

Review Article

Chronic venous insufficiency: a review

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ABSTRACT

Chronic venous insufficiency (CVI) comprises a complete spectrum of morphological and functional abnormalities of the venous system including any long-term functional and morphological alteration. CVI accounts for several abnormalities of the venous system. It is a highly prevalent disease that causes serious economic consequences, a decrease in the quality of life and can lead to serious complications. An exhaustive review was performed with the available literature, using the PubMed, ScienceDirect, Scopus and Cochrane databases from 2004 to 2021. The search criteria were formulated to identify reports related to chronic venous insufficiency. The pathophysiology of chronic venous insufficiency begins with chronic venous hypertension and the dilation of the vessel, this leads to a series of pathological changes in the venous wall and surrounding tissues, in advanced stages of CVI, skin lesions are associated with an increased proliferation of skin capillaries and microcirculatory abnormalities that may be the result of an altered level of factors responsible for the angiogenic response, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2) and angiostatin. In this review, updates on pathophysiology, clinic, diagnosis, classification and treatment of this disease are analyzed, with special emphasis on therapeutic options. Chronic venous insufficiency is a disease that affects the patient at several levels, mainly diminishing his/her quality of life. Currently there are various treatments ranging from habit modifications, pharmacological, to endovenous and surgical treatment.

Keywords: Chronic venous insufficiency, Sclerotherapy, Phlebotonics, Vompresion stockings, Radiofrequency, Endovenous therapy, Angiology

INTRODUCTION

The classic symptoms include; burning pain, heaviness, tired legs, itching, hot spots “sensation”, restless legs, venous claudication, aesthetic discomfort and signs such as telangiectasia and varicose veins in different presentations. The term chronic venous insufficiency (CVI) refers to an advanced stage of the disease, cases in which there is edema, trophic disorders in the skin and / or the presence of ulcers, it is currently considered a common condition caused by valve dysfunction with or without associated valve obstruction.^{3,4} Chronic venous disorders of the lower extremities are common vascular pathologies and carry big medical and socioeconomic impact, currently demanding 1–2.5% of medical care budgets in developed countries; they are prevalent in a large part of the world population (prevalence of up to 73% in women and 56% in men) and significantly reduce the quality of life of affected patients.⁵

METHODS

An exhaustive review was performed with the available literature, using the PubMed, ScienceDirect, Scopus and Cochrane databases from 2004 to 2021. The search criteria were formulated to identify reports related to chronic venous insufficiency. We use the following keywords: chronic venous insufficiency, sclerotherapy, phlebtonics, compression stockings, radiofrequency, endovenous therapy, angiology. We also include the author's experience in the management of these patients.

RESULTS

The pathophysiology of chronic venous insufficiency begins with chronic venous hypertension and the dilation of the vessel, this leads to a series of pathological changes in the venous wall and surrounding tissues, in advanced stages of CVI, skin lesions are associated with an increased proliferation of skin capillaries and microcirculatory abnormalities that may be the result of an altered level of factors responsible for the angiogenic response, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2) and angiostatin.⁶ VEGF is a five-member protein family; however, two of them VEGF-A and VEGF-C have the most increased activity and stimulate vessel formation as well as an increase endothelial cell permeability through the formation of vesicular-vacuolar organelles, providing transport of plasma proteins such as fibrinogen and plasminogen from the bloodstream to the surrounding tissues.⁷ Transforming growth factors, particularly the TGF- β family, play a crucial role in the pathophysiology of the vascular wall, both in the early (C2) and late (C6) stages, different isoforms of TGF- β and its signaling receptors can actively participate in the imbalance of matrix metalloproteinases (MMPs) and their inhibitors (tissue metalloproteinase inhibitors (TIMPs) (MMP / TIMP) throughout CVI progression, (proteins widely known for the elastin degradation of the extracellular matrix of the vascular wall

and the protective glycosaminoglycan layer of the endothelium), allowing for harmful interaction between leukocytes and the endothelial cell membrane.⁸⁻¹⁰ Angiotensin is an angiogenesis inhibitor, targeting on endothelial cells. It inhibits cell proliferation and migration, stimulates apoptosis, blocks microvascular formation and decreases cellular vessel permeability, plasminogen (PLG), considered a precursor to the formation of pro-inflammatory interleukins such as IL-6, is an important component of the inflammatory cascade related to a variety of vascular diseases.^{11,12}

