

REVIEW

Chronic Venous Disease and Its Intersections With Diabetes Mellitus

Radka JAROŠÍKOVÁ^{1,3}, Karel ROZTOČIL², Jitka HUSÁKOVÁ¹, Michal DUBSKÝ¹, Robert BÉM¹, Veronika WOSKOVÁ¹, Vladimíra FEJFAROVÁ^{1,3}

¹Diabetes Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, ²Department of Transplant Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, ³Second Faculty of Medicine, Charles University, Prague, Czech Republic

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Summary

Chronic venous disease (CVD) is a vascular disorder in which blood return is severely compromised and CVD is usually characterized by venous hypertension. Along with obesity and diabetes mellitus, CVD is one of the most common civilization diseases. In general, the estimated prevalence of CVD ranges from 60-80 %. Early diagnosis and adequate treatment are important for preventing progression to more severe stages of the disease like venous leg ulcers. Clinical manifestations of CVD in initial stages of the disease are often asymptomatic. However, as CVD progresses, symptoms begin to develop. Treatment of CVD could be divided into conservative and surgical. Conservative therapy consists of compression, pharmacological treatment and lifestyle change. In cases where conservative therapy is ineffective, surgical or endovascular treatment may be required. The intersections between diabetes mellitus (DM) and CVD are not to be underestimated. CVD and DM have often the same risk factors. Symptoms of CVD can be modified by late complications of DM, but the incidence of different CVD degrees seems to be the same as in diabetics as in non-diabetics population. We are particularly concerned in diabetics about worse compliance with treatment due to their often-poorer adherence to treatment of DM and lifestyle changes. Moreover, there exist a higher risk of CVD and peripheral arterial disease in diabetics patients. Patients with CVD should always be inspected for the presence of DM, considering its presence can have a bearing on CVD symptoms, diagnostic procedures, and therapeutic strategies.

Key words

Chronic venous disease • Diabetes mellitus • Risk factors • Classification • Therapy

Corresponding author

R. Jarošíková, Diabetes Centre, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Praha 4, Czech Republic. E-mail: jaar@ikem.cz

Introduction

Chronic venous disease (CVD) is a vascular disorder in which blood return is severely compromised. CVD is usually characterized by venous hypertension [1]. Along with obesity and diabetes mellitus, CVD is one of the most common civilization diseases [2]. Varicose veins (VV), which appear as dilated and elongated superficial veins, are the most common manifestation of CVD [3]. Other venous signs of CVD include telangiectasias and reticular veins, which are small, dilated veins 1 mm to 3 mm in diameter [3]. CVD is a potentially serious and often underestimated disease [4]. This review documents CVD and its crossover with diabetes mellitus (DM) in pathophysiology and clinical practice.

Epidemiology

In general, the estimated prevalence of CVD ranges from 60-80 % [5-7]. Most cases of CVD are defined as stages C0 and C1 (Table 1), with

Table 1. CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification of CVD modified according to the updated 2020 CEAP classification system and reporting standards **Chyba! Nenalezen zdroj odkazů..**

<p>C – Clinical classification</p> <p>C0: No visible or palpable signs of venous disease C1: Telangiectasies or reticular veins C2: Varicose veins; distinguished from reticular veins by a diameter of 3mm or more C3: Edema C4: Changes in skin and subcutaneous tissue secondary to CVD C4a: Pigmentation or eczema C4b: Lipodermatosclerosis or atrophie blanche C5: Healed venous ulcer C6: Active venous ulcer</p>
<p>E – Etiological classification</p> <p>Ec: Congenital Ep: Primary Es: Secondary En: No venous cause identified</p>
<p>A – Anatomical classification</p> <p>As: Superficial veins Ap: Perforating veins Ad: Deep veins An: No venous location identified</p>
<p>P – Pathophysiology classification</p> <p>Pr: Reflux Po: Obstruction Pr/o: Reflux and obstruction Pn: No venous pathophysiology identifiable</p>

approximately 25 % of patients diagnosed with VV (C2). Stages C3-C6 occur in only a small percentage (5 %) of patients with CVD [8-9]. Early diagnosis and adequate treatment are important for preventing progression to more severe stages of the disease [2]. Venous leg ulcers (VLU) represent the most severe manifestation of CVD, with prevalence at 0.5-1 % [2]. Healing is often difficult, with only 50 % of venous leg ulcers resolving within 12 months [10]. Another major challenge associated with VLU is the high recurrence rate, which can reach 50-70 % at 6 months [11]. In patients with CVD, the condition can also lead to lower limb amputation and increased overall morbidity [2]. VLU medical care is an economic burden for states, with up to 14 % of a typical health expenditure budget spent on treatment [12].

Pathophysiology

The pathophysiology of CVD is complex. Interactions between genetic and environmental factors are responsible for an increase in intravenous pressure,

leading to substantial changes in the overall structure and function of the venous system [13]. CVD primarily occurs due to impairment of the venous walls, but it can also manifest as a reaction to thrombosis resulting in obstruction or venous reflux [2]. Additionally, limb muscle pump dysfunction can contribute to the onset of the disease [2].

