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Chronic Venous Disease as Part of Continuum of Cardiovascular Disease – Shared Pathophysiology, Risk Factors and Novel Pharmacological Treatment Paradigms

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ABSTRACT

Chronic venous diseases (CVeD) are widely recognized as serious medical and social problems. They are a common, progressive group of diseases that have a significant negative influence on patients' quality of life and put an immense burden on healthcare systems around the world. An increasing number of studies in recent years have indicated that CVeD is more than just a local vein concern. Instead, it may sit on a broader cardiovascular continuum—reflecting systemic vascular dysfunction, sharing many of the same risk factors, and potentially flagging a higher risk of serious cardiac events. Both CVeD and cardiovascular diseases (CVDs) involve endothelial dysfunction, systemic inflammation, and oxidative stress. All these mechanisms are interconnected and mutually mediate. There is a need for a better understanding of the biological pathways shared by CVeD and other cardiovascular diseases to prevent and treat them more effectively. Understanding these common mechanisms can help develop new treatments that improve outcomes for both conditions, as well as more integrated preventive strategies. New research will be needed to prove, on the one hand, that modern pharmacotherapy of chronic venous diseases has not only regional but also systemic significance and, on the other hand, based on the similarity of pathogenesis, that in these diseases, neurohormonal and other therapies can also have the same beneficial effect as in several cardiovascular diseases.

Keywords: Cardiovascular diseases (CVDs); chronic venous diseases (CVeD), diosmin; endothelial dysfunction; micronized purified flavonoid fraction (MPFF) formulation; oxidative stress; systemic inflammation; oxidative stress.

INTRODUCTION

Chronic venous diseases (CVeD) are a widespread, progressive set of conditions that significantly impact patients' quality of life and place a substantial burden on healthcare systems globally.[1] However, in the last few years, growing evidence has shown that CVeD is not just a problem with the legs alone; it is part of a larger cardiovascular continuum that indicates systemic vascular problems, shares risk factors, and suggests a higher risk of serious events like stroke, coronary artery disease, and heart failure, with the severity of CVeD being associated with a higher risk.[2]

Both diseases affect the vascular system (especially the endothelium) and share common pathophysiological factors, including endothelial dysfunction, systemic inflammation, and oxidative stress, linking venous problems (varicose veins, ulcers) with arterial disease and highlighting the need for a comprehensive cardiovascular assessment in patients with CVeD.[3] All these mechanisms are interconnected and mediate each other.[4]

Endothelial dysfunction

Endothelial dysfunction is a core, shared pathophysiological mechanism for both CVeD and various CVDs, such as atherosclerosis, hypertension, and heart failure. In both CVeD and CVDs, endothelial dysfunction involves similar underlying processes. A key feature is reduced synthesis or increased degradation of nitric oxide (NO), a potent vasodilator and anti-inflammatory mediator, thereby impairing vasodilation and regulation of vascular tone. Increased expression of adhesion molecules (such as ICAM-1 and VCAM-1) that attract leukocytes to the vessel wall results in a dysfunctional endothelium developing a pro-inflammatory and pro-thrombotic state. Chronic inflammation and mechanical stress lead to structural changes in the vessel walls, contributing to the progression of disease in both the arterial and venous systems. In conditions like atherosclerosis and hypertension, endothelial dysfunction facilitates the infiltration of low-density lipoproteins (LDL) into the arterial wall, leading to plaque formation and arterial stiffness. In the venous system, altered blood flow (due to venous hypertension and valvular incompetence) triggers endothelial activation. This leads to inflammation, weakening of the vein walls and valves, and subsequent dilation and remodeling (e.g., varicose veins and ulcers).[5,6]

Systemic inflammation

Both conditions are linked to endothelial dysfunction, in which the lining of blood vessels (endothelium) loses its protective, anti-inflammatory, and antithrombotic properties. Increased permeability and the influx of inflammatory cells into the vessel wall result from this. Both chronic venous insufficiency and arterial atherosclerosis are associated with increased levels of pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and TNF-α. These mediators encourage persistent tissue damage and inflammation. In both conditions,

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inflammatory cells, such as macrophages and monocytes, adhere to the vessel walls and penetrate the tissue, where they release proteolytic enzymes and harmful metabolites that accelerate tissue damage. The inflammatory response may also increase ROS production, thereby exacerbating oxidative stress and worsening vascular dysfunction and disease. In arterial diseases, this may contribute to the development, progression, and rupture of atherosclerotic plaques that may cause conditions such as coronary heart disease, heart attack, and stroke. In venous disease, this inflammation contributes to venous wall remodeling, valve dysfunction, and microcirculatory changes, leading to symptoms such as pain and edema and progression to advanced stages.[6]

Oxidative stress

Oxidative stress, an imbalance between the production of ROS and the body's antioxidant mechanisms, is a major contributing factor to atherosclerosis, hypertension, heart failure, and cardiac arrhythmias. An excess of ROS reduces NO availability, an important vasodilator, thereby affecting blood flow and vascular resistance.[7] ROS act as signaling molecules that activate pro-inflammatory pathways (such as NF-κB), leading to the recruitment of immune cells and the release of inflammatory cytokines, which further exacerbate vascular damage.[8] Oxidative stress promotes the oxidation of low-density lipoproteins (ox-LDL), which are then taken up by macrophages to form foam cells, an initial step in plaque formation. It also plays a role in plaque instability and rupture. ROS can directly damage key cellular structures, leading to cellular dysfunction, apoptosis, and adverse cardiac remodeling (hypertrophy and fibrosis). Mitochondria are both a major source and a primary target of ROS, and mitochondrial dysfunction in the heart significantly contributes to impaired energy production and contractile dysfunction.

