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TWO COMMON PROBLEMS IN PHYSIATRY CLINICS: VENOUS DISEASE AND LOWER LIMB PAIN

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ABSTRACT

Venous diseases and lower limb pain are common problems in physiatry clinics. Because of having different treatment modalities, it is necessary to distinguish whether they are associated or not. Learning more about venous diseases is crucial for physiatrists, so we tried to review the literature for overview our knowledge. A PubMed search was performed for studies relating to venous diseases and lower limb pain from 2005 to 2015. Publications were retrieved by using search terms for venous diseases and lower limb pain. Relevant references from these studies were also retrieved. No filters were applied to limit the retrieval by study type. Patients with lower limb pain should be asked for symptoms of venous diseases which may include burning, tingling, muscle cramp, swelling, sensation of heaviness, itching skin, restless leg, leg tiredness and fatigue, as well as pain. Because venous diseases are frequently the cause of pain, discomfort, loss of working days, deterioration of health-related quality of life and disability. As physiatrists, we should know the nature of venous diseases. At least, we should gain adequacy to diagnose lower limb pain related to venous diseases for referring cardiovascular surgery clinics. Physiatrists should provide complementary treatment modalities to reduce edema and pain, and to improve joint mobility and muscle strength in patients with venous diseases.

INTRODUCTION

Venous diseases and lower limb pain are common problems in physiatry clinics [1,2]. Because of having different treatment modalities, it is necessary to distinguish whether they are associated or not. Learning more about venous diseases is crucial for physiatrists, so we tried to review the literature for overview our knowledge.

METHODS

A PubMed search was performed for studies relating to venous diseases and lower limb pain from 2005 to 2015. Publications were retrieved by using search terms for venous diseases and lower limb pain. Relevant references from these studies were also retrieved. No filters were applied to limit the retrieval by study type.

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Definitions and Epidemiology

Varicose veins of the lower limbs are dilated subcutaneous veins that are ≥3 mm in diameter measured in the upright position [3]. Synonyms include varix, varices and varicosities. Varicose veins can involve the main axial superficial veins or any other superficial vein tributaries of the lower limb. Most of them are due to primary venous disease. Although the etiology can also be multifactorial the most common accepted causes are intrinsic morphologic and biochemical abnormalities in the vein

wall [4]. Varicose veins may also be congenital and present as a venous malformation; however, they can also emerge as a result of secondary causes, such as previous deep vein thrombosis (DVT), deep venous obstruction, superficial thrombophlebitis or arteriovenous fistula. We should know that varicose veins are manifestations of chronic venous disease (CVD) [5,6].

Chronic venous disease includes various medical conditions with long duration, which involve morphologic and functional abnormalities of the venous system manifested by symptoms and/or signs. The term CVD is used for the full spectrum of venous abnormalities and includes dilated intradermal veins and venules between 1 and 3 mm in diameter.

Venous diseases which include varicose veins affect millions of people worldwide [1]. Kaplan et al. [7] reported the estimated frequencies of varicose veins and more advanced CVD which includes skin changes and healed or active venous ulcers in the United States, as 23% and 6% of adults, respectively. Other epidemiologic studies reported the similar percents (25%) in Western populations and stated the lower extremity venous disease as a significant cause of morbidity and lower health-related quality of life. In the United States, lower extremity superficial venous disease and varicose veins are frequent and seen in 15 % of men and 30 % of women [8-11].

Varicose veins have long been considered as only a cosmetic problem that affects emotional well-being. But now, we know that varicose veins are frequently the cause of pain, discomfort, loss of working days, disability and lower health-related quality of life [7,12,13]. Severe CVD may also lead to death or loss of limb [14].

Deep vein thrombosis (DVT) refers to the formation of blood clots in ≥1 deep veins, usually of the lower limbs. Deep vein thrombosis of the lower limbs is a frequent disease which threatens life. Estimated incidence of DVT is 1-3/1000 people per year [15-17]. Surgery, malignancy, or inherited coagulation disorders can lead to DVT as well as the spontaneous cases. A number of complications can follow DVT including acute complications such as pulmonary embolism and chronic conditions like post-thrombotic syndrome (PTS) [18-20].

Post-thrombotic syndrome-a common complication of DVT-is characterized by clinical features ranging from leg pain, swelling or minor skin changes to severe ulcers of skin [21,22]. The incidence and outcomes of PTS is less known. This is a chronic condition which affects at least one third of patients who have DVT, [23] and may be associated with leg pain, sensation of heaviness, edema, hyperpigmentation, lipodermatosclerosis and venous ulcers [24,25]. Some prospective studies reported that 20% to 50% of patients with DVT develop PTS [26-31]. Also, about 5% to 10% of patients develop severe PTS, which may include venous ulcers [26,27,30,32]. Post-thrombotic syndrome significantly decreases the health-related quality of life, [33] and it is associated with psychological and economic deterioration [34-36]. In most cases, PTS develops within a few months to a few years after symptomatic DVT [26-31]. However, some studies have reported that the cumulative incidence of PTS continues to increase, even 10 to 20 years after DVT diagnosis [30,31].