GLYCOCALYX IN VENOUS DISEASE / VENOUS INSUFFICIENCY

Glycocalyx is a glycosaminoglycan found on the surface of endothelial cells, it is highly relevant as it prevents leukocyte adhesion, inflammation and thrombosis. Mechanical or stress forces in the vein wall lead to injury and loss of glycocalyx, resulting in endothelial dysfunction and expression of adhesion molecules that attract leukocytes, this provoking an inflammatory response “opening the door” to: (a) the mechano-transduction of acute and chronic stimuli; (b) increased permeability barrier; (c) increases harmful adhesion of blood leukocytes, lymphocytes and platelets; and (d) supports the extravasation of reactive blood cells, capable of inducing inflammation and proteolysis in the microenvironment of blood vessels.¹³⁻¹⁵ The understanding of this concept has made possible the development of drugs that target this situation, for example, sulodexide, which enables the healing of venous ulcers, improving symptoms such as pain, heaviness and edema, exerting a systemic effect by interfering with inflammatory chemokines.¹⁶

RISK FACTORS

Risk factors for the development of progressive chronic venous disease (CVD) and varicose veins include; advanced age, excess body weight, sedentary lifestyles and occupations, family history, and pregnancy Table 1. Poor eating habits and no or little physical activity prevail as the top modifiable factors, these can be mitigated by making lifestyle changes such as stop smoking and increasing physical activity, reducing excess body weight, however, some are not as easily managed, so we must come up with a strategy to treat them.¹⁷ It is believed that constipation stimulates the appearance of CVI due to an increased intra-abdominal pressure, sedentary lifestyle and obesity rise vascular resistance by increasing the weight load in the lower extremities. A study by Pupo et al showed that the age of presentation prevailed between 46 to 55 years (44.9%), followed by 36 to 45 years (20.4%). The female sex having the highest incidence (61.2%).¹⁸ Almost every study shows this predominance of the female sex in a ratio of 5 to 1, attributable to pregnancy and hormonal factors.¹⁹ Authors such as Pupo estimated in their study that 89% of patients have a family pathological history (APF), which they consider as crucial for the development of CVI, followed by chronic constipation (29 for 59.2%); obesity,

sedentary lifestyle (25 for 51.0%), history of deep vein thrombosis (DVT) (22 for 44.9%) and multiparity (20 cases for 40.8%).¹⁸

Table 1: Risk factors for chronic venous insufficiency.

Modifiable factors	Non-modifiable factors
Increased BMI Smoking Sedentary life	Advanced age
	Family history of venous disease
	Ligament laxity
	Trauma in lower limb
	Previous venous thrombosis
	Pregnancy
	Female gender

CLASSIFICATION

To address the complexity of the clinical manifestations of chronic venous disease, a standardized classification system called CEAP was created, it takes into account the pathology, natural and clinical history of this disease. CEAP was created in 1996, revised in 2004 and updated in 2020. The letter C refers to the clinic presentation, within this category is C0, which refers to the absence of visible or palpable signs of venous disease, C1 telangiectasias or reticular veins, C2 varicose veins, to these categories you can add the letter “S” when they are symptomatic or “a” in case of being asymptomatic and the letter “r” in case of recurrence.

Finally, there is category C6 that represents an active venous ulcer. The letter E refers to the classification of etiology, and may be; primary, congenital, unidentified and secondary intravenous and extravenous. The letter A refers to the classification of the anatomical sites of venous disease, which can be superficial, deep, perforating or unidentified, here we can specify the affected venous segment.

Finally, the letter P refers to the pathophysiological classification, including reflux, obstruction, reflux or obstruction and no identified pathophysiology.²⁰

CLINICAL MANIFESTATIONS

The clinical manifestations of CVI vary (Table 2) from telangiectasias or “spider veins”, reticular veins, large varicose veins to venous stasis ulcers, in advanced CVI; pain, edema, itching, hyperpigmentation, eczema, lipodermatosclerosis, scarred or active ulcers, white atrophy.²¹ There may also be episodes of superficial and deep thrombophlebitis.²² The patient may report pain, heaviness or cramps in the distal portion of the legs.⁴

COMPLICATIONS

One of the major complications in chronic venous insufficiency is the appearance of venous ulcers, which have a prevalence of 0.7%, it can be associated with

thromboembolic events, 18-25% of patients can present deep vein thrombosis and it has been reported that up to 7% could present pulmonary embolism, as well as up to a 50% probability of developing post-thrombotic syndrome.²³⁻²⁶ The probability can be determined documenting the signs and symptoms of chronic venous insufficiency that develop after deep vein thrombosis.

Table 2: Clinical manifestations for chronic venous insufficiency.

Signs	Symptoms
Hyperpigmentation	
Eczema	
Lipodermatosclerosis	
Ulcers	Pain
White atrophy	Itching
Thrombophlebitis	Heaviness
Telangiectasias	Cramps
Varicose veins	
Edema	

Table 3: Complications of chronic venous insufficiency.

