveraging the antiplatelet and vasodilatory effects of cilostazol and aspirin, the immunomodulatory properties of hydroxychloroquine, and the hemorheological benefits of pentoxifylline.

The treatment for ulcers due to hydroxyurea primarily involves discontinuation of hydroxyurea. The ulcers may resolve after stopping the drug. Nevertheless, it is not unusual to encounter wounds that remain despite its discontinuation. For patients who require ongoing treatment for their underlying condition, alternative therapies to hydroxyurea should be considered. These alternatives may include other cytoreductive agents such as anagrelide, depending on the specific indication and patient tolerance.[12,28]

Despite the lack of research, compression therapy, due to its anti-inflammatory effect, might be considered an adjuvant treatment, and preventive measure, for all cases of ulcerated AB.[23] In addition, it should be taken into account that venous insufficiency may be also present in these patients.

The ulcers in the context of AB, regardless of their underlying cause, tend to be very painful and resistant to treatment as they appear in scar areas. Taking into account that ulcerated AB can be considered a wound on scar tissue, it must be treated as a hard-to-heal wound. Punch grafting, associated with compression therapy may accelerate wound healing and decrease pain.[29] Even when the wound bed is not in optimal condition for grafting, skin grafts may still take. And even if they do not fully adhere to the wound bed, they can still contribute to healing and pain reduction by releasing growth factors and beneficial cellular components.[30] The key is to minimize dressing changes as much as possible and perform only minimal wound cleansing, in order to preserve the local healing microenvironment.

Pain control is essential in all conditions in the context of ulcerated AB though often more challenging in livedoid vasculopathy due to the neuropathic component of ulcer-associated pain.

Multidisciplinary care is key in the effective management of AB, particularly when associated with complex conditions such as livedoid vasculopathy. Given its multifactorial etiology and potential complications, a collaborative approach involving multiple specialties ensures comprehensive evaluation and treatment, including dermatologists, vascular surgeons, phlebologists, hematologists, pain specialists, and wound care specialists. This coordinated, multidisciplinary strategy allows a more personalized and effective management plan, improving both clinical outcomes and patient quality of life.[1]

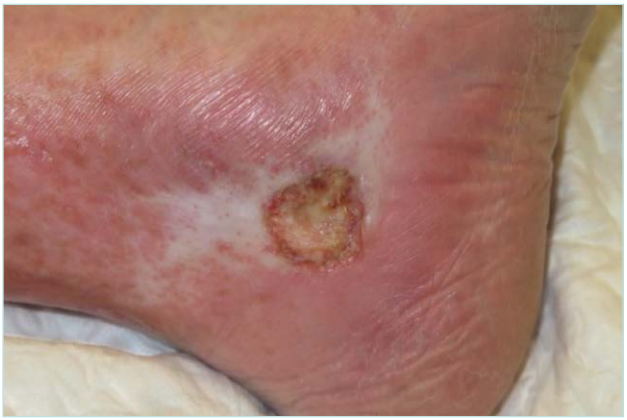

Figure 7. Ulcerated *atrophie blanche*.

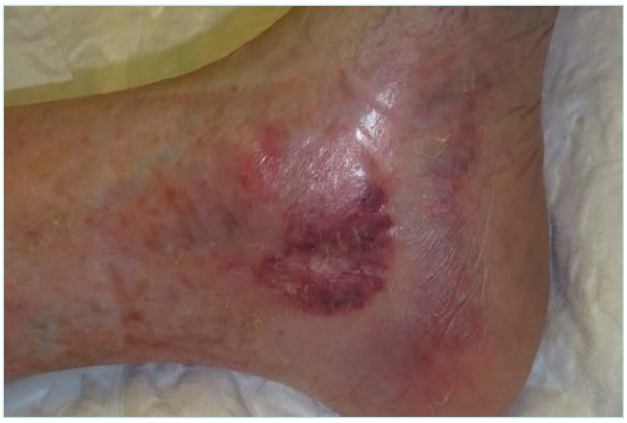

Figure 8. Complete healing and *atrophie blanche* reversal 2 months after punch grafting.

Key takeaways for clinicians

- Patients with AB commonly present in wound care clinics either following a healed ulcer or without preceding ulceration.
- Though often associated with CVI, AB is also observed in thrombotic and inflammatory dermatoses, and recognizing these contexts is critical for timely, individualized care.

- Early and accurate diagnosis, aided by dermoscopy and, when needed, histopathology, is essential to prevent complications like painful, recurrent ulcers.
- Management must be tailored to the etiology: compression therapy and venous interventions for CVI, anticoagulation for livedoid vasculopathy, and drug discontinuation for hydroxyurea-induced ulcers. Adjunctive strategies like punch grafting and proper wound care can accelerate healing and improve quality of life. Multidisciplinary care is often necessary for optimal outcomes.
- Much of the current literature is based on case reports and small observational studies. Randomized controlled trials are urgently needed to define the most effective therapies for each subtype of ulcerated AB. Additionally, the reversibility of AB lesions, as suggested by recent studies, warrants further investigation.

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Combination of transdermal laser and sclerotherapy in treating reticular veins: an evidence-based approach to modern phlebology

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ABSTRACT

Chronic venous disease is a widespread condition, with telangiectasias and reticular veins (C1 disease according to the CEAP classification) among its most frequent and cosmetically concerning early manifestations. Whereas sclerotherapy remains the gold standard for their treatment, newer approaches have emerged aiming to optimize results and reduce complications. Among them, the combination of transdermal long-pulsed 1064-nm Nd:YAG laser with sclerotherapy has gained growing attention, particularly in the form of the cryo-laser cryo-sclerotherapy (CLaCS) technique, which merges laser-induced vessel damage with sclerotherapy, enhanced by cryo-cooling and augmented reality guidance. Additionally, the sequential use of transdermal laser following foam sclerotherapy has also shown clinical value in improving outcomes.

Evidence from randomized trials and long-term follow-up cases points to higher clearance rates, better aesthetic outcomes, and fewer adverse effects when laser and sclerotherapy are used in tandem. The evolving literature, supported by international guideline mentions, reflects increasing clinical acceptance of these multimodal strategies.

Drawing from both personal clinical experience and recent studies, this review takes a closer look at the growing evidence behind CLaCS and other laser-sclerotherapy combinations, exploring their mechanisms, clinical data, and practical advantages as a patient-centered evolution in phlebology, offering effective minimally invasive solutions that align with what today's patients are really looking for.