Varicose veins can also progress to a more advanced form of chronic venous dysfunction such as chronic venous insufficiency (CVI) [20,37]. It is characterized by the persistent venous hypertension of lower limb as a result of venous reflux and failure of pump function of calf muscle [38]. In CVI, increased ambulatory venous hypertension initiates the changes in the subcutaneous tissue and the skin, and symptoms including limb swelling, pigmentation, lipodermatosclerosis, eczema and venous ulcers can develop in these patients [3]. Progression of primary venous disease to severe CVI and venous ulcer is not rare and it is more than PTS (70% vs. 30%) [39].

Anatomy

To learn the pathophysiology of venous diseases we should recognize the anatomy. Superficial veins of the lower limbs are those located between the deep fascia which cover the muscles of limb and the skin. The main superficial veins are the great saphenous vein (GSV) and the small saphenous vein (SSV). The GSV originates from the medial superficial veins of the dorsum of the foot, and ascends in front of the medial malleolus along the medial border of the tibia, next to the saphenous nerve. The SSV is the most important posterior superficial vein of the lower limb, and originates from the lateral side of the foot and joins to the popliteal vein, usually just proximal to the knee crease. The intersaphenous vein ascends in the posterior thigh, and connects the SSV with the GSV [40].

Deep veins accompany the main arteries of the limb and the pelvis. The deep veins of the calf (anterior and posterior tibial veins and peroneal veins) are paired. The popliteal and femoral veins may be paired, too. The gastrocnemius and soleal veins are the deep tributaries. The femoral vein connects the popliteal vein to the common femoral vein. The pelvic veins include the external, internal, and common iliac veins. They all drain into the inferior vena cava (IVC). The left renal vein drains into the IVC on the left, and the large gonadal veins drain on the right. Perforating veins which pass through the deep fascia that separates the superficial compartment from the deep connect the superficial venous system to the deep venous system. The most important perforating veins are the medial calf perforators [41].

Bicuspid venous valves are important for one way flow in the healthy venous system. The GSV usually has at least 6 valves (range from 4 to 25), with a constant valve present within 2 to 3 cm of the saphenofemoral junction in 85% of cases, [42] and the SSV has at least 7 valves (range from 4 to 13) [43]. The deep veins of the lower limb have

valves more than one, but the common femoral vein and external iliac vein have only one valve in about 63% of cases, and 37% have no valve [43]. The internal iliac vein has one valve in 10%, where its tributaries have valves in 9% [44].

Pathophysiology

Venous return is achieved by patent veins, competent venous valves, and the venous pump. Varicose veins are mostly due to primary venous disease. The most frequent cause of varicose vein is likely an intrinsic morphologic or biochemical abnormality in the vein wall. Also a multifactorial etiology can lead to varicose veins. It is suggested by Labropoulos et al. [4] that the local or multifocal structural weakness of vein wall can cause venous reflux in patients with primary varicose veins and this can occur independently or together with valvular incompetence of proximal saphenous vein. Also, muscle pump failure of the calf can result in ambulatory venous hypertension and is therefore considered to be an etiological factor in CVI [45-47]. One possible trigger of pain is venous stasis which is related to the degree of reflux and which is caused by valve damage. This condition results in the incompetence and perforation of deep veins [48].

Risk factors of edema formation at lower limbs should also be kept in mind. Overweight or obese patients are in the risk group because of the possible impedance of venous return and immobility. Also, elder patients with coexisting diseases (like cardiac or renal) and medications like calcium-channel blockers or non steroidal anti-inflammatory drugs are in the risk group [49]. With the increasing age, the skin and underlying superficial fascia relaxes and stretches, [50] and these tissues are unable to withstand the extending force of interstitial fluid that lead to edema formation [51]. Mildly elevated pulmonary artery pressure, such as >30 mmHg in systole, may be associated with edema formation at lower limbs [52].

In CVI, increased ambulatory venous hypertension initiates some changes in the subcutaneous tissue and the skin which include activation of the endothelial cells, extravasation of macromolecules and red blood cells, diapedesis of leukocytes, tissue edema and chronic inflammatory changes most frequently noted at and above the ankles [3].

Pain is the main complaint in venous disease that leads to the diagnosis. Local inflammatory origin is a venous pain mechanism that current hypotheses focus on. It has been accepted that pro-inflammatory mediators released locally by leucocytes can activate nociceptors located in the vein wall (between endothelial cells and smooth muscle cells of the media) and in the connective tissue that forms the perivenous space, in close contact with the microcirculation [53].