Complications	Diagnosis	Treatment
Venous ulcers	Clinical	Debridement of the ulcer, dressings and compression stockings
Superficial thrombophlebitis	Clinical and ultrasound	Supportive measures, elevation of the limb, compression stockings, analgesics
Deep vein thrombosis	Clinical and ultrasound	Anticoagulation, thrombolysis, thrombectomy or inferior vena cava filter
Post-thrombotic syndrome	Clinical and ultrasound	Supportive measures or percutaneous angioplasty
Pulmonary embolism	Clinical pretest probability, D-dimer, CT	Anticoagulation, ventilatory and hemodynamic stabilization

DIAGNOSIS

The diagnosis of chronic venous insufficiency is initially based on the clinical presentation, followed by the physical examination and using the duplex ultrasound (gold standard) for confirmation. This is a simple, inexpensive and minimally invasive method that allows to examine the

morphology and functionality of the venous system. As vein compression is performed, as well as reflux time quantification of incompetent veins. It is considered an incompetent vein if its backflow time is greater than 0.5 seconds for superficial or perforating veins and more than 1 second for deep veins.²⁷

TREATMENT

Surgical methods based on intraluminal fibers (radiofrequency, laser, glue, water vapor) used alone or together, do not manage to completely eliminate all the varicose veins in an extremity, it is not uncommon for incompetent veins to persist and these neglected veins are often responsible for recurrences. The key to therapeutic success in the treatment of venous insufficiency lies in the treatment of venous hypertension and in the complete, rigorous and confirmed elimination of all leg, ankle and foot varicose veins.²⁸

COMPRESSION SOCKS

Compression stockings are often the first line of treatment for varicose veins in people without healed or active venous ulcers. There are different lengths, from knee to full stockings, and apply different gradient of pressure to support blood flow. In the veins, however there is insufficient high-quality evidence to determine whether compression stockings are effective as a sole and initial treatment or whether any type of sock is superior to any other. Conclusions from individual studies regarding the optimal pressure provided by stockings were conflicting, although results from one study suggested that low-pressure stockings (>20 mmHg) may be as effective as higher-pressure stockings (30 to 40 mmHg) to alleviate symptoms. Some authors assure that stronger compression does not deliver more benefits, so we use moderate compression stockings, never more than 23 mmHg.²⁸ Regarding the optimal length of the stockings were inconclusive despite the fact that no serious or lasting side effects were observed.²⁹

PHLEBOTONICS

Natural or synthetic phlebotonics along with compression stockings, are considered the first pharmacological line for symptomatic treatment of varicose veins, reducing capillary permeability, releasing inflammation mediators and improving the overall venous vessel tone.³⁰ In a randomized study from Zapata et al there was a comparison between the use of phlebotonics and placebo, where moderate-quality evidence shows that phlebotonics may have beneficial effects on edema and improve some specific signs and symptoms (quality of life) related to CVI, such as trophic disorders, cramps, restless legs, swelling and paresthesia. However, compared with placebo, they also produce more adverse effects, being gastrointestinal disorders the most frequent one. In an interesting conclusion, phlebotonics did not show advantages compared to placebo in ulcer healing.⁴

Diosmin is a natural compound, a flavonoid, commonly found in citrus fruits and in the Rutaceae family. It has been shown to improve lymphatic drainage, support microcirculation and increase venous tone and elasticity it also has an anti-inflammatory effect relieving oxidative stress, it is considered an important therapeutic tool in the treatment strategy of chronic venous disorders.³¹⁻³⁵ In a study, Feldo et al denoted that oral administrations of 600 mg of diosmin twice daily for three month significantly decreased the plasma level of selected pro-inflammatory and pro-angiogenic factors, for example, TNF alpha, IL-6, FGF2, VEGF-A and VEGF-C. It could affect the reduction of interstitial edema, the reduction of the inflammatory stage and pain, and the negative regulation of the processes related to VEGF.³⁶ Other flavonoids that have also been studied are rutin, grape seed extract, hydroxymethyl, ruscus and Indian chestnut. It has been documented that *Ruscus aculeatus* decreases the diameter of the deep veins and reduces edema of the affected limb and venous stasis. The horse chestnut reduces edema of inflammatory or lymphatic origin and inhibits enzymatic and non-enzymatic peroxidation.³⁷