Keywords

aesthetic phlebology | combination therapy | cryo-laser cryo-sclerotherapy (CLaCS) | minimally invasive techniques | Nd:YAG 1064 nm | reticular veins | sclerotherapy | telangiectasias | transdermal laser | venous disease treatment

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Introduction

Chronic venous disease (CVD) includes a broad spectrum of vascular conditions affecting millions worldwide. Reticular veins, bluish subdermal vessels between 1–3 mm in diameter, often coexist with telangiectasias and feed superficial venous networks. Although often perceived as cosmetic, these conditions may significantly impact a patient's quality of life, and their aesthetic prominence often motivates treatment, demanding effective, low-risk interventions.[1,2] The prevalence of CVD is increasing, with lifestyle factors such as prolonged standing or sitting, obesity, and lack of physical activity contributing to its development, making patient education and awareness vital components of management strategies.

Sclerotherapy—liquid or foam—remains the gold standard for treating reticular veins.[3-5] Though effective, it is not without drawbacks, especially with foam: the risk of postsclerotherapy hyperpigmentation (PSH), session volume limitations, variable results depending on vein size and operator experience, and reports of major systemic complications. Additionally, patients may experience discomfort during the procedure and require multiple sessions to achieve optimal results.[6,7] Microphlebectomy also yields satisfactory results but requires surgical expertise and, though minimally invasive, involves a longer downtime and is not free from the risk of scarring, which makes it not suitable for some patients.[8]

Over the past few years, transdermal laser therapy has become a significant adjunct, which can enhance treatment efficacy and cosmetic results, when associated with sclerosing agents. This hybrid approach provides a treatment option with a lower risk of complications and quicker recovery times. Laser precise treatment of reticular veins gives better patient satisfaction and results. As research continues, the combination of laser therapy and traditional treatments shows great potential for the development of new and improved treatments of reticular veins.

Evolving use of transdermal lasers

The concept of transdermal lasers for vascular medicine focused initially on the treatment of port-wine stains and has expanded to include conditions such as telangiectasias and reticular veins. Initial clinical observations showed that the long-pulsed (LP) 1064-nm Nd:YAG (neodymium:yttrium-aluminum-garnet) laser was successful in treating deeper vascular lesions, for its wavelength allows deeper penetration at the same time that it targets deoxyhemoglobin (principles of selective photothermolysis), but risks were also identified. Bruising, edema, blistering, and scarring were the most reported complications and have been primarily attributed to the high-energy settings necessary for optimal treatment, particularly in the absence of adjunctive cooling mechanisms designed to reduce epidermal damage.[9,10]

With the development of dynamic cooling devices such as contact coolers and cold air blowing equipment, it became easier to preserve the epidermis and lower the incidence of thermal-related adverse effects, increasing the range of those who can benefit from this kind of treatment. Also, as the cold can cause numbing of the skin, it significantly improves patients' comfort during the treatment.[11,12] These continued innovations in laser technology emphasize the importance of both efficacy and safety when searching for ideal treatment of vascular lesions.

Despite technology's constant development, it was noted that the results for laser treatment of reticular veins were not consistent and were sometimes unsafe. As the quest to treat reticular veins with laser alone was met with limited success, the stage was set for techniques like cryo-laser cryo-sclerotherapy (CLaCS), in which the laser is not a standalone, but a partner to enhance the action of sclerosant, promoting synergic thermal and chemical treatment effects, thus redefining the role of transdermal lasers in vein treatment: from replacement to enhancement.

Synergistic approach: laser plus sclerotherapy

Recognition that lasers alone could not consistently or safely treat reticular veins led to hybrid approaches. Transdermal laser therapy used in combination with sclerosing agents provided higher efficacy and cosmetic outcomes, while offering reduced risk of complications and quicker recovery times.

The CLaCS method was born in Brazil, developed by Dr Kasuo Miyake and his team at Miyake Clinic. The approach was innovative—using low-energy LP 1064-nm Nd:YAG laser pulses followed by small-volume injections of 75% dextrose (a mild osmotic sclerosant agent), all performed under

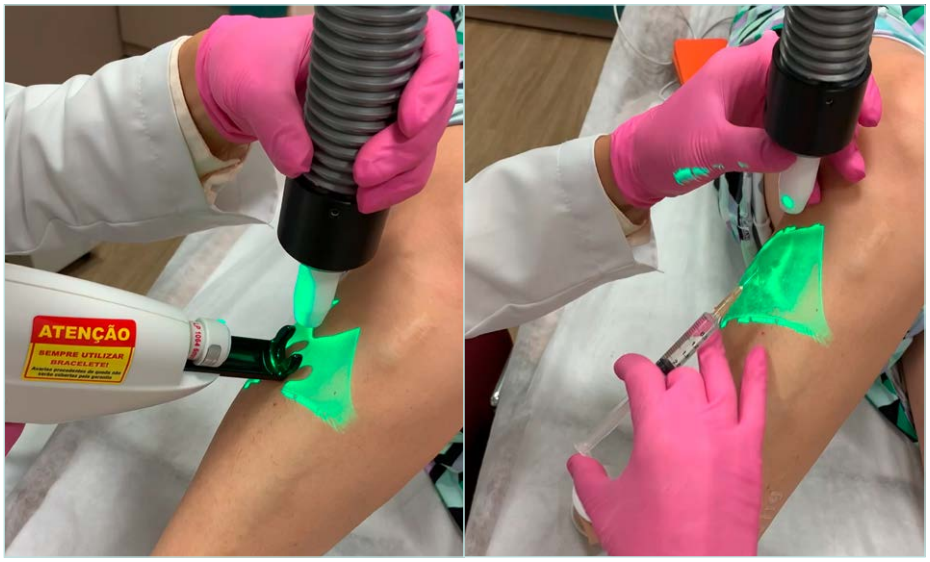

Figure 1. Cryo-laser cryo-sclerotherapy (CLaCS) sequence.
- Skin cooling (- 20 ºC cold air)
- Nd:YAG 1064 LP
- 50-70 J/cm² – Spot size 6 mm / 15-ms pulse duration /1-2 shots / 5 mm
- Dextrose 75% injection
- Blood stop with cotton balls and tape

continuous cryotherapy. In 2003, the technical foundation of CLaCS and their 1-year follow-up were presented in a Joint International Laser Conference in Edinburgh, confirming that the approach offered long-lasting cosmetic results with fewer complications compared with monotherapy. In 2019, the white paper describing the details of the technique was published.[13] The laser parameters, typically a 6-mm spot size, 15-ms pulse, and 50–70 J/cm² fluence, were carefully selected to achieve the perfect balance between depth and safety. Cryo-cooling made it possible to deliver enough energy to target the vein wall while protecting the skin from burns. The goal: improve cosmetic results while minimizing complications.