Also, unmyelinated C fibers were identified in the wall of varicose veins which were arising from adventitia and spreading out into the external part of the media [54]. These unmyelinated C fibers may acting in symptom onset [55]. Chronic venous pain conditions may be associated with peripheral or central sensitization and with impairment of central nervous system inhibitory pathways in severe stages; [56] but these conditions have been little studied. In a study conducted with postmenauposal women with venous lower limb pain, [57] it is reported that this chronic inflammatory process may sensitize Aδ and C fibers peripherally and may trigger the central activation of different mediators, including cyclooxygenase enzymes. These changes can enhance the release of neurotransmitters such as glutamate, thereby increasing the likelihood of N-methyl- D-aspartate receptor activation [58]. This dysfunction in the N-methyl-D-aspartate receptor-dependent disinhibition of temporal summation may contribute to central sensitization. Furthermore, ischemia caused by venous microangiopathy and increased endoneurial pressure may result in nerve impairment, which may lead to the neuropathic pain [56]. Although pain mechanism of CVD has been little studied it is reported to be possibly associated with peripheral or central sensitization and with impairment of central nervous system inhibitory pathways in severe stages [56]. Ferrandiz et al. [57] reported lower pain threshold and increased pain sensitivity among women with osteoarthritis and CVI. Also they found the level of venous pain associated with peripheral venous reflux and osteoarthritis-related functional limitations. In this study, reflux was the main risk factor for pain in CVI.

Also, reduced physical activity and a history of prolonged standing or sitting impact pain levels in patients [57]. Also, certain sitting or standing positions can facilitate venous stasis [59]. Several studies [60,61] have demonstrated that the periodic contraction of calf muscle significantly decreases venous stasis, and that restriction of ankle mobility can impact on venous outflow. This may explain the association between reduced physical activity and pain, and slowed venous circulation may contribute to higher pain scores [57]. Chronic venous insufficiency may increase the leukocyteendothelial inflammatory reaction, which is considered the main stimulator of nociceptors in the venous wall and in paravasal tissue and this may be the explanation for the lower pain threshold [62]. Also, it has been stated that increased pain sensitivity in nonpainful regions may be a pain modulation disorder in conditions involving long lasting pain [63,64] and may indicate secondary hyperalgesia [65,66].

Clinical examination

Patients with varicose veins may present with no symptoms, except the cosmetic problem and underlying psychologic effects. But psychologic effects, related to the cosmetic problem will reduce a patient's health-related quality of life in many cases [67]. However, venous diseases and associated complications may also lead to

chronic pain, disability, lower health-related quality of life and loss of working days [13,14]. History, physical examination and diagnosis have great importance for the management of these patients. The aim of the clinical examination is not only to determine the presenting signs and symptoms and the type of venous disease, but also to exclude other etiologies, including peripheral arterial disease, rheumatologic disease, radiculopathy, infection, tumor or allergies. The physician should also evaluate the degree of disability caused by the venous disease and its impact on the patient's health-related quality of life.

History

A detailed medical history is essential for the patients with venous diseases. Questions to patients who present with varicose veins should address previous medical conditions such as DVT or thrombophlebitis, established thrombophilia, medication history (particularly birth control pills), smoking, pregnancies and a family history of varicosity or thrombotic disorders [8-11]. Premenopausal women with varicose veins should also be questioned for the symptoms of pelvic congestion syndrome (pelvic pain, aching, or heaviness; dyspareunia). A positive family history of varicosity, female sex, advanced age and multiparity are risk factors for varicose veins, and a positive family history, advanced age and obesity are risk factors for CVI [68].

All related symptoms may accompany all stages of CVD. Symptoms related to varicose veins or more advanced CVD include pain, burning, tingling, muscle cramps, swelling, sensation of heaviness, itching skin, restless leg, leg tiredness and fatigue [67]. Some patients may have history of thrombophlebitis or bleeding from superficial varicose veins. Although not pathognomonic, if these symptoms are exacerbated by heat and relieved by elevating the legs and resting or by wearing elastic stockings or bandages, we may diagnose CVD [5]. Pain during and after exercise that is reduced with leg elevation and rest -which is defined as venous claudication- may also be emerged by the obstruction of venous outflow due to previous DVT or by narrowing or obstruction of the common iliac veins (May-Thurner syndrome) [44,67,69]. However, local pain usually occurs by the poor venous circulation in bulging varicose veins and diffuse pain is often due to axial venous reflux. Patients with CVD may also present with symptoms and signs of eczema, lipodermatosclerosis, pigmentation, atrophie blanche, corona phlebectatica (ankle flare or malleolar flare) and healed or active ulceration, as well as lower limb pain [18-20,70].