In CVeD, oxidative stress is part of a vicious cycle with other pathophysiological mechanisms, including venous hypertension, inflammation, and impaired hemodynamics. The increased local oxidative stress in vein walls also contributes to the degradation of the extracellular matrix and loss of biophysical properties, leading to vein dilation and the development of varicose veins. ROS directly damage venous endothelial cells, disrupt the vascular barrier, and increase leukocyte and platelet adhesion, thereby contributing to thrombosis. Oxidative stress potentiates the activity of matrix metalloproteinases (MMPs), which degrade the venous wall, and enhances local inflammation, accelerating the progression toward severe complications such as venous leg ulcers.

In both scenarios, an imbalance in redox homeostasis plays a critical, causative role, making it a promising target for novel therapeutic strategies.

In addition to the pathophysiological similarities between CVeD and cardiovascular diseases, there are also commonalities in risk factors:9 First, age, since the risk of developing it increases in both diseases; overweight and obesity are among the main risk factors present in both cases. It contributes to the development of arterial hypertension and diabetes, which further increases the risk of cardiovascular diseases; A sedentary/physically inactive lifestyle: low levels of physical activity are associated with obesity, arterial hypertension and lipid metabolism disorders; Tobacco use (smoking) damages blood vessels and increases the risk of atherosclerosis and blood clots; Arterial hypertension is a major risk factor for cardiovascular diseases and may be associated with the progression of chronic venous insufficiency; Impaired lipid metabolism, in particular high levels of LDL cholesterol, which contributes to the formation of plaques in the arteries; Diabetes mellitus can damage blood vessels of any caliber; Genetic predisposition/family history; Chronic inflammation is the main pathological mechanism of progression of both diseases; Female Sex and Hormonal Changes: women, especially during pregnancy or due to progesterone levels and oral contraceptive use, are at higher risk; According to the Framingham risk score, obesity, smoking, and age increase the risk of developing chronic venous insufficiency, especially class C4-6 (The CEAP classification system (Clinical, Etiology, Anatomy, Pathophysiology), which in turn increases the risk of cardiovascular disease. Both chronic venous disease and cardiovascular disease often involve similar lifestyle modifications, emphasizing a healthy diet, regular physical activity, weight management, and smoking cessation.[10]

There is some controversy over the pharmacological treatment modality for CVeD. The main modes of action of venoactive drugs (VADs) are to decrease capillary permeability, reduce the release of inflammatory mediators, or improve venous tone.[9-14]

For patients with symptomatic chronic venous disease who are not undergoing interventional treatment, are awaiting intervention, or have persisting symptoms and/or oedema after intervention, medical treatment with VADs should be considered to reduce venous symptoms and oedema, based on the available evidence for each drug. Class Level References ToE IIa A.[15]

Diosmin and hesperidin are VADS used to treat CVeDs. They have been proven effective in treating CVeDs by improving venous tone, reducing inflammation, protecting microcirculation, and promoting lymphatic drainage, thereby alleviating symptoms such as pain, heaviness, and swelling in the legs. Diosmin and hesperidin, often used in a micronized purified flavonoid fraction (MPFF) formulation (typically 90% diosmin and 10% hesperidin), address multiple aspects of CVD pathophysiology: Increased Venous Tone, the combination prolongs the activity of norepinephrine on the venous wall, causing smooth muscle contraction, reducing vein distensibility and blood pooling (stasis); Anti-Inflammatory Effects, they inhibit the adhesion and migration of leukocytes (white blood cells) to the endothelial cells of the veins, thereby reducing the release of inflammatory mediators like prostaglandins, thromboxane A2, TNF-α, and interleukins; Capillary Protection, they normalize capillary permeability and

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increase capillary resistance, which helps prevent fluid leakage into tissues and the formation of edema (swelling); Improved Lymphatic Drainage, the compounds enhance lymphatic flow and drainage by increasing the tone and frequency of contraction of lymphatic capillaries, reducing intralymphatic pressure; Antioxidant Activity, they possess antioxidant properties that help protect endothelial cells from damage caused by free radicals.[15]

CONCLUSIONS

Chronic venous diseases are now being recognized not in isolation, but as an integral part of the CVD continuum. This is primarily based on the presence of risk factors, systemic inflammation, oxidative stress, and hemodynamic dysfunction, and thus requires a more holistic approach to treating CVeD that considers both the venous and arterial circulations. In atherosclerosis, these shared pathophysiological factors contribute to stenotic processes in the arterial system and ischemia of vital organs, and, in dilatational processes in the venous system, to chronic venous insufficiency.

Understanding the common mechanisms underlying the pathogenesis of CVeD and CVDs is imperative for designing effective integrated prevention and therapeutic interventions for both conditions. There has been a wealth of research demonstrating a link between CVeD and CVDs.

Patients with advanced CVeD, compared to less severe forms of controls, have more often CVD at presentation or will develop, during follow-up, CVD events leading to a higher CV mortality;

New research will be needed to prove, on the one hand, that modern pharmacotherapy of chronic venous diseases has not only regional but also systemic significance and, on the other hand, based on the similarity of pathogenesis, that in these diseases, neurohormonal and other therapies can also have the same beneficial effect as in several cardiovascular diseases.

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