The sequence used in CLaCS *(Figure 1)* allows the laser to promote thermal lesion and edema of the vein wall, causing immediate vasospasm and partial collapse of the vessel. The smaller internal diameter of the vessel then prolongs the contact time of the sclerosant with the endothelium—enhancing its effect even at lower doses. This dual action leads to efficient closure with fewer side effects like pigmentation or inflammation.

The photo documentation of treatment progress is a steppingstone in CLaCS, and its importance has been reinforced by a 2018 publication that showed the shift of patients' perception of cosmetic outcomes after being shown before and after pictures *(Figure 2)*.[14]

The addition of augmented reality devices, such as VeinViewer, allowed more precise targeting of feeder veins, further refining the technique. In fact, the development of this technology was itself linked to the evolution of CLaCS. In 2006, Miyake and colleagues introduced a novel near-infrared imaging system that projects real-time processed images of subdermal veins directly onto the patient's skin. At that time, the device was proven to easily show veins that were too deep for the naked eye and too shallow for ultrasound detection.[15] By allowing both laser application and sclerosant injections to be guided in real time, without the device being put in direct contact with the skin, this technology helped transform CLaCS into a more controlled and anatomically precise method.

As clinical experience expanded, so did scientific support. In 2012, Moreno-Moraga and colleagues demonstrated that

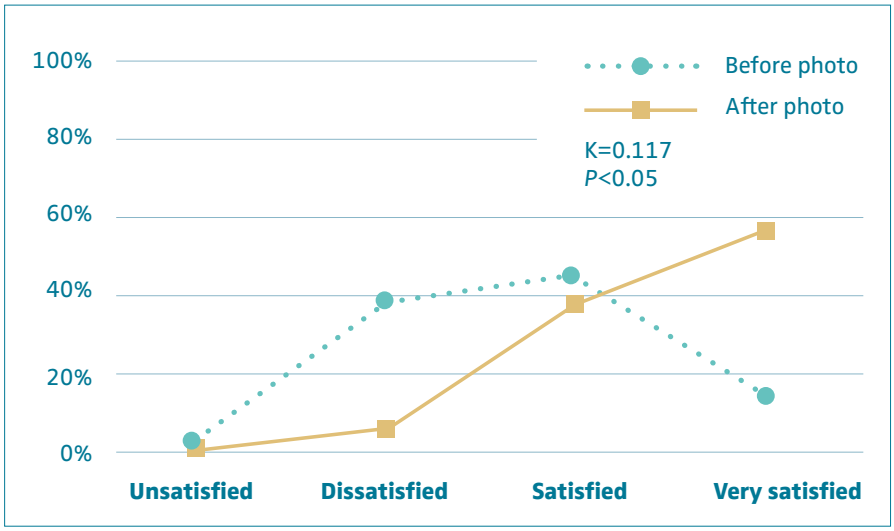

Figure 2. Patients' satisfaction before and after viewing a photograph at the 2-month follow-up.
After reference 14: Santiago et al. *Phlebology*. 2018;33(4):282-287.

combining polidocanol with repeated low-fluence laser pulses provided superior results, reducing the risk of pigmentary changes in Fitzpatrick IV patients, who are known to be more prone to postsclerotherapy pigmentation due to increased melanocyte activity.[16] Two years later, a large randomized trial by the same group involving 517 legs confirmed that Nd:YAG laser used after foam sclerotherapy significantly improved long-term clearance.[17] The sequence here is different from CLaCS, as the laser is applied after the sclerosant. The reasons for success of this approach aren't totally understood yet, but the fact that the foam enhances the light scattering in the tissue and then the beam absorption becomes larger[18] plays an important role in it.

Cryotherapy became especially valuable for patients with higher Fitzpatrick skin types.[12] Later insights from Miyake's team emphasized that cryo-cooling enhanced thermal selectivity and procedural safety, supporting the method's broader application in diverse patient populations.

Recognizing the growing interest and supporting evidence, a 2020 publication laid out the state-of-the-art on CLaCS. This expert summary contextualized the technique as a major advancement in venous treatment and highlighted its efficacy for reticular veins and telangiectasias, especially in patients seeking less invasive and low-risk procedures, with high aesthetic payoff. It also upholds the importance of standardizing laser parameters, sclerosant concentration, cryotherapy settings, and imaging tools, advocating for a reproducible and globally adoptable approach.[19]

In 2023, a triple-blind randomized clinical trial added to that evidence comparing 2 sclerosants—75% dextrose and 0.3% polidocanol diluted in dextrose—under the same CLaCS protocol. Both agents were effective, but lower posttreatment pain and slightly better clearance at augmented reality analysis were achieved with polidocanol diluted in dextrose. The findings highlight the flexibility of the method, with both agents performing well under controlled, standardized conditions.[20]

That same year, the long-term promise of CLaCS was confirmed in a case report from Miyake et al, detailing an 11-year follow-up of a patient treated with augmented reality–guided CLaCS. The results were sustained vein clearance, minimal recurrence, and high satisfaction, supporting the technique's durability and the added value of image-guided precision.[21]

In 2024, a randomized controlled trial compared CLaCS against foam sclerotherapy alone. In this trial, CLaCS achieved complete clearance in 100% of treated limbs versus 85.3% in the foam group, with significantly fewer pigmentation events (36.9% vs 78.7%), further solidifying the method's safety and aesthetic outcomes.[22]

A recent case report introduced the "Cryo Laser after Foam" (CLAF) technique,[23] expanding the scope of combination therapy to include larger-caliber reticular veins. In this approach, foam sclerotherapy with polidocanol is also administered first, followed by immediate application of 1064-nm Nd:YAG laser along the same vein pathway, all under continuous cold air cooling, targeting veins greater than 2.5 mm—and up to 5 mm in diameter. The reported patient had excellent clearance of the targeted reticular varicosities with good cosmetic results. The authors note that combining modalities helped mitigate common sclerotherapy side effects like hyperpigmentation and matting. This single-case experience aligns with emerging evidence that foam plus laser in one session can improve efficacy and minimize side effects, particularly in blue reticular veins that often show suboptimal response to monotherapy.

Guidelines and future directions

In the past few years, scientific validation has aligned with clinical enthusiasm regarding the combination of transdermal lasers and sclerotherapy for treating reticular veins and telangiectasias, with a growing body of studies supporting the efficacy and safety of this multimodal approach, particularly CLaCS, and International Guidelines have started to acknowledge the potential of this association in managing superficial venous disorders.

The European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines[3] state that "Cryo-Laser Cryo-Sclerotherapy guided by augmented reality (CLaCS) is a new option for treating telangiectasias, reticular and feeder veins, with promising results, although more studies are required."