Chronic venous insufficiency (CVI) is a common disorder that has a significant impact on lower limb pain and health-related quality of life. It is characterized by the persistent venous hypertension of lower limb [38]. Prolonged venous hypertension can increase calf muscle failure and cause sensation of heaviness, nocturnal muscle cramps, restless leg, itching and pain [71]. Although, pain in patients with CVI has long been ignored, it is now considered to be an important and common problem because of its higher prevalence and its impacts on health-related quality of life [72]. Working conditions that require prolonged sitting or standing are associated with an increased risk of CVI [73,74]. Moreover, in a study conducted among patients with leg ulcer, it is reported that fear and avoidance beliefs are frequent among patients with CVI and are associated with low physical activity and more severe pain [75].

Evaluation of pain is very important and there are commonly used rating scales like visual analogue scale (VAS) and McGill Pain Questionnaire (MPQ). Also, generic instruments like Short Form-36 (SF-36), [76,77] or disease specific instruments are being used widely for measuring the severity of disease. The most frequently used validated venous disease specific instruments include the Venous Insufficiency Epidemiologic and Economic Study of Quality of- Life (VEINES-QOL/Sym) questionnaire scale, the Chronic Venous Insufficiency Questionnaire (CIVIQ), the Aberdeen Varicose Vein Questionnaire (AVVQ), and the Charing Cross Venous Ulceration Questionnaire (CXVUQ) [78-82].

Clinical, Etiological, Anatomical and Pathophysiological classification (CEAP) has common usage in clinics. CEAP classification allows more detail to be recorded. Symptoms of CVD, including pain, tightness, skin irritation, heaviness and muscle cramps are denoted by the letter S in subscript, for example C2S (symptomatic) or C2A (asymptomatic) [83]. Clinical classification according to CEAP is shown in Table 1. Padberg et al. [84] reported significantly worse sensory neuropathy signs in women with severe (C5) versus mild (C2) CVI. However, Rabe and Pannier [85] stated that CEAP classification cannot be considered a severity scale because C2 summarizes all types of varicose veins and C3 does not distinguish between venous and other causes of edema. This classification may be limited to explain the relationship between degree of pain and CEAP classification. Conway et al. [86] reported that pain was more frequent in women with saphenofemoral junction reflux, and Broholm et al. [87] reported higher health-related quality of life scores and less pain in women with patent veins and competent valves than in women with reflux and occluded veins. In a study evaluated the relationship between venous leg ulcers and concomitant medical conditions, a statistically significant association between osteoarthritis and venous leg ulcers of recent onset was found, which may be explained by limitations in mobility and range of motion. These conditions may be related to the level of pain [88]. Hendiani et al. [89] reported significantly higher VAS pain scores and tactile hypoesthesia and significantly lower pain threshold in women with osteoarthritis in comparison with healthy individuals.

Physical examination

Clinical examination should focus on signs of venous disease. Standardized physical examination of the standing patient in a warm room, with good light, should include the size, location and distribution of varicose veins. Inspection and palpation are the essential parts of physical examination. Auscultation is particularly helpful for diagnosing the bruit in vascular malformation and arteriovenous fistula [69]. Varicose dilations, venous aneurysms, palpable cord in the vein, tenderness, possible thrill, bruit or pulsatility, spider veins, telangiectasia, limb swelling that is usually partially pitting or nonpitting, induration, pigmentation, lipodermatosclerosis, atrophie blanche, eczema, dermatitis, skin discoloration, increased skin temperature and healed or active ulcers should be recorded. Ankle mobility should be examined, because patients with advanced venous disease frequently have decreased mobility in the ankle joints. Sensory and motor functions of the limb and foot are assessed to help differentiate from diabetic neuropathy or any underlying neurologic problem or musculoskeletal problem. Also, an abdominal examination may be helpful for diagnosing an abdominal mass or lymphadenopathy which may be the clue to venous compression or obstruction. Corona phlebectatica is a pattern of small intradermal veins located around the ankle or the dorsum of the foot. This is considered an early sign of advanced venous disease. The pattern of the varicose veins should be recorded, because perineal, vulvar or groin varicosity can be a sign of iliac vein obstruction or internal iliac vein or gonadal vein incompetence causing pelvic congestion syndrome. Scrotal varicosity may be a sign of gonadal vein incompetence, left renal vein compression between the superior mesenteric artery and the aorta (nutcracker syndrome) or occasionally, even IVC lesions or renal carcinoma. Varicose veins of the upper thigh may be due to inferior gluteal vein reflux [90,91].

Physical examination may be complemented with clinical classification like CEAP (Table 1). Pain is an important variable of the scales. Pain scoring in Revised Venous Clinical Severity Score (which also includes scores for Varicose veins, Venous edema, Skin pigmentation, Inflammation, Induration, Number of active ulcers and Use of compression therapy) is shown in Table 2 [92]. Most of the skin manifestations of CVI are found in CEAP classification of C3-6 [93,94]. Mobility and range of motion were found affected in women with CVI, who are generally middle-aged or older in a study conducted by Moreira et al [95]. They also stated that a loss of muscle strength in women after menopause makes it more difficult for them to perform strength-dependent activities [95]. Musculoskeletal impairment is mainly related to gastrocnemius muscle dysfunction [96] and reduced range of ankle motion, [60] especially dorsiflexion, which is thought to be required for normal functioning of the calf muscle pump.

