Chronic venous disease: Literature review

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Abstract

The venous system is responsible for bringing blood from the lower limbs to the heart. To achieve this, various mechanisms are activated that work against gravitational force. A very important mechanism is the function of the venous valves. A family history of venous disease is most commonly associated with valve dysfunction, which can lead to venous hypertension, amongst several other risk factors, thus activating a cascade of events characterized by venous dilation and leukocyte migration. Chronic complications can be very expensive in relation to quality of life and the health system. At present, venous disease studies include several diagnostic methods that, together with a wide range of therapeutic tools, have achieved excellent results in the quality of life of patients.

Key words: Endovenous thermal ablation. Saphenous vein. Vascular surgery. Venous insufficiency.

Introduction

Chronic venous disease (CVD) is a common disease with an estimated worldwide prevalence of 83.6%. Varicose veins of the lower extremities are the most common cause of chronic venous insufficiency (CVI) and the most severe form of the disease is venous ulceration. It is estimated that 30-40% of the adult population has varicose veins and up to 6% of patients with varicose veins develop ulcers at some time in their lives. Up to 30% of varicose veins may progress to more severe forms of CVI. Almost 1% of the general population may develop venous ulceration at some time and the prevalence of open venous ulceration is approximately 0.1-0.3%¹. The incidence of varicose veins is estimated to be about 2%/year². Congenital venous valve abnormalities are proposed to be the cause of varicose veins³.

According to the Framingham Heart Study, the 2-year incidence of varicose veins in women and men was 2.6% and 2.0%. CVI can occur as a result of primary and secondary causes (70% and 30% of cases, respectively)⁴.

Venous ulcers can affect at least 1-2% of the elderly population with a significant burden in terms of quality of life and health-care costs⁵.

Pathophysiology and epidemiology of venous disease

Thirty genetic loci strongly associated with varicose veins have been identified, with the strongest associations occurring in the intron region CASZ1 (rs11121615; $p = 3.71 \times 10^{-65}$), which has been implicated in blood pressure. In addition, mutations in the HFE gene have previously been associated with venous ulceration and

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thromboembolism⁶. Studies seem to suggest an increase in varicose veins in type I collagen content and a decrease in type III collagen content, the latter being a factor in venous elasticity, both elastin, and laminin content decreases in varicose veins. Laminins are a group of glycoproteins of high molecular mass (140-400 kDa) that is part of the basal lamina associated with other proteins such as collagen, entactin, proteoglycans, and fibronectins⁷. The calf muscle pump is the most important pump in providing venous return of the lower extremity, but the quadriceps and hamstring muscle pumps in the thigh are of importance in pumping blood to the heart⁸.

Recently in a study by Rusinovich, the C6 CEAP classification (Table 1) compared to C2 was associated with higher atrial contribution to right ventricular filling, higher atrial contraction, and higher atrial ejection force. Clinical class C6 CEAP was associated with impaired relaxation or diastolic dysfunction of the right heart⁹. The Vein Consult program is an international, observational, prospective survey to collect global epidemiological data. It reports on CVI; it estimates the global prevalence of CVI at 83.6% (C0-C6) with a global prevalence of C1 to C6 at 63.9%¹⁰. In a meta-analysis, it was observed that 4677 (35.0%) of 13,361 women with parity > 1 developed varicose veins. In the control group with 3746 women with no history of pregnancy, only 782 (20.9%) cases of varicose veins were reported. Progesterone inhibits smooth muscle contraction, while estrogen causes vasodilatation. Both mechanisms may result in venous insufficiency caused by increased capacity and dilatation of the venous system, together with venous outflow obstruction by the pregnant uterus and increased weight gain during pregnancy. More research is needed to explain the association between pregnancy and venous insufficiency. Pregnancy increases the risk of developing varicose veins (odds ratio, 1.82; 95% confidence intervals [CI], 1.43-2.33) 1.82-fold¹¹. Venous outflow obstruction affecting the ilioacaval segment has been identified in 10%–30% and is therefore of paramount importance in deep system analysis of CVI¹². A prevalence of both deep (1.7%) and superficial (2.2%) vein thrombosis of the venous systems was reported in patients with CVI undergoing ultrasound scans¹³.