Additionally, the same guidelines highlight that "combining 1064 nm Nd:YAG long-pulse laser with foam sclerotherapy has demonstrated improved efficacy over foam sclerotherapy alone. Specifically, studies have shown that this combination leads to better clearance rates and sustained results over time." This inclusion reflects the growing recognition of CLaCS and other combined treatments as valid alternatives for the aesthetic and functional management of superficial venous conditions. This multimodal approach aligns with patient expectations for faster, more complete results, with fewer complications.

The 2020 update to the CEAP (Clinical-Etiology-Anatomy-Pathophysiology)[24] classification system further encourages standardized assessment of venous disease classification in clinical trials of new techniques, enhancing the system's precision and applicability in research and clinical practice.

The demand for evidence-based, efficient, and cosmetically favorable outcomes makes it likely that these hybrid techniques will continue to gain prominence in clinical practice.

A bit of my own perspective

Having incorporated the LP 1064-nm Nd:YAG transdermal laser into my practice in 2011—initially as a cosmetic touch-up tool for treating small telangiectasias, after reticular veins sclerotherapy or phlebectomy—it was not until 2017 that I began performing the full CLaCS technique.

The most striking difference I observe with combined techniques is the consistent delivery of faster and more refined results, with significantly fewer sessions required. *Figure 3* illustrates an example of a patient that underwent a single session of CLaCS, before and 3 months after treatment.

Also, there is no surgical downtime and, notably, much less pigmentation in patients with darker skin types. Even when treating larger veins with foam, the contrast in outcomes between using foam alone and combining it with laser is easy to spot.

I am often asked—or even challenged—about whether lasers are necessary, with colleagues arguing that excellent results can be achieved without them. I agree that traditional approaches like sclerotherapy and microsurgery can yield solid outcomes, and I understand how difficult it may be to move away from familiar methods, even when alternative techniques begin to show clearer benefits. Still, it is impossible to overlook both the technological progress and the increasing volume of data showing that combining transdermal lasers with sclerotherapy consistently leads to fewer complications, especially when it comes to cosmetic results.

The doubts about whether to incorporate (or not) laser therapy in one's practice tend to appear mostly when we get to the subject of the initial investment and how to return it. These novel techniques involve technology—laser equipment, cooling devices, illuminating devices and so on—and they all have a cost to be taken into consideration. That is the main reason hybrid approaches often find their place in private practice settings. When the decision is made wisely, respecting the physician's professional and financial moment, it is very unlikely that one will later refrain from using it. On the contrary, enthusiasm will probably grow with experience and with supporting literature continuously expanding.

Considering time is by far one of our most valuable assets nowadays, treatments that offer faster outcomes, fewer clinic visits, and minimal downtime—while also reducing complications—represent a true competitive edge. Patients recognize this, and they are willing to pay for it.

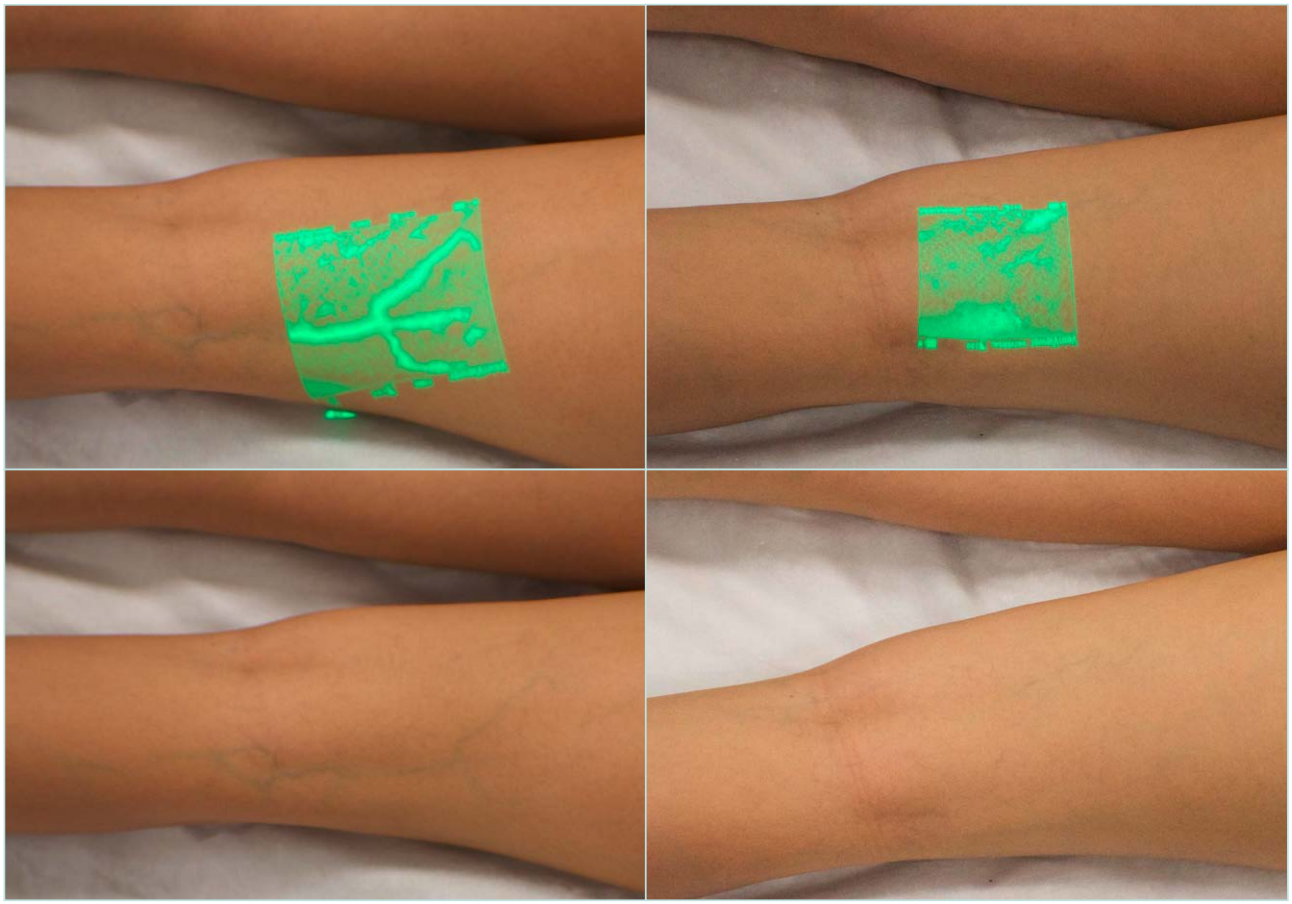

Figure 3. Example of a patient that underwent a single session of cryo-laser cryo-sclerotherapy (CLaCS), before and 3 months after treatment.