Diagnosis

It's known that the physical examination can be complemented by a handheld Doppler examination, although the latter does not replace examination of the venous circulation with color duplex scanning. These examinations are not common in physiatry clinics, whereas they are routine in cardiovascular surgery clinics.

Patent veins, competent venous valves and the venous pump are essential for venous return. When venous disease is suspected, a duplex scan of the venous system is generally performed to detect any anatomical venous problems. When no abnormalities are detected, venous disease is often excluded, although this does not exclude the possibility of venous pump deficiency. Duplex scanning is recommended as the first diagnostic test for all patients with suspected CVD [97]. The test is safe, cost-effective, noninvasive and reliable. Duplex scanning has much better diagnostic accuracy in the assessment of CVI than continuous-wave Doppler ultrasonography [98]. It is stated that B-mode imaging permits accurate placement of the pulsed Doppler sample volume, and facility of adding color makes it easier to detect obstruction, turbulence and the direction of venous and arterial flow [99]. Duplex scanning is reported as an excellent method for the evaluation of infrainguinal venous obstruction and valvular incompetence [100]. It also distinguishes acute venous thrombosis and chronic venous changes [101,102].

Plethysmography (air, photo, strain-gauge) is another method which is used for the noninvasive evaluation of calf muscle pump function, global venous reflux and venous obstruction [103-105]. Plethysmography quantifies venous reflux and obstruction. It was used to monitor venous functional changes in CVI and assess physiologic outcome of surgical treatments [104]. This is a complementary examination to duplex scanning.

Contrast venography, Computerized Tomography and Magnetic Resonance venography and intravascular ultrasonography are other different radiological modalities to investigate venous diseases [2].

Differential Diagnosis

In the differential diagnosis of venous diseases and lower limb pain, a complete pulse examination should be performed to exclude underlying peripheral arterial disease. Palpable masses should be inspected to avoid misdiagnosis. For example, an aneurysmal saphenous vein can be misdiagnosed as a femoral hernia or vice versa. Outflow obstruction at ilio-femoral segment with or without valvular incompetence in the femoral and/or popliteal vein can lead to venous claudication described as a "bursting" pain while walking, only achieve symptomatic relief by rest or even better by elevation and must be differentiated from neurological claudication. Venous claudication can be due to DVT in the ilio-femoral segment and may lead to a bursting pain affecting the buttocks, thighs or legs when walking [83].

Congenital factors are present from birth. They are associated with the disorders in the development of the venous system. Some examples of congenital anomalies are Klippel-Trenaunay syndrome (KTS), Parkes-Weber syndrome (PWS) and vascular malformations. The presence of a longer limb, lateral varicosity noted soon after birth and associated capillary malformations are clues for recognizing congenital venous malformation; Klippel-Trenaunay syndrome [106,107]. Klippel and Trenaunay first described this condition in 1900, after observing two patients with skin lesions associated with asymmetric soft tissue and bone hypertrophy [108]. Vascular malformations can be single or combined depending on the components of the circulatory system that are involved in the lesion [109]. Klippel-Trenaunay syndrome is a syndrome characterized by capillary, venous and lymphatic abnormalities, without significant arteriovenous shunt. It is very rare and emerges in 1/20000-1/40000 live births with an unclear origin [110]. Patients with this condition are characterized by the clinical triad of port wine stain, varicose veins and soft tissue and/or bone hypertrophy. The diagnosis of KTS is made according to the clinical findings. Patients may present with symptoms including pain, swelling, bleeding from superficial varicosities and superficial thrombophlebitis [111]. Pain is a significant complaint, with up to 88% of patients experiencing varying degrees of discomfort [112]. Various factors causing pain in patients with KTS have been identified, including varicose veins, CVI (C3-C6), cellulitis, superficial vein thrombosis, DVT, vascular malformations, arthritis and neuropathic pain [110,113]. Parkes-Weber syndrome has similar symptoms to KTS but has a distinct pathophysiological mechanism. Parkes Weber first described this syndrome in 1907. The incidence is sporadic with no racial or gender predilection. Klippel-Trenaunay syndrome is a low flow malformation involving the capillary, venous and lymphatic systems, whereas PWS is characterized by fast flow arteriovenous abnormalities. It is present from birth and frequently affects the lower limbs like KTS. Parkes-Weber syndrome is characterized by capillary cutaneous malformations and limb hypertrophy, in addition to arteriovenous malformations which can result in bone or soft tissue hypertrophy by the high flow between arteries and veins. High flow to epiphysis results in increasing bone length, width and temperature of the affected limb. A bruit may be audible and palpable. High flow from the arterial to the venous system can result in systemic effects like cardiac preload that leads to congestive cardiac failure [114].