The starting point for the development of CVD is capillary hypertension, which arises from all of the above factors. Capillary hypertension leads to increased vessel permeability and impairment of the lymphatic microcirculation. This can in turn lead to extravasation of fluid, proteins and blood cells [14], which then penetrate into the interstitium and stimulate fibroblasts to produce connective tissue (hypodermitis) [15]. Permeable fibrinogen and other proteins form pericapillary fibrin cuffs, which act as a barrier to the diffusion of oxygen into tissue, this can induce hypoxia. Moreover, these conditions curtail healing in patients with diabetic foot syndrome and CVD. Capillary hypertension also leads to elongation and dilation of the capillaries, with blood flow retarded as a direct result. This state facilitates the adhesion

and activation of leukocytes on the endothelium (especially valves), releasing enzymes and free radicals. The combined effect of these states is to initiate inflammation and damage to the venous walls and valves [15].

At a macroscopic level, these pathophysiological changes manifest in valve insufficiency, which contributes to dilation and elongation of the veins and the formation of varices. With the progression of venous hypertension and valve insufficiency, blood flow stagnates, and trophic changes appear. Further progression of CVD may result in venous ulcers [15].

Peripheral arterial disease, diabetes mellitus, and the impaired supply of oxygen and nutrition all serve to enhance CVD progression and accelerate the onset of venous ulcers [16].

Risk factors

The main non-modifiable risk factors for CVD include older age, female gender, height and a positive family history [17]. CVD is most likely a polygenic inherited disease. But although heredity appears to be a principal risk factor, corresponding genetic mutations have yet to be identified [18]. Patients have a 90 % risk for developing varicose veins in cases where both parents have also had CVD with varicosities [19]. Ongoing research has yet to rule out links to obesity genes [18].

Modifiable risk factors include obesity ($BMI > 30 \text{ kg.m}^{-2}$), occupations involving prolonged sitting or standing, reduced physical activity and multiparity [17]. The number of pregnancies is also understood to be a variable for acquiring CVD [2].

According to recent studies, hormonal contraception and substitution therapy do not increase the risk of CVD [2]. Other traditional risk factors, such as smoking, arterial hypertension, and chronic constipation, are understood to exacerbate rather than directly cause the disease. As such, they are considered less significant [2].

Classification

CVD stage is categorized according to the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification devised by the American Venous Forum (AVF), an internationally accepted standard and the most widely used CVD classification system (Table 1) [20].

Based on clinical, etiological, anatomical and pathological states of the vein system [20], CEAP is the most comprehensive classification for delivering accurate

prognoses and identifying appropriate therapies [2]. According to the CEAP classification, patients with CVD grade 3 or above should be followed and treated by an angiologist [21].

Symptoms

Mild clinical symptoms include the presence of telangiectasias or reticular veins, while severe forms are connected to venous ulcers [2]. Symptoms of CVD may not necessarily correlate with the severity of local findings [2]. Clinical manifestations in initial stages of the disease are often asymptomatic. However, as CVD progresses, symptoms begin to develop [22]. The most common include lower limb pain in the form of heaviness, itchiness, discomfort and muscle cramps, which usually occur in the calves and, less commonly, in the thighs [23]. Patients frequently exhibit lower limb edema, which begins in the perimalleolar region. Edema worsens in situations where venous pressure increases or lymphatic drainage becomes impaired or insufficient [23].

It should be noted that all of these symptoms are non-specific and can be ascribed to many other diseases [2]. Therefore, differential diagnosis is recommended in order to exclude other causes of peripheral edema, such as cardiac insufficiency, hypoalbuminemia or hypothyroidism, among others [24].

Symptoms usually present during the day, especially when sitting or standing for long periods, and also during warm weather [2]. Women may notice a worsening of symptoms during menstruation and pregnancy or after taking hormonal contraceptives [2]. On the other hand, walking, elevating and cooling the lower limbs together with the use of compression stockings/bandages bring relief [2].

Diagnostics

In most cases, CVD is diagnosed based on medical history and physical examination [2]. A full clinical history of the patient should factor in family history of CVD, personal history of thromboembolism, cardiovascular or other relevant diseases, as well as the presence of specific symptomatology of CVD [2]. Physical examination should be performed in a standing position to inspect for edemic changes in the legs, swelling, skin changes, reticular veins, varicose veins in the large and small saphenous vein basins, and scars after healed venous ulcers/operations [2].

Color duplex ultrasound (CDU) is the most widely used diagnostic procedure [25]. CDU is non-invasive, reproducible, easy to use, and provides data on morpho-haemodynamic changes in the affected limb/s [26]. CDU is also used to screen for anomalies in the anatomy such as the presence of venous reflux, patency of the deep venous system, thrombophlebitis and varicophlebitis [2]. CDU examination is recommended for patients with advanced stages of CVD (CEAP stage 3 and higher) and before each vascular surgical procedure [2].

