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REVIEW

Type 2 Diabetes Mellitus and Chronic Venous Disease of the Lower Extremities: A Narrative Review

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ABSTRACT

Chronic venous disease (CVD) is a highly prevalent but often under-recognized condition, affecting up to 60% of the general population. In patients with diabetes mellitus, the burden of CVD appears to be higher, with more severe clinical manifestations, suggesting shared pathophysiological mechanisms between the two disorders. This narrative review explores the relationship between diabetes mellitus and CVD, focusing on underlying mechanisms, clinical implications, and management strategies. A comprehensive review of the literature was conducted, integrating evidence from clinical studies, mechanistic research, and current guidelines. Epidemiological data indicate that diabetes mellitus is more frequently observed in patients with CVD compared with the general population (17.8% versus 8.6%; $P<0.0001$). Diabetes contributes to the development and progression of CVD through multiple interconnected mechanisms, including endothelial dysfunction, chronic inflammation, oxidative stress, and microangiopathy, leading to structural and functional alterations such as valvular incompetence, venous reflux, and sustained venous hypertension, which may exceed 60 mmHg at the capillary level in advanced stages. Patients with diabetes are more likely to develop advanced manifestations, including edema, skin changes, and venous ulceration. Impaired wound healing due to microangiopathy and immune dysfunction increases the risk of infection and ulcer chronicity. In addition, the coexistence of peripheral arterial disease further complicates diagnosis and management, often resulting in mixed-etiology ulcers. Chronic venous disease and diabetes mellitus share overlapping risk factors and pathophysiological pathways that contribute to disease progression and clinical complexity. Early recognition, accurate diagnosis, and a multidisciplinary management approach are essential to improve outcomes. Targeted strategies, including glycemic control, compression therapy, lifestyle modification, and

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appropriate pharmacological interventions, may help reduce complications and improve quality of life in this high-risk population.

Keywords: Chronic venous insufficiency; Chronic venous disease; Diabetes mellitus; Diabetic ulcer; Microangiopathy

Key Summary Points
Chronic venous disease is highly prevalent and has several etiologies in common with diabetes mellitus.
The shared pathophysiology includes capillary damage, which leads to microangiopathy and increases in venous pressure.
Though greatly overlooked, manifestations of chronic venous insufficiency in people with DM include pain, edema, venous ulcers, and limb-threatening complications.
Management involves risk factor modification, glycemic control, exercise, weight management, compression therapy, venoactive medications, and surgical interventions.

INTRODUCTION

Over the last few decades, diabetes mellitus (DM) has become a public health problem owing to its high incidence, presenting multiple complications that impact quality of life and decrease life expectancy in affected people. The incidence continues to increase. In 2019, an estimated 463 million people globally were living with diabetes, with a projection of reaching 700 million, or a 51% increase, by 2045 [1]. Furthermore, the diagnosis of the disease in younger patients is also increasing, which, together with the large proportion of undiagnosed patients, will make chronic complications from diabetes one of the main disabilities and impacting factors resulting in a decline in quality of life and life expectancy in the future [2].

In recent years, significant emphasis has been placed on cardiovascular outcomes of diabetes owing to the impact on people's life expectancy, high cost to health systems, and the development of new drugs that are able to modify the natural history of these complications. However, there are several other complications or conditions associated with diabetes that also impact the quality of life of patients living with DM. One of the chronic problems, which are generally overlooked by health professionals, owing to a lack of recognition of its manifestations and the magnitude of the problem it represents, is chronic venous disease (CVD) [1, 2].

CVD is an umbrella term describing long-duration morphological and functional abnormalities of the venous system, whether symptomatic or not. Chronic venous insufficiency (CVI) represents the more advanced stages of CVD, typically corresponding to Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification C3–C6, in which sustained venous hypertension leads to edema, skin changes, and venous ulceration [3]. Venous hypertension refers to sustained elevation of ambulatory venous pressure, typically exceeding normal physiologic levels during standing or ambulation, leading to capillary leakage and tissue edema [4]. Venous ulcers are most commonly located in the gaiter region, particularly near the medial malleolus [4].

The presence of persistent ambulatory venous hypertension is the cause of the most common manifestations of CVD. These include telangiectasias, reticular veins, and varicose veins, combined with the predominant symptoms of pain, edema, skin changes, and ulcerations [5].

Several studies have been conducted to estimate the prevalence of venous disease. The Edinburgh Vein Study analyzed 1566 participants with ultrasound to evaluate the presence of venous reflux. The prevalence of chronic venous insufficiency in this study was 21% in men and 12% in women over the age of 50 years. In the San Valentino Vascular Screening Project, 30,000 subjects were evaluated with a 7% prevalence of varicose veins reported, but < 1% of subjects reported symptomatic chronic venous insufficiency. These findings were more frequent in older patients, with no significant difference

based on the sex of participants [5]. Finally, the Vein Consult Program evaluated more than 91,000 subjects in different geographic regions and found a clinically significant prevalence of CVD of approximately 60%. CVD was more prevalent in developed and industrialized countries compared with developing countries. Associated risk factors included age, sex, family history of venous disease, obesity, pregnancy, phlebitis, and previous limb injury. Contributing environmental factors included prolonged standing and possibly prolonged sitting associated with work [6]. Recent reviews, including Jarošíková et al. [6], have explored the potential association between diabetes mellitus and chronic venous disease, highlighting the limited causal evidence and the need for further research to clarify mechanistic pathways. The present review expands upon prior analyses by integrating updated molecular insights, including endothelial dysfunction and matrix metalloproteinase activation, as well as emphasizing practical clinical management considerations specific to patients with diabetes [7].