Professor Kasuo Miyake, from whom I learned the CLaCS technique back in 2017, used to say to us: "CLaCS: Present is telling. Future will give the evidence." And as evidence keeps building, what was once considered an innovation surrounded by skepticism is steadily redefining what we now expect from reticular vein treatment.

Conclusions

By combining the effects of transdermal laser, sclerotherapy, and the protective effects of skin cooling, these hybrid techniques offer a comprehensive solution tailored to modern phlebology. Providing enhanced effectiveness while minimizing adverse effects, they represent a significant evolution in the treatment of reticular and telangiectatic veins, particularly for patients seeking better aesthetic outcomes with fewer sessions and less complications. Allied with continued research and refining, they are already transforming venous disease management.

While formal recommendations remain conditional and pending further high-quality evidence, the accumulation of positive clinical outcomes is shaping the perception of laser-assisted sclerotherapy as a practical, effective, and viable alternative to traditional sclerotherapy methods, particularly in cases where standard sclerotherapy may fall short.

The question is no longer whether to choose between laser and sclerotherapy—but how best to use them together for safer, more effective, and longer-lasting results.

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Management of special cases in chronic venous disease: what do I do?

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ABSTRACT

Chronic venous disease is one of the most frequent consultations in our daily practice, so we must consider the management of complications and special cases that are more frequent than expected. If as physicians we seek to improve patients' quality of life, we need multidisciplinary management to achieve this goal.

Keywords

age | chronic venous disease | coagulopathy | complication | elderly | obesity | treatment

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Introduction

If we understand the etiology, natural history, and evolution of venous disease, we know that genetics, age, female sex, obesity, pregnancy, prolonged periods of standing, and greater height are factors that contribute to the development of varicose veins.[1]

Age and obesity have also been described as factors that contribute to the development of varicose veins in both the Edinburgh Venous Study and the Framingham Study.[2-4]

Venous disease in patients with obesity

Obesity is one of the known triggering factors of chronic venous insufficiency (CVI). If we add to this the fact that most obese patients are sedentary, the percentage of chronic venous disease (CVD) is higher. Often, patients with chronic obesity also present with flat feet, which is a lowering of the plantar arch. As the arch is lower than usual, the foot falls inward, causing pain in the muscles on the inner side of the leg, resulting in tendonitis. Another cause is posterior tibial dysfunction. This means that the muscle that supports the arch stops working, causing the foot to fall further inward. Another cause of pain also occurs on the back of the foot when the arch collapses, causing the bones in the dorsal area to produce osteoarthritic spikes. Any of these causes of flatfoot, over time, creates a vicious cycle of pain, failure of the pump of the ankle joint and distal calf muscle, immobility, sedentary lifestyle, and obesity as observed in studies by Belczak et al[5] and Cavalheri et al.[6] In the 2013 study by Belczak et al, increasing body mass index (BMI) correlates with reduced joint mobility (Kruskal-Wallis test: $P<0.0001$); an increase in clinical, etiological, anatomical, and pathophysiological (CEAP) classification also correlates with decreased joint mobility; and an increase in age is associated with increased CEAP classification (Kruskal-Wallis test: $P<0.0001$); thus, it was concluded that obesity is associated with impaired joint mobility and worsening of CVD.[5] In the 2008 study by Cavalheri et al, the clinical course of ankles affected by venous disease correlates with reduced joint mobility and hemodynamic changes, identified by plethysmography.[6]

In the 2002 study by Danielsson et al, it was observed that weight appears to be an independent factor for CVD. The correlation of BMI with clinical severity independent of reflux measurements indicates that the effect of being overweight may involve a mechanism independent of local effects on venous flow. Being overweight appears to be an independent risk factor for increased severity of cutaneous changes in patients with CVD.[7]

In the 2013 study by Vines et al,[8] there was a close relationship between body weight and clinical severity of primary venous disease. Both overweight and obesity were analyzed, and both appear to be separate risk factors for increased severity in patients with chronic primary venous disease, with no correlation with disease duration. The CEAP classification and venous clinical severity score (VCSS) were used to accurately assess disease severity, with excellent correlation between the 2 scores. Concomitant primary deep venous reflux was observed more frequently in obese patients, with less abolition after superficial reflux eradication than observed in normal-weight and overweight patients. Regarding sex

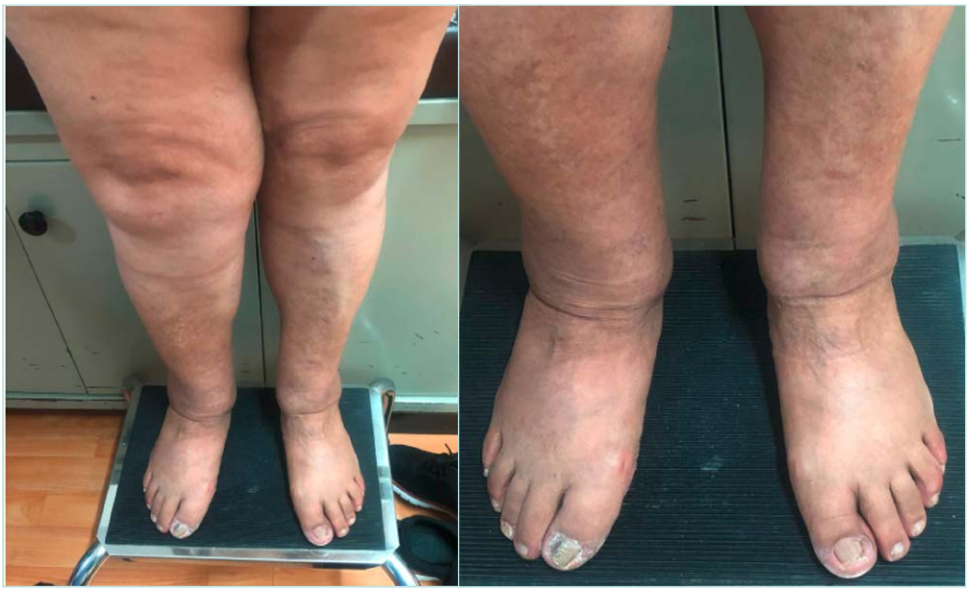

Figure 1. Patient with obesity, flat feet, lowering of the plantar arch. The foot falls inward, causing pain in the muscles on the inner side of the leg, resulting in tendonitis. In chronic cases, it can affect the knee joint, causing gonarthrosis.

differences, a 2011 study by Musil et al[9] on BMI, age, and severity of CVD showed that BMI, in terms of venous reflux frequency, is a risk factor in the entire group of female patients, but not in men. Multiple linear regression showed BMI, along with age, to be significant predictors of clinical CVD grade ($P<0.05$) according to the CEAP classification. Regarding the influence of BMI on clinical severity/grade of CVD (CEAP), the results of this study support BMI as an important risk factor.[8,9]