COMBINED PHLEBOTONICS

A study carried out by Cabrerizo et al showed beneficial effects when combining Aescin with procyanidin in patients with CVI, they assessed the changes in patients treated through quality of life questionnaires and by determining the safety of this association (SF-36v2 and VEINES -QOL / SYM), the results showed that the VEINES-SYM questionnaire significantly improved in the parameters "swollen legs", "night cramps", "heat / burning" and "restless legs" compared to the usual care group, however significant differences were not detected compared to the usual care group (monotherapy).³⁸

Diosmin / hesperidin are two flavonoids, they are micronized to increase absorption, this combination has showed several benefits with fewer adverse effects, they reduce symptoms such as pain, heaviness and paresthesia, improve skin changes and overall quality of life.³⁹ Calcium dobesilate acts along the endothelium and in the capillaries' base membrane by blocking hyperpermeability, inhibiting blood hyperviscosity and platelet aggregation, showing long-term benefits in chronic venous disease.⁴⁰

SCLEROTHERAPY

Sclerotherapy is a minimally invasive technique that has been used for over a hundred years being especially useful for treating small caliber veins. However, it also has several limitations such as dilution disparities, its progressive inactivation and the inaccuracy of the desired effect once injected in the blood vessel. These glitches have been replaced by placing these liquids in the vessel periphery in the form of microbubbles, physically displacing the blood contained in the vessel and making it easier to have the desired effect in the corresponding

segment (foam sclerotherapy). Because of its proven efficacy color Echo-Doppler-guided micro foam sclerotherapy is the treatment of choice when the anatomical and functional removal of pathological venous defect is indicated.²⁸ Nevertheless, recent publications have exposed cases of air embolism with ischemic and cerebrovascular symptoms after the administration of homemade foams, rising the concern for the safety of their use without following strict precautions.⁴¹ Reticular veins are subdermal veins located in the lower limbs and are mainly associated with aesthetic complaints. Although sclerotherapy is the treatment of choice for reticular veins in the lower limbs, no consensus has been reached regarding to the optimal sclerosant.⁴² The recommendations of the Tegernsee Consensus, dictate the moderate maximum recommended volume to be injected.⁴³

ENDOVENOUS TREATMENT

There are two main options for endovenous treatment, radiofrequency ablation (RFA) and endovenous laser therapy (EVLT), both techniques are especially useful when dealing with veins that follow a straight path and/or do not have a complex anatomy. Its main advantage is using an advanced endoluminal catheter that can be ultrasound guided to the site of venous incompetence, commonly below the epigastric vein at the saphenous-femoral valve. These are energy-based therapies and produce endothelial damage that leads to fibrotic occlusion and ultimately to the vein ablation. These are minimally invasive procedures that could even be performed under local anesthesia. Among its adverse effects we find; pain, ecchymosis, edema, hematomas, superficial thrombophlebitis, hyperpigmentation of the skin, paresthesia. Severe but rare adverse effects are deep vein thrombosis, pulmonary embolism and endovenous heat-induced thrombosis.⁴⁴ Endovenous therapy is currently considered the first line of treatment in superficial venous incompetence according to the 2013 NICE guidelines and the 2016 American College of Phlebology guidelines, being open surgery the second-best option.

RADIOFREQUENCY

Extraction of the saphenous vein by classic surgical open treatment causes morbidity, disability and increased recurrences, consequently the use of endovascular methods offers an effective and safe alternative to conventional procedures. A study carried out by Jiménez and Quiroga in 2016 evaluated the use of radiofrequency in the treatment of varicose veins in the lower limbs. Using the visual analog scale of pain and echo-Doppler, they evaluated pain during and after the procedure, use of analgesics, postoperative complications, ulcer healing, work incapacity and how long it took to fully return to work activities, it was concluded that the use of radiofrequency for the treatment of varicose veins is an effective and safe method, the patients returned to their activities in an average of 5 to 7 days, with little use of

analgesics; patients with venous ulcer were fully healed at 3 months in 95% of cases and no complications or clinical recurrence or by echo-Doppler were reported in the follow-up, facilitating the early return to work activities of the patients, mainly in those who had contraindications for having a surgical procedure.⁴⁵

Complete resolution can only be achieved when we can be reasonably sure that all veins that may constitute a source of recurrence have also been removed. The deep anatomical and functional knowledge that echo-Doppler provides, makes it an elemental tool to reach this goal, when used to perform exhaustive examinations in subsequent visits, between 3 and 5 months, after the first treatment. During this period is when we start treating newly and recanalized veins that are also detected in the 6,9- and 12-month follow-up consultations. Surgery or endoluminal techniques are of no use here, since varicose disease is considered an essentially evolutionary condition; however, the correct application of treatment can abruptly reduce its recurrence.²⁸

LASER

Endovenous laser therapy is a novel form of venous ablation. This method uses thermal energy to produce endothelial damage leading to fibrotic occlusion and ablation of the vein. Ultrasound guidance and local anesthesia are used to place a catheter in the saphenous vein, a laser fiber is then introduced and positioned below the saphenous femoral junction. Local anesthesia is injected and the fiber is slowly withdrawn while the energy of the diode laser (having a wavelength between 810 and 1054 nm) is applied in short pulses.⁴⁶ This action is repeated throughout the vein until it shuts the saphenous femoral coupling and the access point.⁴⁷

LASER OR RADIO FREQUENCY?