In general, its etiology is divided between venous reflux, obstruction, or a combination of both. Venous reflux is mediated by various mechanisms such as valve incompetence, hemodynamic factors, venous hypertension, and inflammation of the vessel wall [8]. Inflammation of the vessel wall is linked to multiple metabolic diseases, including DM, where chronic inflammation plays a dominant role in the pathogenesis of these diseases. Chronic inflammation, combined with venous hypertension and venous hemodynamic changes, are responsible for the release of multiple vasoactive substances from the endothelium and overexpression of adhesion molecules, chemokines, and inflammatory mediators, as well as injury to the endothelial glycocalyx and perpetuation of the local inflammatory response [9].

The high concomitant incidence of both diabetes and CVD and the commonalities in the pathophysiology of both diseases raise the question about the possible synergy between both processes, which may even share a causal link [10].

For this reason, we investigated the relationship between the development of DM and CVD to establish points of confluence in the pathophysiology, which could provide future insights into the natural evolution of the disease. By clarifying this relationship, we can increase awareness about the prevalence of CVD in patients with diabetes, and with greater focus on this complication, avoid a delay in diagnosis and establish more timely initiation of treatment. With early intervention, complications of CVD may be delayed or avoided. In addition, it will allow us to explore new treatments that could affect the development of both diseases [11].

This review is based on previously published studies and does not involve any new studies with human participants or animals conducted by the authors. Therefore, formal ethical approval was not required.

CONTRIBUTING PATHOPHYSIOLOGICAL FACTORS IN DIABETES MELLITUS AND CHRONIC VENOUS DISEASE

Diabetes mellitus is frequently associated with comorbidities such as obesity, dyslipidemia, and hypertension, which are established cardiovascular risk factors [12]. Among the traditional comorbidities and cardiovascular risk factors are obesity, dyslipidemia, and hypertension [9]. Other comorbidities include vascular changes, and although there is more focus on the arterial system, important associations to the venous system have also been described.

DM is frequently accompanied by a prothrombotic state due to various pathophysiological mechanisms such as increased plasma coagulation, reduced fibrinolysis, and platelet hyper-responsiveness. This is an important consideration, since the spectrum of venous disease is not only varicose veins without severe complications, such as deep vein thrombosis or pulmonary embolisms [13].

CVD occurs in approximately 10–20% of the general population, depending on risk factors. The etiopathologic factors that cause CVD, such as sedentary lifestyle related to lack of exercise, overweight, and obesity, are

common contributing factors to other chronic diseases, including DM [8, 14]. To date, a clear cause–effect relationship between DM or vice versa has not been identified as there are insufficient data on the presence of varicose veins in patients with diabetes mellitus.

Despite this, some studies suggest a greater association of DM with CVD due to structural or functional changes in the venous system, especially those associated with changes in microcirculation, which manifests as valve incompetence, venous reflux, as well as a pro-inflammatory and prothrombotic state. Based on these concepts, it has been proposed that patients with DM could have more severe forms of CVD, such as venous ulcers [15]. In people with diabetes, there is a predisposition to developing ulcers due to alterations in immune and structural functions such as collagen degeneration. In addition, patients with diabetes may develop mixed ulcers involving both venous and arterial components owing to the frequent coexistence of peripheral arterial disease. Therefore, careful vascular assessment is essential when evaluating lower-extremity ulcers in this population [16].

A study by Fejfarová et al. evaluated the incidence of DM in patients with CVD and investigated its severity, type of treatment, and risk factors. It was a cross-sectional observational study including 197 patients with chronic venous disease. The mean age was 65.3 years, 46.2% men/53.8% women, and the mean body mass index (BMI) was 28.6 kg/m^2. The results of this cross-sectional study were very interesting. DM was present in 17.8% of patients with CVD, which was significantly more frequent than in the general population (17.8% versus 8.6%; $P<0.0001$; 95% confidence interval [CI] 12.7–23.9%) [17].

Although the pathophysiological cause or relationship needs further investigation, the association of DM with CVD is frequent. Earlier and more aggressive preventive and therapeutic measures in these patients could prevent the development of edema, deep vein thrombosis, CVD progression, and post-thrombotic syndrome and improve quality of life [18]. Furthermore, management must be conducted by a multidisciplinary team including an endocrinologist, vascular surgeon, nutritionist, and diabetes educator. This comprehensive, multidisciplinary approach is a central pillar in the management of patients with CVD, with the potential to reduce complications related to CVD progression and the occurrence of thromboembolic events [19].

Although vascular disorders may involve arterial, venous, and microvascular components, these conditions differ in their primary mechanisms. Arterial disease is mainly characterized by atherosclerotic plaque formation and progressive luminal narrowing. In contrast, chronic venous disease is primarily driven by venous hypertension resulting from valvular incompetence and venous reflux. Microvascular alterations, particularly in patients with diabetes, are largely related to hyperglycemia-induced endothelial dysfunction, oxidative stress, and capillary basement membrane thickening. Despite these differences, overlapping inflammatory pathways and endothelial injury contribute to vascular remodeling across these vascular systems [20].