Health costs involved in the care of patients with venous disease

In the United States, it has been estimated that the direct medical costs of CVD range between \$150

Table 1. The 2020 update of the CEAP classification system and reporting standards

Summary of clinical © classifications			
C class description			
C0		No visible or palpable signs venous disease	
C1		Telangiectasia or reticular veins	
C2		Varicose veins	
C2r		Recurrent varicose veins	
C3		Edema	
C4		Changes in skin and subcutaneous tissue secondary to CVD	
C4a		Pigmentation or eczema	
C4b		Lipodermatosclerosis or atrophie blanche	
C4c		Corona phlebectatica	
C5		Healed	
C6		Active venous ulcer	
C6r		Recurrent active venous ulcer	
Summary of etiologic (E) classification		Summary of pathophysiologic (P)	
E class Description		P class Description	
Ep	Primary	Pr	Reflux
Es	Secondary	Po	Obstruction
Esi	Secondary – intravenous	Pr, o	Reflux and obstruction
Ese	Secondary – extravenous	Pn	No pathophysiology identified
Ec	Congenital		
En	No cause identified		
Summary of anatomic (A) classification			
A Class Description			
As	Superficial		
	Old New* Description		
	1. Tel Telangiectasia		
	1. Ret Reticular veins		
	2. GSVa Great saphenous vein above knee		
	3. GSVb Great saphenous vein below knee		
	4. SSV Small saphenous vein		

(Continue)

Table 1. The 2020 update of the CEAP classification system and reporting standards

Summary of anatomic (A) classification	
A Class Description	
	AASV Anterior accessory saphenous v
	5. NSV Non-saphenous vein
Ad	Deep
	Old New* Description
	6. IVC Inferior vena cava
	7. CIV Common iliac vein
	8. IIV Internal iliac vein
	9. EIV External iliac vein
	10. PELV Pelvic veins
	11. CFV Common femoral vein
	12. DFV Deep femoral vein
	13. FV Femoral vein
	14. POPV Popliteal vein
	15. TIBV Crural (tibial) vein
	15. PRV Peroneal vein
	15. ATV Anterior tibial vein
	15. PTV Posterior tibial vein
	16. MUSV Muscular veins
	16. GAV Gastrocnemius vein
	16. SOV Soleal vein
Ap	Perforator
	Old New* Description
	17. TPV Thigh perforator vein
	18. CPV Calf perforator vein
An	No venous anatomic location identified

CVD: chronic venous disease

*New specific anatomic location (s) to be reported under each P (pathophysiologic) class to identify anatomic location (s) corresponding to P class.

million and \$1 billion annually. In the United Kingdom, 2% of the national health budget per year (USD 1 billion) is spent on leg ulcer management. The cost of caring for patients with CVI is estimated at EUR 600-900 million in Western Europe, representing 2% of health-care expenditure. The estimated average direct cost for treating each ulcer is EUR 9000, representing 90% of the total expenditure for CVI patients¹⁴.

Venous disease clinical diagnosis and laboratory study

In a study on biomarkers regarding CVI by Mosmiller, it was observed that the neutrophil count and neutrophil/lymphocyte ratio were significantly higher in the severe-to-mild CVI group. Moreover, the neutrophil/lymphocyte ratio can serve as an independent predictor of severity of CVI when it is > 2.91 with 74% sensitivity and 77% specificity¹⁵.