Edema is a common sign of venous diseases but this condition may have different causes. For example, physicians should keep in mind chronic lymphedema that has the signs including edema of the dorsum of the foot, squaring of the toes, thick skin and nonpitting edema. Lymphedema can affect the musculoskeletal structures which may lead to additional disability [115,116] and can decrease the health-related quality of life [117]. Lymphatic system plays a major role in microcirculation as well as the arterioles, capillaries and venules, particularly in returning interstitial proteins back to the circulation and regulates the tissue fluid, so the edema. Microcirculation describes the process of delivering nutrients and removing waste products from the tissues as well as regulating blood flow and pressure, tissue perfusion, body temperature and tissue fluid [115,118]. If there is a mechanical or metabolic failure that affects the lymphatic system then lymphedema occurs. Mechanical failure may be due to anatomical abnormalities of lymph nodes, vessels or tissues. These abnormalities can be inherent (primary lymphedema) or due to trauma (secondary lymphedema) [115,119-121]. Rockson et al. [122] reported the estimated prevalence of lymphedema including both the lower and upper limbs as 1.3-1.4/1000. In the United States, it is reported that the incidence is above this estimated percents up to 10-40% among breast cancer survivors who went under surgery and who went under replacement surgeries like hip or conditions like cellulitis [118]. According to the Consensus Document of the International Society of Lymphology, lymphedema is defined as low output failure of the lymphatics and should be distinguished from high output failure, so edema in immobile patients can frequently be misdiagnosed as lymphedema [123]. As shown in a study conducted with lymphangioscintigraphy, lymph transport was normal or even accelerated in immobile patients [124]. Thus, they noted that this type of edema should not be diagnosed as lymphedema. One of the features of this type of extremity edema is that the severity of chronic inflammation and the edema were significantly influenced by gravity, as demonstrated in this study by subcutaneous ultrasonography. They also reported that edema was most severe in the lateral aspect of the lower leg [124].

Edema can also be seen both in DVT and PTS. There is a considerable degree of overlap between the acute symptoms resulting from DVT and those of PTS [125-127]. The Ginsberg score was designed in a cross sectional study looking at PTS developing after hip or knee arthroplasty. According to this study, PTS is diagnosed in case of reported leg pain and swelling of a chronic nature (everyday, at least 1 month) aggravated by prolonged standing and improved by leg elevation and occurred at least 6 months after the initial DVT [127]. Soosainathan et al. [24] stated that patients could be diagnosed with PTS only if they had both leg pain and swelling and if there was objective evidence of valvular incompetence. It is considered a syndrome because it manifests as a spectrum of symptoms and signs of CVI, which vary from patient to patient [5,128]. Clinical characteristics of PTS are shown in Table 3.

Non-traumatic Reflex Sympathetic Dystrophy (RSD) should also be kept in mind in patients with lower limb pain and edema [129]. Non-traumatic RSD is a disease which occurs spontaneously or with any detected

cause obtained by clinical and laboratory investigations. Especially, this condition can be misdiagnosed as PTS. As emphasized in a report, allodynia, painful passive motion, the very regional edema that does not resolve with rest and get better with exercise, the hyperemia that does not change with rest, the absence of vascular skin signs, presence of hair and nail changes point RSD rather than PTS [129].

Treatment

By the studies emphasized the venous disease of lower limb as a significant cause of morbidity and lower health-related quality of life, improvements in the treatment options and an increasing awareness of the disease were came out. Although, in some studies surgical treatment for varicose veins was found more effective on symptomatic relief and improvement in health-related quality of life, [130] compression therapy is still the basic and common treatment modality for varicose veins, venous edema, skin changes and ulcers. Compression is recommended to decrease ambulatory venous hypertension of patients with CVD. It is reported that pressures to compress the superficial veins in supine patients range from 20 to 25 mm Hg, whereas when upright, pressures of 35 to 40 mm Hg are needed to narrow and pressures >60 mm Hg are needed to occlude superficial veins [131]. Compression therapy also improves pump function of calf muscle and decreases reflux in vein segments in patients with CVI [132,133]. Lifestyle modifications that include weight loss, exercise and elevation of the legs during the day whenever possible are also recommended as complementary. The different forms of ambulatory compression techniques and devices are used like elastic compression stockings, paste gauze boots (Unna boot), multilayer elastic wraps, dressings, elastic and nonelastic bandages and nonelastic garments. Pneumatic compression devices (Intermittent Pneumatic Compression, IPC) applied primarily at night, are also used in patients with refractory edema and venous ulcers [83,134].