HOW CAPILLARY DAMAGE IN PEOPLE WITH DIABETES INCREASES CHRONIC VENOUS DISEASE OF THE LOWER EXTREMITIES

Circulatory concepts are essential to understand the pathophysiology in the venous system, and the damage of capillaries, especially in patients with diabetes. In addition, circulation concepts provide information on the difference between patients with venous disease and venous disease in people with diabetes, and how capillary disease in people with diabetes increases venous load. Although there is insufficient evidence to demonstrate a direct causal relationship between diabetes mellitus and the development of chronic venous disease, diabetes is associated with chronic inflammation and histopathological alterations in the venous wall that may contribute to the progression and severity of venous disease [21, 22].

The presence of ulcers in CVD results from the final process of hypertension and stasis at

the capillary level. Critical hypertension (more than 60 mmHg) occurs in people with and without diabetes, therefore there is no difference between the formation of ulcers among these populations. The complication and healing of the venous ulcer is compromised in people with diabetes owing to diabetic microangiopathy (capillary damage) [23]. The main molecular and hemodynamic mechanisms linking diabetes mellitus to the development and progression of chronic venous disease are summarized in Fig. 1.

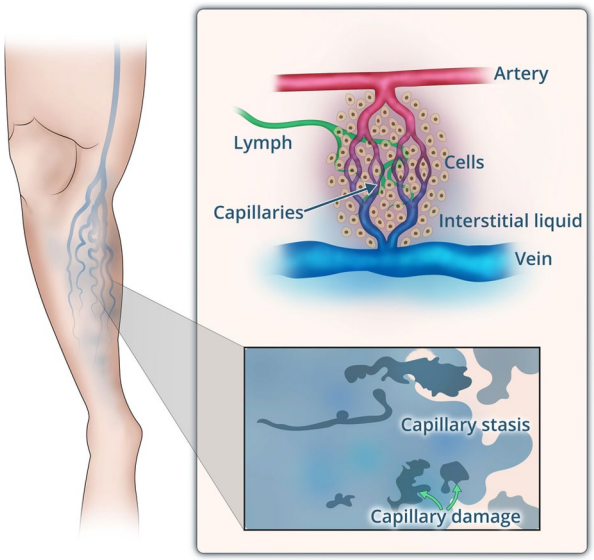

Fig. 1 Pathophysiological interactions between diabetes mellitus and chronic venous disease

Diabetic microangiopathy depends on glycemic control, and hyperglycemia causes capillary endothelial damage, subendothelial edema, and thrombosis. This damage can be reversible when glycemia is controlled, but the persistence of chronic hyperglycemic states decreases the capillary reserve, as occurs in diabetic nephropathy and in retinal damage [24]. In patients with diabetes, delayed ulcer healing is primarily related to hyperglycemia-induced microangiopathy, endothelial dysfunction, impaired leukocyte function, and peripheral neuropathy, which increase susceptibility to infection and tissue breakdown [25].

This deviation increases capillary venous flow, conditioning capillary venous hypertension and edema. In patients with chronic venous disease, the increase in venous capillary flow causes greater venous hypertension, which can lead to the presence of edema and skin damage [26]. The principal mechanisms linking diabetes mellitus to chronic venous disease are summarized in Table 1

Table 1 Proposed pathophysiological links between diabetes mellitus and chronic venous disease

Mechanism	Pathophysiological process	Clinical implications
Hyperglycemia-induced endothelial dysfunction	Chronic hyperglycemia leads to oxidative stress, advanced glycation end-product (AGE) accumulation, and endothelial injury	Impaired vascular regulation and increased susceptibility to microvascular damage
Chronic inflammation	Activation of inflammatory pathways, including nuclear factor-kappa B (NF-κB) signaling and cytokine release (TNF-α, IL-6, and IL-1β)	Promotes venous wall remodeling and valvular dysfunction
Microangiopathy	Capillary basement membrane thickening and reduced microvascular perfusion	Delayed wound healing and increased risk of ulceration
Matrix remodeling	Increased expression of matrix metalloproteinases (MMP-2 and MMP-9) and imbalance with tissue inhibitors (TIMPs)	Degradation of extracellular matrix and venous wall dilation
Venous hypertension	Sustained increase in ambulatory venous pressure due to valvular incompetence	Edema, skin changes, and venous ulcer formation

Venous Macroangiopathy

Activation of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, upregulation of adhesion molecules (ICAM-1 and VCAM-1), and increased expression of proinflammatory cytokines such as TNF-α and IL-6 contribute to venous wall remodeling and microcirculatory dysfunction [27]. A key early protective structure affected is the endothelial glycocalyx, a surface layer of glycosaminoglycans and proteoglycans that supports vascular barrier function and mechanotransduction. Glycocalyx injury (from abnormal shear stress, inflammation, and/or hormonal or genetic factors) exposes endothelial cells, facilitating leukocyte adhesion and transendothelial migration and amplifying local inflammatory signaling [28, 29].

The damaged glycocalyx allows diapedesis of polymorphonuclear cells, releasing inflammatory substances that alter the subendothelium and the muscle. These substances include proinflammatory cytokines and chemokines (MCP-1, VEGF, TNFα, IL6, IL8, and IL1B) and promote the release of other proinflammatory substances, such as prostaglandins and metalloproteinases (Fig. 2) [30, 31].