Clinical assessment is found in CVD-related signs and symptoms. Unfortunately, they are non-specific and difficult to associate with venous disease. Symptoms associated with CVD include leg heaviness, aching and throbbing, tiredness, fatigue, itching, tingling or burning sensation, and nocturnal cramps¹⁶. At present, research in patients with superficial venous insufficiency is invariably limited to assessment of the presence and sites of reflux. Flow volume measured by plethysmography may be more representative as indicated in a recent publication on venous reflux quantification. However, the anterograde saphenous volume has been shown to be a determinant of the resulting reflux volume. Thus, the recirculation index may be an improvement in venous reflux quantification¹⁷.

The anatomical and functional assessment of the venous system should be performed by Doppler ultrasound, the ideal method, as it is reproducible and non-invasive. A Doppler flow duration of > 500 ms with a diameter of > 3.5 mm was considered as pathological perforators. Color Doppler shows a sensitivity of 80% with an accuracy of 10% and the desired CI of 95%³.

Venous reflux has traditionally been managed first. However, advances in diagnostic and imaging techniques, mainly intra-vascular ultrasound, have allowed us to understand better the obstructive physiology of venous disease. In fact, venous outflow obstructions affecting the ilioacaval segment have been identified in 10-30% of patients with severe venous insufficiency¹⁸. By means of diagnostic equipment, v

enous disease analysis is more specific to differentiate the affected segments to be treated.

Venous healthcare and medical treatment of venous disease

The Society for Vascular Surgery (SVS) and the American Venous Forum have developed clinical practice guidelines for the care of patients with varicose veins of the lower limbs. They follow compression therapy for patients with symptomatic varicose veins

(GRADE 2C) but recommend against compression therapy as primary treatment in patients who are candidates for saphenous vein ablation (GRADE 1B). We recommend compression therapy as primary treatment to aid healing of venous ulceration (GRADE 1B). To decrease the recurrence of venous ulceration, we recommend ablation of incompetent superficial veins in addition to compression therapy (GRADE 1A)¹⁹. In one study, we observed the change in ankle joint range of motion and muscle strength values measured with an isokinetic dynamometer, pain scores, quality of life scale, and venous return time in patients with CVI. In conclusion, it has been determined that increased muscle strength affects the venous pump and this improvement ensures venous function²⁰. Compression is not recommended in patients with ABI < 0.5²¹.

Venoactive drugs are deemed an important component of the medical (conservative) treatment of CVD. According to available evidence, four drugs (MPFF, hydroxyethylrutin, ruscus extract, and diosmin) are able to act in reducing edema. The first three showed significant reduction compared to placebo whereas diosmin did not. MPFF was significantly superior to hydroxyethylrutin and ruscus extract^{5,22}. Several landmark studies have demonstrated the cascade of interactions that correlate with increased venous pressure and capillary perfusion: white blood cell adhesion and migration, endothelial leukocyte activation, capillary permeability, increased vascular proliferation and altered lymph flow, leukocyte trapping, and skin pathology. Elevated L-selectin during venous hypertension was considered an indication that leukocyte binding occurred. A systematic literature review focused on the use of micronized purified flavonoid fraction (MPFF) in the treatment of CVD. An overall level of evidence supports the recommendation of the therapeutic use of MPFF with beneficial outcomes without serious adverse events²³. MPFF significantly improved nine defined leg symptoms, including pain, heaviness, swelling, cramps, paraesthesia, burning sensation, and pruritus (itching). MPFF is highly effective in improving leg symptoms, edema, and quality of life in patients with CVD²⁴.

Sulodexide protects the endothelium by restoring endothelial glycocalyx, preventing venous endothelial cell apoptosis and inhibiting endothelial cell release of reactive oxygen species and pro-inflammatory chemokines and interleukins (IL), such as monocyte chemoattractant protein and IL-6²⁵. Sulodexide has a venoactive effect on the main signs and symptoms of venous disease, such as pain, cramps, heaviness, and edema without

increasing the risk of adverse effects. It is also likely to exert a systemic effect on the course of CVD by interfering with inflammatory chemokines²⁶.