Graded compression was found effective as the primary treatment to aid healing of venous ulcers and as an adjuvant therapy to interventions to prevent recurrence of venous ulcers [135]. It is found that venous leg ulcers heal more quickly when treated with compression therapy and walking exercises [83,136]. Intermittent pneumatic compression was found effective on reducing symptoms of CVI and aiding the healing of chronic ulcers [136-139]. Intermittent pneumatic compression have been used in the management of CVI for a long time. Initially, this therapy was targeted at the prevention of DVT and pulmonary embolism but today, it is also used to reduce lymphedema [140]. Sequential gradient compression therapy can be used for patients with venous ulcers who cannot tolerate sustained compression [141]. Compliance with compression therapy is important. Compression therapy using moderate pressure (20 to 30 mm Hg) is suggested for patients with symptomatic varicose veins, but high compression pressures of at least 40 mm Hg at the ankle level are recommended to promote ulcer healing [83].

Venotonic drugs (eg. Calcium dobesilat) should be considered as a treatment option for swelling and pain in patients with CVD. Venoactive drugs including diosmin, hesperidin, rutosides, sulodexide, pentoxifylline, micronized purified flavonoid fraction or horse chestnut seed extract can be an option in addition to compression for patients with pain and swelling due to chronic venous disease, but zinc, oral antibiotics, horse chestnut seed extract and pentoxifylline are not recommended in patients with venous ulcers [83].

Sclerotherapy is the injection of dilated veins, including major refluxing trunks or tributary varicosities, venules or telangiectasias, with liquid or foam chemical agents-including polidocanol, sodium tetradecyl sulphate, morrhuate sodium, glycerin and hypertonic saline- to damage the endothelium and ablate the veins [83]. It is recommended for telangiectasia, reticular veins and varicose veins [2,83]. It is not recommended as the first choice treatment of C2-C6 CVD due to saphenous vein incompetence, but it can be used for patients who are not eligible for surgery or endovenous ablation. It is recommended as primary treatment for patients with recurrent varicose veins and elderly patients with leg ulcers [83]. Cost-effectiveness analysis showed that surgery was significantly more cost-effective than both sclerotherapy and conservative management; sclerotherapy was less cost-effective than surgery but was still significantly more cost-effective than conservative treatment. Severe complications after sclerotherapy, such as death, anaphylactic reaction, pulmonary emboly, stroke and large areas of skin necrosis, are very rare (<0.01%) but possible [83,142-145]. Severe but rare complications also include thrombophlebitis, nerve damage (saphenous, sural), DVT or arterial injection of the solution [146,147]. Most frequent complications (observed in up to 30% of the cases) of sclerotherapy are minor and include matting, pigmentation, pain, allergy and skin urticaria [148].

Surface transcutaneous laser (TCL) is another treatment modality that can be used for the treatment of telangiectasias and reticular veins only when sclerotherapy is not applicable. It works by endothelial injury of the vein by heating the hemoglobin and eventually obliterating the lumen [83].

Endovenous techniques in the treatment of saphenous vein incompetence is recently become very popular as being a minimal invasive, generally safe and effective method which is alternative to classical surgery, with reduced convalescence and less pain and morbidity [2]. The two most frequently used techniques are endovenous laser ablation (EVLA) and radiofrequency ablation (RFA). Another endovenous thermal ablation (EVTA) technique is steam ablation. Other more recently introduced techniques are mechanochemical ablation

(MOCA) and injection of cyanoacrylate glue. For the treatment of GSV and SSV reflux in patients with symptoms and signs of CVD endovenous thermal ablation techniques are recommended [83].

For many years the gold standard for treatment for CVD patients with superficial venous incompetence was surgery. Still for the treatment of incompetent GSV, high ligation and inversion stripping of the saphenous vein to the level of the knee is recommended. Also the technique of ambulatory phlebectomy is used. It is removal or avulsion of varicose veins through small incisions performed with hooks and forceps and it is a safe and effective procedure for the treatment of varicose veins. Phlebectomy should be considered to treat tributary varicose veins, as well as the treatment of varicose veins, performed with saphenous vein ablation, either during the same procedure or at a later stage [2,83].