Following endothelial activation and glycocalyx disruption, leukocyte adhesion and transmigration occur. Inflammatory cells, including neutrophils, macrophages, and T lymphocytes, release cytokines (e.g., TNF-α and IL-1β) and reactive oxygen species that amplify endothelial injury and sustain chronic inflammation. In parallel, matrix metalloproteinases (MMP-2 and MMP-9), zinc-dependent proteolytic enzymes, are upregulated in response to venous hypertension and inflammatory signaling. An imbalance between MMPs and their tissue inhibitors (TIMPs) contributes to excessive degradation of collagen and elastin within the venous wall and valvular apparatus. Additionally, inflammatory cells such as macrophages and T lymphocytes amplify this process by releasing cytokines and reactive oxygen species, further perpetuating extracellular matrix remodeling and impaired wound healing (Fig. 3) [32–34].

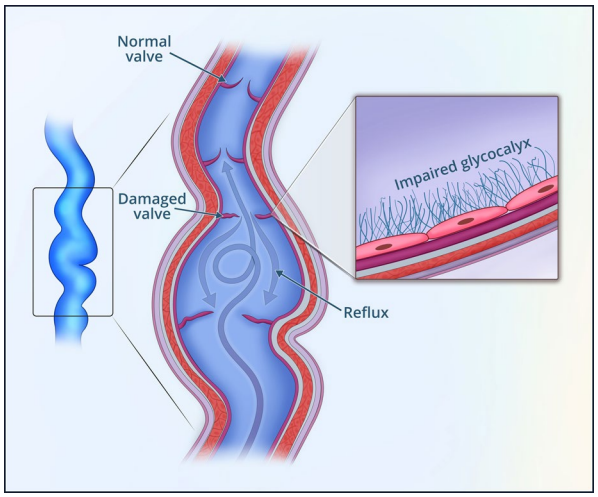

Fig. 2 When the glycocalyx is damaged, the middle venous layer is affected by severe inflammation, affecting tissue elasticity and causing valve damage, which leads to hypertension

In diabetes, microvascular complications such as diabetic retinopathy are primarily driven by chronic hyperglycemia-mediated endothelial injury, oxidative stress, and accumulation of advanced glycation end-products. However, elevated retinal venous pressure and venous congestion have also been proposed as modulators of capillary leakage and retinal edema. These hydrostatic components may contribute to microvascular dysfunction but do not replace hyperglycemia as the principal pathogenic driver [35]. Studies using ophthalmodynamometry have reported increased retinal venous pressure in patients with diabetes retinopathy, and retinal venous congestion has been discussed as a contributor to retinal edema and reduced perfusion pressure. These observations support the concept that venous congestion/hydrostatic pressure can modulate microvascular leakage in diabetes, analogous to the role of venous hypertension in lower-limb skin changes and ulceration [36–38].

Video capillaroscopy and retinal fluoroangiography studies provide sufficient evidence to confirm when there is mixed and generalized microangiopathy in the circulatory system. Therefore, it is concluded that

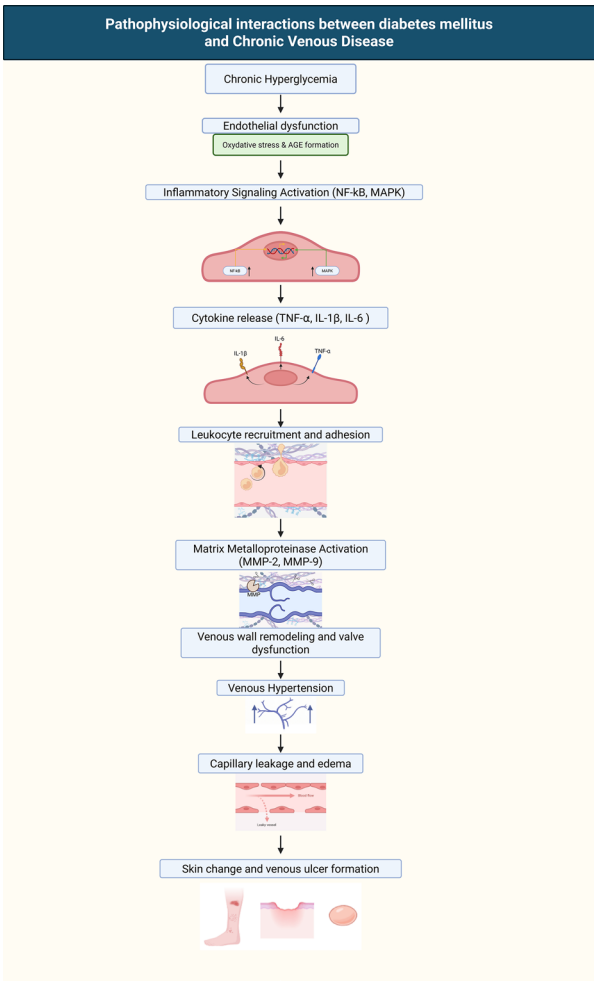

Fig. 3 Activation of cytokines and matrix metalloproteinase links diabetes mellitus with chronic venous disease by promoting endothelial dysfunction, vascular leakage, inflammation, and extracellular matrix degradation, leading to impaired venous remodeling and progression of chronic venous disease in patients with diabetes.Created in BioRender. Zingg, D. (2026) https://BioRender.com/g5t8srg

the complications of chronic venous disease in people with diabetes are due to microangiopathy caused by hyperglycemic states [39]. The capillaroscopic abnormalities documented in patients with type 2 diabetes indicate a compromised capillary reserve and increased microvascular resistance, both of which may exacerbate venous hypertension by reducing microcirculatory adaptability [23].