There are undoubtedly multiple pharmacological options, and every day new properties are discovered that improve the consequences caused by venous hypertension in patients with CVD.

Surgical treatment of CVD

Surgical treatment of varicose veins has two objectives. On the one hand, it is aimed at correcting the problem that caused the varicose veins. On the other hand, the aim is to eliminate the visible veins that have become dilated. Nowadays, there are different techniques for varicose vein surgery. High ligation with vein stripping (open surgery) involves the closure of the femoral saphenous junction and its branches through several incisions. Thermal ablation is a catheter-assisted procedure that uses radiofrequency or laser energy causing the vein to collapse. Foam sclerotherapy for large veins makes it possible to close and seal the vein. Endoscopic surgery by means of camera-guided trocars for perforator vein clamping and finally non-thermal and non-tumescent methods (mechanicochemical ablation and cyanoacrylate glue) (Fig. 1).

In response to less invasive treatment with endovenous treatment, radiofrequency ablation (RFA) and endovenous laser ablation (EVLA)²⁷ have been developed. Endovenous thermal ablation (EVTA) in a meta-analysis review showed that technical success rates were 84.8% for EVLA, 88.7% for RFA, and 32.8% for ultrasound-guided foam sclerotherapy (UGFS). In conclusion, both EVLA and RFA are effective in long-term great saphenous vein occlusion²⁸. EVTA with EVLA or RFA is safe and effective for the treatment of recurrent varicose veins resulting from residual insufficiency of greater saphenous vein surgical treatment. RFA is superior to 980 nm EVLA in terms of post-procedure ecchymosis²⁹. Endothermal ablation is an effective treatment for CVI and most patients remain free of reflux. Recanalization of an isolated venous segment after RFA, although shown in recent literature to be affected by anatomical risks, appears to be a sporadic phenomenon with respect to clinical risk factors³⁰. Laser treatments must sometimes be accompanied by other therapeutic options, although obliteration of the GSV above the knee improves symptoms independently of persistent below-knee reflux, the latter appears to be responsible for residual symptoms and a greater need for sclerotherapy for residual varicose veins³¹.

Figure 1. Surgical ultrasound marking and endovenous 1470 nm laser ablation with radial fiber for chronic venous disease.

Regarding the long-term effectiveness of thermal ablation of GSVs by radiofrequency (RPSA) or EVLA with less traumatic radial tip fibers (RTF), we have concluded that both procedures have an equally high long-term GSV obliteration rate and the treatments are equally clinically effective³². Thermal ablation treatments have the highest incidence of endothermic heat-induced thrombosis (EHIT) after EVTA with RFA than with EVLT. However, the overall incidence of EHIT is relatively low³³. The incidence of thrombotic complications after EVTA of varicose veins is uncertain. Similar results were found when the RFA and EVLA groups were analyzed separately³⁴. In a 20-centre trial, early endovenous ablation resulted in faster healing of venous ulcers and more ulcer-free time than delayed endovenous ablation³⁵.

In conclusion, EVLA/RFA should be preferred to open surgery and foam sclerotherapy in the treatment of venous incompetence³⁶.

As for the surgical technique of foam sclerotherapy for great saphenous vein treatment, the results are inferior to surgery to eliminate venous reflux but the advantage in some studies is that patients returned to daily activities more quickly. Vein diameter greater than 6 mm had worse closure results than those with a

diameter of five or less. Patients undergoing ultrasound-guided sclerotherapy (UGS) have better quality of life than surgical patients do, after 4 weeks of treatment due to less pain. In the literature, most studies show reduced evidence due to selection and randomization bias. Long-term results are still lacking and need to be controlled by randomized trials^{1,37}. We compared the effectiveness of EVLA, RFA, and UGFS versus conventional surgery in the treatment of varicose veins. UGFS effectiveness compared to conventional surgery in the treatment of small saphenous varicose veins (SSV) is uncertain³⁸.