Oxidative stress is one of the possible causes of obesity increasing CVD. Increased local production of reactive oxygen species (ROS) is considered a mediator of vessel wall changes that lead to endothelial damage and may be the mechanism leading to decreased blood flow and venous stasis. Obesity is a known clinical factor influencing venous blood flow in the lower extremities. In the 2009 study by Kózka et al,[10] which reviewed 31 patients with CEAP C2-C3 local ROS production was assessed based on the production of malonyldialdehyde (MDA), a lipid peroxidation product, in blood samples taken from varicose veins of the lower extremities, as well as blood collected from the forearms of patients undergoing surgery for varicose veins in the lower extremities. The correlation between MDA levels and BMI was also examined. CVD is associated with increased oxidative stress, as measured by MDA levels in blood plasma. MDA measurement may be a useful marker in the assessment of vascular changes in patients with CVD. Obesity increases the risk of lipid peroxidation and influences increased oxidative stress in the CVD patient group.[10]

So, how can we treat these patients? In most cases, we can talk to the patient, send them for a baropodometric study of their gait and the need for insoles, and then begin progressive exercise to improve range of motion, as well as diet and weight loss prior to surgery *(Figure 1)*.

Chronic venous disease in the elderly

The term ''elderly'' refers to patients over 65 years of age, which implies that the older the patient, the higher the prevalence of CVD. Therefore, there is an association between advanced age and more advanced clinical stages in the CEAP classification. Some of these patients ask for treatment, and after the preoperative protocol they are allowed surgery, but sometimes age is a limitation—should it be?

Life expectancy among the global population has increased, so a great proportion of elderly patients are older than 80 years old. The population over 60 years of age represented 12% of the population in 2015. By 2020, it was reported that there were more people over 60 years of age than children under 5 years of age, with an estimate that this age group will increase to 22% of the population by 2050. It is currently estimated that there are 125 million people over 80 years of age worldwide, a figure that may increase to 434 million by 2050, of whom 80% will live in low- to middle-income countries.[11]

Over the past decade, varicose vein treatment has shifted from the operating room to the office. Although recent studies demonstrated the safety of office-based venous ablation in the elderly, there is a paucity of published data on contemporary outcomes of varicose vein surgery in the operating room. This study, conducted by Kim et al,[12] analyzed trends and outcomes of varicose vein surgery in the elderly using a large database from the American College of Surgeons' National Surgical Quality Improvement Program from 2005 to 2017, with a total of 48 615 venous operations. Patients who underwent vein ablation or open surgery (high ligation, stripping, and phlebectomy) were identified by Current Procedural Terminology codes and principal diagnosis. Patients were stratified into 3 age groups—under 65 years, 65 to 79 years, and over 80 years—and preoperative and operative characteristics and outcomes were compared. Logistic regression was used to identify risk factors associated with any adverse event, defined as any morbidity or mortality. Varicose vein surgery was concluded to be safe in all age groups and is increasingly being offered to the elderly. High-risk patients may benefit from ablation staging and open procedures and avoiding general anesthesia can minimize adverse events. Conservative measures should be exhausted before surgery in the dialysis population.[12]

A 2020 study by Kibrik et al[13] to assess the safety and efficacy of endovenous ablations in octogenarians, nonagenarians, and centenarians showed that whereas there is a relatively higher likelihood of endovenous heat-induced thrombosis (EHIT) and recanalization in the age group >80 years, the majority of EHITs were class 1 and class 2. According to this study, venous ablation is safe and effective in all age groups, and age alone should not be used to deny patients venous ablations.[13]

Another review conducted in 2020 by Garza-Herrera[11] regarding the surgical treatment of CVD in octogenarians aimed at understanding the behavior of venous pathology in these age groups, as well as the safety and efficacy of its treatment, in order to clarify and determine treatment guidelines for the coming years. The investigator concluded there was superiority for endovenous ablation techniques compared with traditional surgical techniques or conservative management for treating advanced stages of CVD in patients over 80 years of age. On the basis of these results, age should not be a limitation for offering an endovenous procedure. The results of the Vascular Quality Initiative Varicose Vein Registry (VQI VVR) allow us to better understand this group of patients, who are not usually considered for clinical trials. Although the before-mentioned studies are retrospective reviews, they may provide sufficient information to consider this therapy in elderly patients.[11]

Chronic venous disease in patients with coagulopathies

Subjects with truncal varicose veins and those with CVI had higher levels of each hemostatic factor than those without truncal varicose veins and without CVI. Although unit increases in tissue-type plasminogen activator (t-PA) and von Willebrand factor (vWF) were initially associated with a significantly higher risk of CVI in men, and both factors with an elevated risk of truncal varicose veins in women, multiple adjustment for age, smoking, and BMI reduced the odds ratios to nonsignificance. However, this does not completely rule out the possibility of a pathogenetic role for hemostatic factors in venous disease; rather, it indicates the need for further experimental and epidemiological studies.[14]

In an observational study of a cohort of 132 adult patients with CVD, symptoms reported by patients with CVD of the leg were recorded and correlated with systemic inflammatory markers, including vWf. No correlation was found between patient-reported symptoms and the internationally agreed clinical stages of venous disease from C2 to C5. There was also no correlation between levels of inflammatory mediators and patient symptoms. The symptoms reported by patients with CVD cannot be explained by the anatomical distribution of venous disease in the lower extremity veins or by the systemic inflammatory response in venous disease.[15]

Conclusions

Each patient should have a complete medical history, as well as a physical examination complemented by color duplex Doppler ultrasound. This evaluation should be carried out individually. Depending on their BMI, comorbidities such as age, medical history, anticoagulant medication use, or other concomitant diseases, the type of treatment can be chosen. This may include just taking venoactive drugs, use of compression stockings, and in the absence of contraindications, performance of one of the current endovenous procedures, whether thermal or nonthermal, which have been shown to be safe, effective, and long-lasting in most cases.