Clinical Presentation and Diagnostic Considerations of Chronic Venous Disease in Patients with Diabetes Mellitus

CVD is an umbrella term describing long-duration morphological and functional abnormalities of the venous system that may manifest with symptoms and/or clinical signs. Chronic venous insufficiency (CVI) refers to the more advanced end of the CVD spectrum, typically corresponding to CEAP C3–C6, where sustained venous hypertension leads to edema and/or skin changes (e.g., hyperpigmentation or lipodermatosclerosis) and may progress to venous ulceration [40, 41]. Risk factors for developing CVI include work conditions that require standing or sitting for extended periods, age > 50 years, pregnancy, the use of oral hormones, sedentary lifestyle, obesity, DM, and a family history of venous disease [42]. In people with diabetes, CVD/CVI may be under-recognized because peripheral neuropathy can reduce pain perception and mask typical symptoms (heaviness and aching), while edema may be attributed to cardiac/renal comorbidity. Coexisting peripheral arterial disease (PAD) and diabetes-related microangiopathy can contribute to mixed-etiology ulcers and increase infection risk, which affects both diagnosis and treatment selection (including the safe use of compression). Therefore, careful lower-limb vascular assessment (pulses, ankle–brachial index [ABI], and/or toe pressures where appropriate) and venous duplex ultrasound are particularly important in this population [43, 44]. Although arterial, venous, and capillary vascular diseases have different initiating triggers (atherosclerotic plaque biology in arteries, venous hypertension/abnormal shear stress in veins, and hyperglycemia-mediated injury in capillaries), they share overlapping downstream responses, including endothelial activation, inflammatory signaling, oxidative stress, and extracellular matrix (ECM) remodeling; in CVD/CVI the dominant driver is venous hypertension with leukocyte trapping and chronic microcirculatory inflammation [45].

There is an association between CVD and DM as they share similar risk factors and pathophysiological mechanisms responsible for CVD progression and endothelial dysfunction.

Dysfunction of the valves inside the veins causes stasis and an increase in venous hydrostatic pressure, which distends the venous wall and increases shear forces at the endothelial level. This increase in friction force produces hypoxia and endothelial dysfunction mediated by overexpression of endothelial growth factors. At the microcirculation level, the consequences of this genetically mediated overexpression include inflammation, abnormal neovascularization, interstitial edema, hypercoagulability, formation of free radicals, and accelerated apoptosis. At the macrovascular level, it manifests as fibrosis and degeneration of the venous wall, perpetuating the pathophysiological cycle [46].

When a patient presents with a lower-extremity ulcer, differential diagnoses include venous, arterial, neuropathic, pressure-related, and mixed ulcers. In patients with diabetes, distinguishing between venous and neuropathic ulcers is critical. Venous ulcers typically occur in the gaiter region, are shallow with irregular borders, and are associated with edema and varicosities. Neuropathic ulcers often occur on plantar pressure points, may be painless owing to sensory loss, and are frequently surrounded by callus. Arterial ulcers are typically distal, painful, and associated with diminished pulses and reduced ankle–brachial index [47].

Classification

Chronic venous disease is classified on the basis of the CEAP classification system and reporting standard (2020 revision) [24] (Table 2). Capillaroscopy may be a useful noninvasive adjunct tool to document microvascular impairment in patients with diabetes with chronic venous disease, as the characteristic abnormalities reflect early and progressive microangiopathic changes [23].

Venous Ulcers in Patients with Diabetes Mellitus

Ulcers in the lower extremities are one of the most frequent complications in patients with diabetes [48]. Without a doubt, adequate diagnosis and treatment are essential to avoid complications, which can become serious. An ulcer is a nonspecific term that is defined as loss of continuity in the skin. It is vital to identify the cause of the ulcer, since the treatment and prognosis of the patient depend on this. In patients with diabetes, it is common to diagnose various ulcers such as venous, arterial, neuropathic, or mixed [49].

Table 2 CEAP classification system and reporting standard (2020 revision)

C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C4a	Pigmentation or eczema
C4b	Atrophie blanche
C4c	Corona phlebectatica
C5	Healed
C6	Active venous ulcer
C6r	Recurrent active venous ulcer

C clinical manifestations, *E* etiology, *A* anatomic distribution, *P* pathophysiology

Venous ulcers are defined as loss of skin continuity between the knee and the ankle joint in the presence of venous disease. Although the epidemiology in patients with diabetes has not been studied extensively, in the general population, it is the most common cause of leg ulcers [50]. These ulcers represent the most advanced form of chronic venous disorders such as varicose veins and skin damage. Risk factors for the development of venous ulcers include older age, female sex, obesity, trauma, immobility, congenital absence of veins, deep vein thrombosis, phlebitis, and factor V Leiden mutation [51].

A chronic venous leg ulcer results in the loss of years of productive life with significant financial implications and a poor quality of life. In addition, when there are complications, it represents substantial increased hospital costs. In these patients, a detailed evaluation of the ulcer is essential to

ensure timely targeted treatment based on suitable treatment algorithms, which will save time and money [52]. Currently, noninvasive physiological tests provide a detailed evaluation of the superficial and deep venous system, for example, a Doppler ultrasound. A global evaluation of the vascular system, including the arterial system, is also recommended using noninvasive tests such as the ankle–brachial index or digital plethysmography. Specifically, in patients with diabetes, the key is an appropriate diagnosis and treatment by a multidisciplinary team [53, 54].