A third treatment option, first described by Hauer in the 1980s, subfascial endoscopic perforator surgery (SEPS), has been performed to treat incompetent perforator veins in cases with advanced skin changes³⁹. SEPS, which is performed for perforator ligation, requires endoscopic installation and expertise. The most commonly performed operation to address perforator incompetence is still open subfascial ligation or puncture phlebectomy³.

Finally, there are cyanoacrylate adhesive devices (CAC) for saphenous vein closure or devices that inject foam into the saphenous vein while rotating at high speed inside it. The combination of the chemical effect of the foam with

the mechanical effect of the catheter rotation maximizes its effect and makes it faster. The 36-month follow-up of the first human use of cyanoacrylate adhesive for the treatment of saphenous vein incompetence was 94.7%. Intravenous polidocanol foam (Varithena; sclerosing agent) demonstrated a 1-year occlusion rate of 73%⁴⁰. A study comparing early and 2-year outcomes for N-butyl cyanoacrylate, EVLA in the treatment of varicose veins, concluded that no difference in occlusion rates was observed in the three modalities, but superior NBC appeared with respect to pain during the procedure, return to work, and decreased pre-operative venous clinical severity scores⁴¹. In a 12-month follow-up with (CAC) and radiofrequency (RFA), almost identical occlusion rates were demonstrated in the target veins (96.8% in the CAC group and 95.9% in the RFA group). However, the time to complete occlusion was shorter and recanalization was greater with CAC than with RFA⁴². By month 24, closure rates for CAC and RFA were also equivalent (95.3% and 94.0%, respectively) and the recanalization-free rate remained higher in the CAC group, demonstrating the continued non-inferiority of CAC to RFA⁴³. In the WAVES study, 1-year results demonstrated the safety and efficacy of CAC for the treatment of GSVs up to 20 mm in diameter, small saphenous veins (SSVs) and/or accessory saphenous veins, with a 98% occlusion rate in all veins⁴⁴. CAC does not produce significant thrombosis because the vein walls adhere to the adhesive immediately through the application of external compression resulting in an inflammatory and eventual fibrotic reaction rather than a thrombotic one⁴⁵. The VenaSeal system (non-thermal, non-tumescent, and non-sclerosing technologies) is a promising therapeutic option for anatomic success at 6 months, with fewer adverse effects in patients with venous insufficiency compared to other interventions⁴⁶. Initial 3-months results from the VeClose trial reported non-inferiority of cyanoacrylate endovenous closure (CAC) to RFA with saphenous vein closure rates greater than 99% for the CAC group and 96% for the RFA group⁴⁷. Regarding mechanochemical modalities, initial data showed successful GSV occlusion rates with the ClariVein device (through a mechanochemical ablation catheter) at 94% comparable to RFA (thermal ablation)^{15,48}.

This latest mechanochemical alternative seems very promising, but time is required to appreciate all its advantages, but its benefits are supported by the non-use of heat, which is associated with low pain rates, a quick return to normal activities and a better quality of life. What is certain is that every day, there is more and more technology available to treat patients that allow them a quicker return to their daily activities.

Conclusions

The treatment of CVD is now more specific, thanks to diagnostic methods, as they help us to better identify diseased segments, thus allowing for targeted surgery with the construction of a surgical map. We can assess blood flow within the vein lumen and venous reflux analysis, measure vascular structures and detect complications in the deep venous system, confirm that it is indeed a primary disease and rule out secondary causes. They are a fundamental part of surgery and allow for post-operative vigilance. This technology has been extended to surgical tools that are now minimally invasive with early recovery and are more accessible to patients with higher risk conditions. In addition, they ensure greater safety measures and provide better results such as less postoperative pain as well as better quality of life, with early recovery of the patient to their daily activities.

Conflicts of interest

The author declares have not any conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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