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Prevalence of neuropathic pain in patients with venous disease in the Guatemalan population

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ABSTRACT

Chronic venous disease changes the hemodynamics of venous return, causing intraluminal hydrostatic hypertension and congestion. All of this triggers inflammation, tissue damage, and possible nerve damage due to low oxygen levels. Prevalence of neuropathy was identified in patients with chronic venous insufficiency. In a transversal descriptive study, a nonprobability sample of 370 adult patients with chronic venous insufficiency classified as CEAP 3 to 6 (according to clinical, etiological, anatomical, pathophysiological classification) were evaluated in 4 clinics in Guatemala City where they were assessed for neuropathy via the DN4 scale (douleur neuropathique questionnaire). The prevalence of neuropathy in patients with chronic venous insufficiency (CEAP 3 to 6) was 44.6% [95% CI, 28.9-39.9]. No significant differences were observed in the prevalence of neuropathy by sex and age (P=0.655 and P=0.463, respectively); but according to CEAP classification (P<0.001), the higher the degree of CEAP, the higher the prevalence of neuropathy. It was concluded that more than two-fifths of patients with chronic venous insufficiency may develop neuropathy, with this prevalence being higher in patients with more advanced venous disease.

Keywords

microangiopathy | neuropathy | venous disease | venous insufficiency

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Introduction

For many years, the term chronic venous insufficiency (CVI) has been used generically, but nowadays we prefer to talk about chronic vein disease (CVD) when referring to any morphological or functional alteration of long evolution of the venous system (especially in the lower limbs). And we reserve CVI for advanced clinical stages (C3-C6).[1]

CVI is a very common public health problem worldwide, causing a significant impact on the quality of life and economic impact on both patients and the health system. In the United States, up to 7 million people are reported to have chronic venous disease (in France, an estimated 12 million people have varicose veins) at a cost of $40 000 over the lifetime of each of these patients,[2-4] and if such patients develop ulceration, the cost to the health care system would be even higher, eg, in the United Kingdom, it can be as much as £100 to £400 million per year. Also, in the United Kingdom, more than 200 000 hospitalizations per year are estimated due to the problem.[4,5] The DETECT-IVC study (an epidemiological survey on CVI in Spain) found that 71% of people reported some symptom or sign dependent on CVI.[6]

There are several symptoms that are described in patients with CVD but none of these alone are pathognomonic of the disease and therefore could have a different origin and cause as they are nonspecific.[1,3,4]

The symptoms of CVD are so uncertain that even some authors, as in the Edinburgh Vein Study, question whether the symptoms described in surgical textbooks really correspond only to venous disease.[7]

Most of the venous symptoms such as the heaviness described in large population-based studies, for example, the Edinburgh Vein Study or Bonn Vein Study[3,4,7,8] have been investigated in depth. However, there is an understudied range of symptoms that are neuropathic.[9]

The symptoms described as cramps, dysesthesia, pins and needles sensations, and paresthesia[10] seem to correspond more to peripheral neuropathies such as those found in diabetes mellitus; also the ones caused by neurotoxic drugs and vitamin B-12 deficiency and alcohol-related neuropathies, peripheral arteriopathies with microangiopathy, among others.[10-13] Peripheral arteriopathies with microangiopathy can produce ischemic polyneuropathy mainly due to tissue hypoxia with consequent neurological damage.[10]

In CVD there is a sustained ambulatory venous hypertension with capillary distension and extravasation of fluid into the interstitial space. This causes decreased oxygen diffusion and endothelial edema with consequent release of interleukins and free radicals, which can cause damage to all peripheral tissues and may include nerve fibers.[2,5,10,14,15]

Although neuropathic symptoms are sometimes not adequately recognized in CVD, there is scientific evidence that neurological damage occurs in venous disease at the molecular level where oxidative stress and angiogenesis play the primary role in the development of perfusion-dependent peripheral neuropathy.[13]

Clinical and electrophysiological methods can be used to evaluate neuropathic pain, the latter being the most accurate for evaluating peripheral nerve, radicular, and plexus lesions, but their cost and complexity limit their use. Among the clinical methods, the most accepted is the DN4 (*douleur neuropathique questionnaire*), developed in France and the only test validated in Spanish. This questionnaire contains 10 questions and 3 elements of physical examination. It is useful to differentiate neuropathic pain from nociceptive pain with a sensitivity of 83% and specificity of 90%.[16]

The aim of this study was to determine, in the Guatemalan population, the presentation of neuropathic symptoms in patients with CVI and without suffering from neurodegenerative diseases such as diabetes mellitus or rheumatic disease. Also, whether there was a correlation between the severity of CVI and the neuropathic symptoms.

These results may provide the basis for further research to verify the improvement of neuropathic symptoms following treatment aimed at correcting venous disease.

Objectives

To determine, by means of a validated neuropathic pain scale, the frequency with which patients with CVI (CEAP 3 to 6) present neuropathy.

To determine the frequency of neuropathy according to sex, age, and CEAP classification.

Patients and methods

A prospective cross-sectional descriptive study was carried out from April to September 2023.

The study was carried out in 4 clinical centers in Guatemala City dedicated to the study and treatment of venous pathologies.

Patients were evaluated clinically, and subsequently venous echo-Doppler examination was performed. Patients were evaluated in a standing position and the presence of venous reflux was determined in any segment of the path of the great or small saphenous veins of both lower limbs. The latter was defined as a return of blood greater than 0.5 seconds after performing a Valsalva maneuver or distal compression of the ipsilateral calf.

Patients over 18 years of age with chronic venous disease (CVD) classified as CEAP C3 to C6 were included: C3 corresponding to edema, C4 to skin changes, C5 to closed ulcer, and C6 to active ulcer.

After meeting the above criteria, an interview was performed using the approved form for neuropathies, DN4. Developed by the French Neuropathic Pain Group, it has a sensitivity of 83% and a specificity of 90%. It consists of 10 questions. If the patient answered yes to at least 4 of them, then the pain was considered to have neuropathic characteristics.

Patients with concomitant neurodegenerative diseases such as diabetes mellitus, rheumatic disease, or alcohol-related neuropathies, or polyradiculopathies caused by neurotoxic drugs, vitamin B-12 deficiency or peripheral arteriopathies[10-13] were excluded from the study.

The data were tabulated and analyzed in jamovi software version 2.3.28. Variables were described by frequency and percentage. The population prevalence of neuropathy was estimated with a 95% confidence interval of proportions. The evaluation of the statistical association was done with Pearson's chi-square tests and the estimation of the size of the association with the odds ratio (OR) and their 95% confidence intervals.

To calculate the sample size, the formula for estimating a population proportion was chosen:

$$n = \frac{Z_{\alpha}^2 * p * q}{d^2}$$

Where

$Z_{\alpha}^2 =$ Standardized z-value, for a confidence level of 95% $(1.96)^2$

$p =$ Proportion of the event of interest, approximately 40% of patients with chronic venous disease are expected to have neuropathic symptoms (0.40).

$q =$ Complement of the proportion of the event of interest obtained by subtracting the value of the event proportion from 1 (1-0.4 = 0.6).