Treatment of chronic deep venous obstruction includes percutaneous transluminal angioplasty (PTA) and stenting or surgical correction, usually bypass. For treatment of recurrent varicose veins, ligation of the saphenous stump, ambulatory phlebectomy, sclerotherapy or endovenous thermal ablation are suggested. To treat pelvic congestion syndrome and pelvic varices coil embolization, plugs or transcatheter sclerotherapy can be used [2,83]. In recently published guidelines physiotherapy is not recommended as a measure to enhance healing of venous leg ulcers but it is recommended to keep the patients as mobile as possible [83]. Physiatrists should provide complementary treatment modalities to reduce edema and pain, and to improve joint mobility and muscle strength in patients with venous diseases. Leg massage may be considered as an adjuvant treatment to reduce edema in patients with CVD [83]. Anything that alters the pump function of calf muscle increases the risk of CVI, which then increases the risk of venous leg ulcers [149]. The pump function of calf muscle has been referred to as "peripheral heart" because of its role in providing venous return from the lower limbs to the heart [150]. It works during walking and other lower limb exercises, and has three components: competent venous valves, functional gastrocnemius and soleus muscles and unsheathing fascia and skin surrounding these muscles. These components compress the veins during locomotion and pump the blood flow towards the heart. Increased pressure on the external walls of the deep veins by the contraction of gastrocnemius and soleus muscles, open valves on the wall of veins which are needed for avoiding reflux, to let the blood flow upward. During relaxation period of the calf muscles, by the decreasing hydrostatic pressure, veins refill. The negative pressure that results from venous emptying provides the flow of arterial blood into skeletal muscles. Failure of the pump function of calf muscle was found related to the severity of venous ulcers [46,151]. Furthermore, venous insufficiency and severity of the disease was found related to reduced range of motion at the ankle [152]. Exercise programs can reduce the detrimental effects associated with impaired calf muscle function and may improve hemodynamic performance and prevent ulcers [153]. Walking exercises is a practical suggestion for patients who are ambulatory [154].

Manual lymphatic drainage techniques also can contribute to the care of patients with chronic lower limb edema associated with venous insufficiency [136]. The efficacy of manual lymphatic drainage is due in large part to enhancing venous blood flow, most likely in the femoral and GSV. Some guidelines support the use of this technique to reduce tissue edema in individuals with CVI, but there is no data linking manual lymphatic drainage to ulcer healing [138,139,155]. Bakar et al. [156] reported that CVI treated with complete decongestive physiotherapy (skin care, manual lymphatic drainage, compression bandaging and exercise) significantly reduces the limb edema and pain associated with CVI.

Biophysical energy from electromagnetic and acoustic energy (ultrasound treatment) spectra for stimulation of wound healing is recommended by the guidelines for wound healing [136]. The evidence supports use of electrical stimulation in treating venous ulcers. It is stated that high-voltage pulsed current or pulse-controlled electrical stimulation applied to chronic leg ulcers may reduce the wound surface area over a 4-week treatment period to approximately one half the initial wound size [157,158]. Also, there is evidence to support their use for pain management, muscle strengthening and edema as well as wound healing [159]. Although it is mostly used for breast cancer related upper limb lymphedema low-level laser therapy (LLLT) is suggested for pain management, musculoskeletal symptoms relief and wound healing [159]. Some effects of LLLT include the softening of scar tissue by affecting fibroblasts and the reduction of interstitial fluid by stimulating lymphatic flow, lymphangiogenesis and macrophage activity, [159-161] and may be used in individuals with lower limb CVD with edema.

Table 1. Clinical classification according to CEAP

C0	No visible or palpable signs of venous disease
C1	Telangiectases or reticular veins
C2	Varicose veins
C3	Edema
C4a	Pigmentation and/or eczema
C4b	Lipodermatosclerosis and/or atrophie blanche

C5	Healed venous ulcer
C6	Active venous ulcer
CS	Symptoms, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction
CA	Asymptomatic

Table 2. Pain score in Revised Venous Clinical Severity Score

	None:0	**Mild:1**	**Moderate:2**	**Severe:3**
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning); presumes venous origin	None	Occasional pain or other discomfort (ie, not restricting regular daily activity)	Daily pain or other discomfort (ie, interfering with but not preventing regular daily activities)	Daily pain or discomfort (ie, limits most regular daily activities)

Table 3. Clinical characteristics of postthrombotic syndrome

Symptoms	**Clinical Signs**
Pain	Edema
Sensation of swelling	Telangiectasia
Cramps	Venous dilatation/ectasia
Heaviness	Varicose veins
Fatigue	Redness
Itching	Cyanosis
Pruritis	Hyperpigmentation
Paresthesia	Eczema
Bursting pain	Pain during calf compression
Venous claudication	Lipodermatosclerosis
	Atrophie blanche
	Open or healed ulcers

CONCLUSIONS

Venous diseases and lower limb pain are common problems in physiatry clinics, as well as the general population. Patients with lower limb pain should be asked for symptoms of venous diseases which may include burning, tingling, muscle cramp, swelling, sensation of heaviness, itching skin, restless leg, leg tiredness and fatigue. Because venous diseases are frequently the cause of pain, discomfort, loss of working days, deterioration of health-related quality of life and disability. As physiatrists, we should know the nature of venous diseases to avoid misdiagnosis. It is obvious that musculoskeletal and neurologic causes should be known well to differentiate the origin of lower limb pain. Also, we should gain adequacy to diagnose venous diseases for referring cardiovascular surgery clinics. Current diagnostic approaches and treatment modalities of venous diseases should also be known to meet the information demands of our patients. Finally, physiatrists should provide complementary treatment modalities to reduce edema and pain, and to improve joint mobility and muscle strength in patients with venous diseases.

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