When a person with diabetes presents with a lower-extremity ulcer, a structured assessment is required to determine whether the ulcer is primarily venous, neuropathic (diabetes-related foot ulcer), arterial, pressure-related, or mixed. Venous ulcers typically occur in the gaiter region (often near the medial malleolus), are usually shallow with irregular borders, and are commonly accompanied by edema, varicosities, and/or lipodermatosclerosis. Diabetes-related neuropathic ulcers more often occur on the plantar surface over pressure points (e.g., metatarsal heads/toes), may be painless, and are frequently surrounded by callus with objective sensory loss on examination. Arterial ulcers are often more distal (toes/lateral foot), may be painful, and are associated with diminished pulses and reduced ABI and/or toe pressures. Venous duplex ultrasound, bedside neuropathy testing (e.g., 10-g monofilament), and arterial assessment help identify mixed disease and guide safe treatment (compression and offloading) [55, 56].

Treatment options for venous ulcers include advanced wound management, venotonic drugs, compression therapy, and surgical options to correct superficial venous reflux. In general, the goals of treatment are to reduce edema, improve ulcer healing, and prevent ulcer recurrence [57].

Compression improves ulcer healing by increasing venous flow and enhancing the pumping action of the moving calf. It also prevents ulcer recurrence, especially when used continuously. Special caution should be taken with the use of compression in patients with diabetes. In all cases, the presence of peripheral arterial disease must be ruled out. Finally, the nutritional status of the patient and the goals of diabetes treatment are essential for a favorable prognosis in these patients [58]. Key clinical differences between venous ulcers and diabetes-related neuropathic ulcers are summarized in Table 3.

COMPREHENSIVE MANAGEMENT OF PATIENTS WITH DIABETES AND VENOUS INSUFFICIENCY OF THE LOWER LIMBS

Preventive Measures in Patients with Risk Factors

Established risk factors for venous ulcer development include advanced age, prior venous thrombosis, venous reflux, prolonged standing,

Table 3 Clinical differences between venous ulcers and diabetic (neuropathic) foot ulcers

Feature	Venous ulcer	Diabetic (neuropathic) ulcer
Typical location	Gaiter region, especially medial malleolus	Plantar surface of foot, metatarsal heads, or pressure points
Pain	Mild to moderate	Often painless owing to neuropathy
Ulcer appearance	Shallow, irregular borders	Deep, punched-out lesion
Surrounding skin	Hyperpigmentation, lipodermatosclerosis, edema	Callus formation, dry skin
Pulses	Usually present	May be reduced if peripheral arterial disease present
Associated findings	Varicose veins, venous reflux	Peripheral neuropathy, foot deformities

obesity, and reduced calf muscle pump function. Diabetes mellitus is clinically relevant primarily owing to its association with impaired wound healing, neuropathy, and coexisting peripheral arterial disease, rather than as a proven independent etiological risk factor for venous ulcer formation [59, 60] when modifiable factors, such as prolonged standing or sitting, and two of the high-prevalence factors in DM, such as hypertension and especially obesity (which is the most significant risk factor [30] for CVI in advanced stages characterized by ulceration), are added, treating these factors is the most important in terms of prevention [61].

Preventive Measures to Avoid Deterioration and Disease Progression

Established risk factors for chronic venous disease progression and venous ulceration include increasing age, prior venous thrombosis or venous obstruction, venous reflux, prolonged standing, and reduced calf muscle pump function. Among modifiable factors, obesity and sedentary lifestyle/immobility are particularly important because they worsen venous hypertension and edema. In contrast, diabetes and hypertension are more classically associated with arterial disease; diabetes is clinically important in venous ulcer care primarily because it can contribute to neuropathy, higher infection risk, and impaired wound healing, and because coexisting PAD may limit the safe use of compression. Preventive management in primary care should therefore focus on weight reduction, regular walking/calf muscle exercises, minimizing prolonged standing or sitting (and encouraging periodic leg elevation), and early referral for venous and arterial assessment when chronic edema, skin changes, or ulceration are present [62, 63].

Increased Movement

Regular physical activity plays an important role in improving venous return by enhancing the function of the calf muscle pump. Exercises such as ankle flexion, extension, and rotation; isokinetic resistance training with elastic bands, balance exercises, and treadmill walking at approximately 60% of maximal heart rate; and intermittent pneumatic compression have been shown to improve venous hemodynamics when performed regularly in patients with chronic venous insufficiency [64]. A small clinical study involving patients with severe chronic venous insufficiency and venous ulcers evaluated isotonic calf muscle exercises using plantar flexion against ergometric resistance. The intervention improved muscle strength, endurance, and venous ejection capacity; however, the limited sample size restricts the generalizability of these findings [65]. In addition, a randomized controlled study evaluated the effect of a 12-week home-based exercise program combined with usual care in patients with venous ulcers. The program included ankle mobility, calf muscle strengthening, and stretching exercises. Ulcer healing occurred in 77% of patients in the intervention group compared with 53% in the control group, although the difference did not reach statistical significance, likely owing to the limited number of participants [66, 67].