$d^2 =$ Sampling error of 5% $(0.05)^2$

$$369 = \frac{1.96^2 * 0.4 * 0.6}{0.05^2}$$

$n =$ Minimum sample size of 369 patients

The minimum size calculated was 369 patients, who were randomly selected in a stratified proportional allocation manner from the 4 centers in which the individuals were collected.

Results

In this study, patients with CVI more frequently were female (74.3%), aged between 61 and 70 years (43.2%), and classified as CEAP 3 (60.8%), as shown in *Table I*.

Of the 370 patients with CVI (CEAP 3-6), 165 had neuropathy according to the standardized neuropathic pain scale; therefore, the prevalence corresponded to 44.6%. The 95% CI for the population prevalence of neuropathy ranged from 28.9% to 39.9% *(Table II)*.

The specific prevalence of neuropathy did not vary significantly by sex or age (P=0.655 and P=0.463, respectively), but did vary significantly by CEAP classification, it was determined that as one had a higher grade in the CEAP classification, the prevalence was higher (P<0.001). Patients with a classification of CEAP 4 were 32% more likely to have neuropathy than those classed as CEAP 3; those with CEAP 5 were 5.44 times more likely to have neuropathy than

	f	%
Sex		
Female	275	74.3%
Male	95	25.7%
Age (years)		
41 - 50	35	9.5%
51 - 60	80	21.6%
61 - 70	160	43.2%
71 - 80	85	23.0%
81 - 90	10	2.7%
CEAP Classification		
3	225	60.8%
4	95	25.7%
5	20	5.4%
6	25	6.8%

CEAP, clinical, etiological, anatomical, pathophysiological classification.

Table I. Characteristics of patients with chronic venous insufficiency, April to September 2023, n = 370.

those with CEAP 3, and those with CEAP 6 were more than 100 times more likely to have neuropathy than those with CEAP 3 *(Table III)*.

The higher the CEAP classification, the higher the prevalence of neuropathy, 35.6% in CEAP 3, 42.1% in CEAP 4, 75.0% in CEAP 5 and 100.0% in CEAP 6 *(Figure 1)*.

Neuropathy	*f*	%	95% CI
Yes	165	44.6%	28.9 - 39.9
No	205	55.4%	
Total	370	100.0%	

CEAP, clinical, etiological, anatomical, pathophysiological classification.

Table II. Prevalence of neuropathy in patients with chronic venous insufficiency (CEAP 3 to 6).

	NEUROPATHY						
	Yes		No				
	f	%	*f*	%	*P* value	OR	95% CI
Sex							
Female	125	45.5%	150	54.5%			
Male	40	42.1%	55	57.9%	0.655	1.15	0.72 - 1.84
Age (years)							
41 - 50	15	42.9%	20	57.1%			
51 - 60	35	43.8%	45	56.3%		1.04	0.47 - 2.31
61 - 70	65	40.6%	95	59.4%		0.91	0.44 - 1.91
71 - 80	45	52.9%	40	47.1%		1.50	0.68 - 3.32
81 - 90	5	50.0%	5	50.0%	0.463	1.33	0.33 - 5.45
CEAP Classification							
3	80	35.6%	145	64.4%			
4	40	42.1%	55	57.9%		1.32	0.81 - 2.15
5	15	75.0%	5	25.0%		5.44	1.91 - 15.51
6	25	100.0%	0	0.0%	< 0.001	> 100	0 to infinity

CEAP, clinical, etiological, anatomical, pathophysiological classification.

Table III. Prevalence of concomitant neuropathy according to sex, age, and CEAP classification.

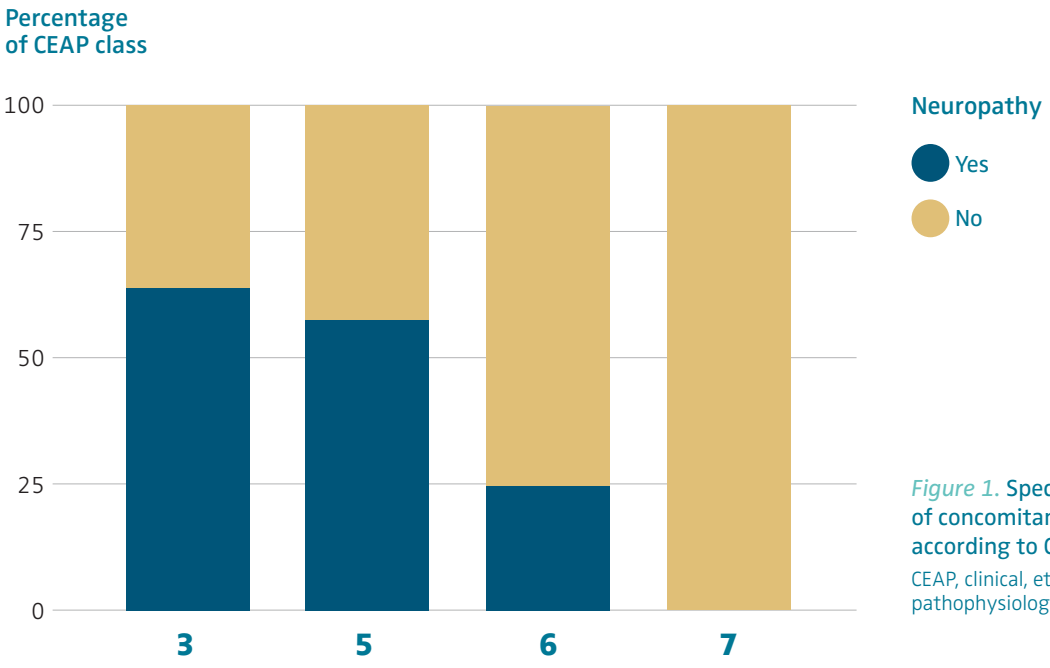

Figure 1. Specific prevalence of concomitant neuropathy according to CEAP classification.
CEAP, clinical, etiological, anatomical, pathophysiological classification.

Conclusions

The prevalence of neuropathy in patients with CVI (CEAP 3 to 6) according to the approved DN4 neuropathic pain scale was 44.6% (95% CI, 28.9 to 39.9).

The prevalence of neuropathy in patients with CVI did not vary according to sex and age (P=0.655 and P=0.463, respectively), but did vary according to CEAP classification (P<0.001). The higher the CEAP grade, the higher the prevalence of neuropathy.

Although the associations with gender and age were not statistically significant, it is important to consider that they could have clinical implications in specific contexts. As Dr Kathleen Ozsvath says "we have little understanding of the gender, socioeconomic, and ethnic disparities in both superficial and deep venous disease presentation." On the other hand, the CEAP classification proved to be a robust and significant predictor of neuropathy, especially in its more advanced stages, which could be useful in risk stratification and clinical decision-making.

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