Peripheral pulses in the lower limbs should also be examined to differentiate from peripheral arterial disease (PAD) and the ankle brachial index (ABI) recorded [2].

Therapy

The aims of CVD therapy are to eliminate clinical symptoms, stabilize local findings and prevent progression to more severe stages of the disease [2]. Different strategies can be used either independently or in combination to maximize the overall effect [27]. The two principal treatment strategies for controlling venous insufficiency are conservative treatment and medical intervention [2].

Conservative therapy consists of compression, pharmacological treatment and lifestyle change [2].

Compression is applied in order to target venous hemodynamics, increase interstitial pressure, decrease the caliber of both superficial and deep veins, reduce venous pressure and edema, and promote contractile activity in the calf muscles [8]. In patients with PAD, compressive therapy interference with blood circulation in the lower limbs should be avoided in order to prevent worsening of underlying disease [29]. Also, compression therapy is contraindicated in patients with an $ABI < 0.5$ [29].

Pharmacological therapy is directed to specific pathophysiological mechanisms of CVD. To that end, various venoactive agents such as saponins, flavonoids, pentoxifylline, micronized purified flavonoid fraction (MPFF), and acetylsalicylic acid [30] can be administered to decrease vascular permeability, ameliorate the inflammatory response, increase vascular tone and operate on platelet aggregation [31].

Regime and lifestyle changes consist of weight reduction, regular physical activity, therapy for constipation, and local skin care, among other interventions [2].

In cases where conservative CVD therapy is ineffective, surgical or endovascular treatment may be required [2]. Methods include: ultrasound-guided sclerotherapy using different chemical agents such as polidocanol, sodium tetradecyl sulphate or glycerine; endovenous thermal ablation in the form of endovenous laser ablation (EVLA) or radiofrequency ablation (RFA); and open surgery such as saphenous junction ligation or stripping [32].

Chronic venous disease and diabetes mellitus (DM)

The association of diabetes with micro- and macro-vascular complications is well known and remains the subject of intensive research [12]. However, the potential association between DM and CVD has yet to receive the same level of attention.

CVD and type 2 DM are linked by the same common causes: a sedentary lifestyle, lack of physical activity, obesity, polygenic inheritance, thromboembolic disease (higher thrombogenicity is one of the clinical features of DM; see below) and hormone therapy (predominantly corticosteroids) [21].

Intersections of DM and CVD

1. According to the Antithrombotic Therapy and Prevention of Thrombosis guidelines (2012), DM is a hypercoagulable state and a risk factor for deep vein thrombosis [33].
2. A pro-inflammatory condition is typical of DM, where hyperglycaemia induces oxidative stress and increases adhesion of leukocytes to the endothelium *via* the release of proteolytic enzymes, elevating local inflammation of the vessel walls and accelerating venous changes [33].
3. Disorders of collagen and binder structures, etc. [1].

Microscopic changes in venous walls can occur due to chronic hyperglycaemia, with accelerated blood flow impairing microcirculation and causing damage to the vasa vasorum. In diabetic subjects, AV shunting can often manifest due to sympathetic denervation. This can alter microcirculation, since shunting decreases tissue oxygenation, which is in turn responsible for advancing trophic changes. At a macroscopic level, incompetence or reduced filling time of the venous system as well as diminished venous output are characteristic features in patients with DM [1].

The independent risk factors of early CVD in diabetic patients are age, gender, and glycated hemoglobin (HbA1c) and triglyceride levels [24]. CVD in diabetic patients has been shown to correlate with higher levels of fasting plasma glucose and total cholesterol [24]. Diabetic patients with early CVD typically display more elevated fasting plasma glucose and total cholesterol in addition to more serious macrovascular complications [24].

Previous studies highlight significantly higher incidence of DM in patients with CVD compared to the general population (17.8 % vs. 8.6 %) and, further, that coincidence of PAD in patients diagnosed with CVD and DM is greater than in the non-diabetic CVD population [21].

DM is a secondary immunodeficiency disease [34] that leads to altered microcirculation and macrocirculation as well as glycation of protein and collagen substances. As such, it can contribute to more advanced stages of CVD. Contrary to our suggestions, however, higher incidence of more severe CVD (especially stages 5 and 6 according to the CEAP classification) has yet to be proved [35]. Treatment of venous ulcers, in particular, is more difficult in the

presence of multiple CVD symptoms, diabetic neuropathy, as well as more frequent infectious complications and coincidence of PAD. Nonetheless, patients with CVD, DM and PAD are likely to benefit from comprehensive treatment, which helps to delay CVD progression and reduce complications as well as thromboembolic events [21].

Conclusions

The intersections between diabetes mellitus and CVD are not to be underestimated. Patients with CVD should always be inspected for the presence of DM, considering its presence can have a bearing on CVD symptoms, diagnostic procedures and therapeutic strategies.

Conflict of Interest

There is no conflict of interest.

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