Compression Treatment with Stockings with Different Degrees of Compression, Elastic Bandages, and Intermittent Pneumatic Compression

Compression therapy represents the cornerstone of conservative management for chronic venous disease and venous ulcers. Graduated compression stockings or multilayer compression bandages improve venous return by applying the greatest pressure at the ankle with progressively decreasing pressure proximally along the leg. This pressure gradient enhances calf muscle pump function, reduces venous hypertension, decreases edema, and promotes venous ulcer healing. Clinical guidelines consistently recommend graduated compression therapy as the first-line treatment for chronic venous insufficiency and venous ulcers [68]. Progressive graduated compression stockings are generally preferred because they more effectively facilitate venous return compared with non-graduated or degressive compression systems. Before initiating compression therapy, it is essential to assess

arterial circulation to avoid complications, particularly in patients with diabetes who may have concomitant peripheral arterial disease. Measurement of the ankle–brachial index (ABI) or toe pressure is recommended to ensure that compression therapy can be applied safely [69, 70].

Additional precautions are required in patients with diabetes, especially those with peripheral neuropathy. Reduced protective sensation may increase the risk of skin injury or pressure-related complications. Therefore, careful fitting of compression garments, regular monitoring, and daily inspection of the skin are recommended to detect early signs of irritation, pressure injury, or ulcer deterioration. Patient education regarding proper use of compression stockings and adherence to therapy is also an important component of successful management [71].

Venoactive Medications

Venoactive drugs may be used as adjunctive therapy in patients with chronic venous disease to improve symptoms such as leg heaviness, pain, and edema. These agents are thought to exert beneficial effects through anti-inflammatory mechanisms, improvement of venous tone, and enhancement of microcirculatory function. However, pharmacologic therapy should be considered complementary to compression therapy rather than a substitute for it [72, 73].

European clinical guidelines support the use of certain venoactive drugs as part of symptomatic management in chronic venous disease, particularly in patients with persistent symptoms despite compression therapy. In contrast, North American guidelines generally consider these agents optional and emphasize compression therapy as the primary treatment strategy. Therefore, venoactive drugs may be considered as adjunctive treatment in selected patients but should not replace standard conservative measures. The recent global initiative, VALID, further reinforces the importance of using evidence-based venoactive drugs (VADs) in a field where many over-the-counter (OTC) products lack scientific validation [74–76].

Ramelet et al. [68] reviewed the active medications for CVI and demonstrated that they act by protecting the venous endothelium, reducing inflammation in the vessel wall, and reducing edema, therefore limiting skin changes that could result in the formation of ulcers. This impact on edema, which has been discussed in volumetric terms as referring to the entire leg, is difficult to analyze as the reduction in the cutaneous and subcutaneous compartments that would provide protection is very difficult to measure.

The use of venoactive drugs (VADs) has been promoted in prevention and to improve symptoms when uncomplicated CVI is detected. Their role in the healing of venous ulcers has also been studied, and it is in this area where the evidence is heterogeneous.

These drugs can be classified as follows:

Synthetic drug products:

- Calcium dobesilate
- Benzarone
- Naftazone

Plant extracts:

- α-Benzopyrones
- Flavonoids (diosmin and micronized fraction of flavonoids [MPFF])
- Saponins
- Others (*gotu kola* and *Gingko biloba*)

Venoactive drugs demonstrate clinically relevant benefits in diabetes-related microvascular complications by improving endothelial function, reducing capillary leakage, and mitigating edema and inflammation [83]. Calcium dobesilate (CaD) is one of the synthetic drugs that has been extensively studied. The benefits of CaD on edema and venous symptoms have been demonstrated in several clinical studies [51–53]. It is worth noting a meta-analysis that included three studies of good methodological quality [34]. Compared with placebo, there was a significant reduction in night cramps and feelings of discomfort. In a subgroup analysis of patients with severe symptoms, this study was the only one demonstrating a significant impact on pain, sensation of weight, paresthesia, limb volume, and ankle edema. These effects were obtained with doses of 1000 mg/day, with higher doses

not demonstrating greater effectiveness. A recent study supports the fact that a higher dose of CaD (2000 mg/day versus 1000 mg/day) over an extended period (up to 12 months) significantly enhances the management of CVI symptoms and signs [61]. Furthermore, a significant improvement in lymph flow and lymphatic drainage with CaD has been shown in patients [62].

The flavonoid group is one of the most studied among plant extracts, in particular the purified micronized fraction of flavonoids (MPFF), which is marketed under a registered name containing 90% diosmine and 10% other active flavonoids. Improvements in edema, inflammation, microcirculation, cutaneous trophism, and ulcer healing [66] were reviewed in a recent meta-analysis [58] and demonstrated significant symptomatic clinical improvements such as trophic changes and ankle circumference.

The current guidelines from the International Union of Angiology (IUA) [75] highlight the importance of the main VADs in the management of symptomatic patients at the earliest stages of CVD (Table 4). According to an expert consensus [77], patients at the earliest stages of the disease (from C0 to C3), with painful heaviness in their legs, edema, or other symptoms of CVD may benefit from VADs and should be continued until remission of symptoms and/or edema [88].

Interestingly, CaD has also demonstrated a significant efficacy in patients with diabetic microangiopathies such as diabetic retinopathy [57, 58], diabetic nephropathy [78], and diabetic peripheral neuropathy [79]. Several pharmacological agents have been investigated for their potential role in improving microcirculatory dysfunction associated with chronic venous disease. These therapies are believed to exert beneficial effects through anti-inflammatory mechanisms, reduction of capillary permeability, and improvement of venous tone and endothelial function. However, the clinical benefit of these agents remains variable across studies, and most guidelines emphasize that pharmacological therapy should be considered adjunctive to standard treatments such as compression therapy rather than a primary therapeutic approach [80, 81] (including the modulation of the VEGF signaling pathway).