Both techniques are recommended as the first choice of treatment for saphenous and accessory vein insufficiency according to the 2016 American College of Phlebology guidelines, as well as the 2013 NICE guidelines.⁴⁸ The authors Ahadiat et al, in 2018 set out to compare endovenous laser therapy and radiofrequency ablation, obtaining the following results. Regarding the effectiveness of the method, defined as the closure of the vein, evaluated in subsequent visits by using ultrasound, both techniques are effective, however the laser showed a better outcome. They found that when using radiofrequency there were fewer cases of pain associated with the procedure, as well as less ecchymosis compared to the laser. This may be due to the fact that the laser reaches higher temperatures in a shorter period of time, unlike radiofrequency, which has longer plateau phases and lower temperatures. Concerning complications such as deep vein thrombosis and pulmonary embolism, no significant difference was found between the two techniques. As for recurrence defined as recanalization of the vein followed by venous incompetence, the laser

method had fewer manifestations. Finally, in terms of satisfaction and quality of life, no statistically significant difference was found between both techniques.⁴⁹

WHAT METHOD TO CHOOSE?

In order to make the best choice possible we have considered the anatomical characteristics and underlying diseases, as well as the particular wishes of the patients.

However, guidelines have already been created to help us offer the correct treatment to patients with chronic venous insufficiency. The 2013 NICE guidelines recommend endovenous radiofrequency or laser therapies as the first line of treatment, ultrasound-guided sclerotherapy as a second line, and finally surgical treatment with high ligation and saphenectomy as a third line.⁵⁰ The American College of Phlebology in 2016 recommended endovenous ablation therapy as the treatment of choice for incompetent saphenous and accessory veins and surgery in veins that are not susceptible to endovenous procedures, although it is associated with increased pain, convalescence, and morbidity. Treatment for anterior or posterior non-truncal, refluxing tributary, or circumflex veins is more complex as we must evaluate its competence, size, tortuosity and depth in relation to the skin. It is recommended that visible veins be treated with phlebectomy or sclerotherapy. In patients where the root of the disease is perforating reflux, treatment with endovenous ablation, ligation, or ultrasound-guided sclerotherapy is suggested. However, we must remember that we treat patients and not diseases thus treatment must be personalized, appropriate to the patient, contemplating the financial resources and the work environment in which we operate.

DISCUSSION

In Mexico, the first contact doctor (general practitioner and family doctor) does not have an essential minimum preparation in CVI since the study program of the main medical schools does not include an angiology subject and the student does not learn the basic elements to diagnose CVI. In family medicine, the only drugs to be prescribed within the institution are pentoxifylline and ASA, since there are no phlebotonic drugs in the public health sector, there is generally a misuse of anticoagulants, antithrombotics, antiplatelet agents and diuretics.⁵¹ Various studies show that varicose disease is highly progressive, Labropoulos et al studied cases of progression in patients who waited or delayed elective varicose vein surgery, it was performed in 116 lower extremities of 90 patients, a duplex ultrasound where the reflux detected was the predominant pathology and was present in 97.4% of the extremities. After a second ultrasound performed 1 to 43 months later, the disease had progressed in 31 extremities (26.7%), of which 14 (12.1%) had a new reflux site and 17 (14.7%) had an extension of the pre-existing reflux. Thirteen limbs (11.2%) had progressed to a new clinical stage: seven went from C2 to C3, four from C3 to

C4, and two from C4 to C6; However, new reflux was detected in only seven of these extremities.⁵²

We consider early treatment of varicose veins in the first medical contact a priority, as it reduces costs and time when treating their complications (active ulcer, chronic ulcer, infection, work incapacity and decreased quality of life). Spot on and early screening will allow the doctor and specialist to intervene mainly to improve the modifiable risk factors and so avoid long-term complications.

CONCLUSIONS

Chronic venous insufficiency is a disease that affects the patient at several levels, mainly diminishing his/her quality of life. Currently there are various treatments ranging from habit modifications, pharmacological, to endovenous and surgical treatment. We must have an extensive knowledge of the pathology to offer the best course of treatment, always considering the characteristics and special requirements of each patient.

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