However, several of the cited studies primarily investigated microvascular complications in patients with diabetes and did not specifically include populations with documented chronic venous disease or venous ulcers, which limits the direct applicability of these findings to venous pathology [82].

Management of Patients with CVI–DM

Among patients with diabetes, venoactive drugs have shown evidence of improving symptoms related to microvascular compromise—including edema, pain, and microcirculatory dysfunction—supporting their inclusion as adjunctive therapy when chronic venous disease coexists with diabetes [83]. The review demonstrates that certain venoactive agents, including calcium dobesilate, possess dual activity on both venous and diabetic microvascular abnormalities, making them uniquely beneficial in individuals presenting with CVD and diabetes simultaneously [83]. Calcium dobesilate (CaD) is a synthetic venoactive drug used in some settings for CVD-related symptoms and edema. CaD has also been investigated in diabetes-related microvascular disease (e.g., retinopathy and nephropathy). Proposed mechanisms include reduced capillary permeability, antioxidant and anti-inflammatory effects, and modulation of endothelial function and growth-factor signaling (including VEGF-related pathways). However, high-quality contemporary trials specifically evaluating CaD in individuals with concomitant diabetes and CVI/CVD remain limited [84].

Treatment Summary

The objective of treatment is to improve the quality of life of patients with CVD and limit disease progression and the shared macro- and microvascular complications. These complications may lead to social and occupational disability and the loss of limbs in extreme cases, including in young patients [85].

Table 4 Evidence-based mechanisms of action of venoactive drugs and level of clinical evidence. [27] Adapted from Mansilha and Sousa

Mode of action	Venous tone	Venous wall and valve	Capillary leakage	Lymphatic drainage	Hemorheological disorders	Free-radical scavengers	Level of evidence			
							Pain (NNT*)	Heaviness (NNT*)	Foot/leg volume (SMD)	Limb edema (NNT*)
Calcium dobesilate	+	+	+	+	+	+	B (1.4)	A (1)	A (−11.4)	A (1.2)
MPFF	+	+	+		+	+	A (4.2)	A (2.9)	ns	
Oxerutins	+		+		+	+	B	B	ns	
Coumarin			+							
HCSE	+		+			+	A (5.1)	A (1)	A (−0.34)	A (4)
Ruscus + HMC + AA	+	+	+		+	+	A (5)	A (2.4)	A (−0.61)	

Table was adapted from Mansilha, A. and Sousa, J. Pathophysiological mechanisms of chronic venous disease and implications for venoactive drug therapy. *Int J Mol Sci*. 2018;19(6):1669, which is distributed under the Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/. Changes were made to the formatting and presentation for this manuscript

Levels of evidence: A = data derived from multiple randomized clinical trials or meta-analyses; B = data derived from a single randomized clinical trial or large non-randomized studies; C = consensus of expert opinion and/or small studies, retrospective studies, and registries

AA ascorbic acid, *CaD* calcium dobesilate, *HCSE* horse chestnut seed extract, *HMC* hesperidin methyl chalcone, *MPFF* micronized purified flavonoid fraction, *NNT* number needed to treat, *SMD* standardized mean difference, *ns* not significant

It is important to perform a comprehensive assessment of the arterial and venous vascular systems, identify the coexistence of both pathologies, stratify the clinical stage, and individualize treatment on the basis of the patient's needs [86].

1. Modification of cardiovascular risk factors
2. Effective glucose control
3. Performance of moderate aerobic exercise based on the patient's age and individual factors
4. Weight control
5. Use of elastic compression (stockings, socks, and bandages) after evaluation of the patient's arterial circulatory status
6. Use of VADs to treat CVD/CVI (e.g., the ones demonstrating add-on efficacy in patients with diabetes and vascular complications)
7. Assessment of the need and appropriate time for surgical intervention (e.g., saphenectomy, thermal ablation of the saphenous vein, or sclerotherapy) [87]

CONCLUSIONS

The association between CVI and DM has not been studied extensively since they have always been addressed in literature as separate pathologies. As previously mentioned, the two diseases have shared risk factors, pathophysiological mechanisms, and complications. In clinical practice, these conditions frequently coexist in patients. Patients with CVI and DM represent a diagnostic and therapeutic challenge for the physician since there are no clinical practice guidelines that consider standardized management or specific recommendations. When treating this group of patients, important treatment considerations include sex, age at presentation, functional status, social and work habits, presence of peripheral arterial disease, and occurrence of macro- and microvascular complications. Capillaroscopic evidence of capillary damage in diabetes combined with the documented efficacy of venoactive drugs in diabetic microvascular dysfunction supports a pathophysiological rationale for early use of venoactive therapy in patients with diabetes with CVD to reduce microvascular congestion, inflammation, and capillary leakage. A future multicenter consensus based on well-designed clinical studies in this group of patients would assist physicians in offering timely, comprehensive, and individualized treatment.

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Declarations

Conflict of Interest. Dr. Juan Rosas Guzman and Dr. Juan Rosas Saucedo have received honoraria from OM Pharma. Dr. Isaac Sinay, Dr. Luis Fernando Flota Cervera, Dr. David González Villordo, Dr. Hugo Laparra Escareño, and Dr. Norma Areli Rivera García report no conflict of interest. Daniel Zingg is an employee of OM

Pharma and receives economic compensation for his work.

Ethical Approval. This review is based on previously published studies and does not involve any new studies with human participants or animals conducted by the authors. Therefore, formal ethical approval was not required.

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