Skin manifestations of Chronic Venous Disease. Current evidence

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Abstract:

Chronic venous disease (CVD) is a common disorder associated with a variety of symptoms, including dermatological manifestations, which exhibit a significant role to the patient's quality of life. The dermatological changes have been classified and updated so that they respond to the severity of the disease according to the CEAP system in an 2020 update. The pathogenesis of dermatological disorders of CVD is enriched with new clinical and laboratory diagnostic findings which can shed light to the mechanisms responsible for the disease and facilitate the design of new therapeutic strategies.

INTRODUCTION

The term Chronic Venous Disease (CVD) of the lower extremities includes a broad spectrum of morphological and functional abnormalities of the venous system, ranging from telangiectasias to venous ulcers. The term Chronic Venous Insufficiency (CVI) describes the functional disorder of the venous system and usually refers to more advanced cases of patients with CVD having edema, skin changes and venous ulcers[1].

The CEAP classification system was introduced in 1994 and remains the most accurate classification method that provides sufficient information[1,2]. CEAP is the acronym for the words "Clinical" for the clinical manifestations, "Etiologic" for the etiologic factors, "Anatomic" for the anatomic distribution and "Pathophysiologic" for the underlying pathophysiology. Based on this classification, the clinical findings (C) are classified as seen in Table 1.

The incidence of varicose veins of the lower extremities with or without the presence of edema (stage C_2 - C_3, CEAP system)[1,2] is approximately 25% of the general population, while the more severe forms of the disease, which are characterized by symptoms such as dystrophic skin changes and leg ulcers (stages C_4, C_5, C_6), represent up to 5% of the cases[3].

The purpose of the current study is to meticulously review the factors related to the development of CVD skin manifestations. We will thoroughly evaluate the predisposing factors of CVD, the impact of pathophysiological disorders of the venous system and the role of inflammation in skin manifestations.

Table 1: Classification of the skin manifestations of CVD based on CEAP system (2020)

Clinical Classification
C_o: No visible/palpable signs of venous disease
C_1: Telangiectasias or reticular veins (Fig.1)
C_2: Varicose veins
C_{2r}: Recurrent varicose veins
C_3: Edema
C_4: Changes in skin and subcutaneous tissue secondary to CVD (Fig. 2)
C_{4a}: Pigmentation/Eczema (Fig. 3)
C_{4b}: Lipodermatosclerosis or atrophie blanche
C_{4c}: Corona phlebectatica
C_5: Healed venous ulcers (Fig. 4,5)
C_6: Active venous ulcers (Fig. 6)
C_{6r}: Recurrent active venous ulcers

Besides the aforementioned, the contribution of the color-flow duplex ultrasound will be assessed, in terms of the hemodynamic CVD parameters, the diagnosis and treatment of the related skin manifestations[1,4,5]. Finally, the importance and specificity of the stages C_4 - C_6 of the CEAP system will also be discussed.

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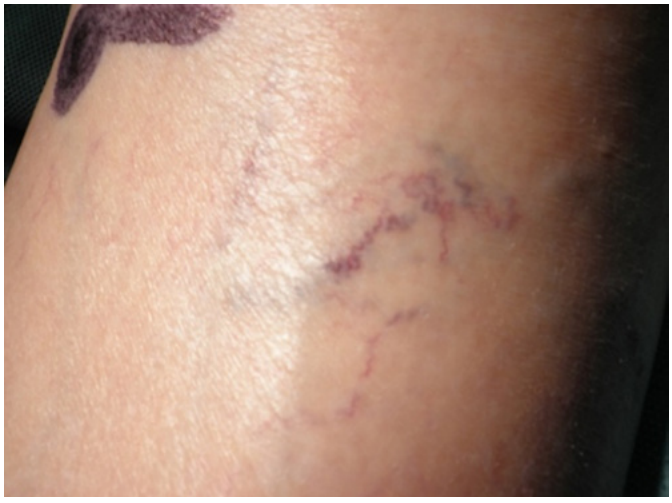

Fig.1: C_1: Telangiectasias or reticular veins

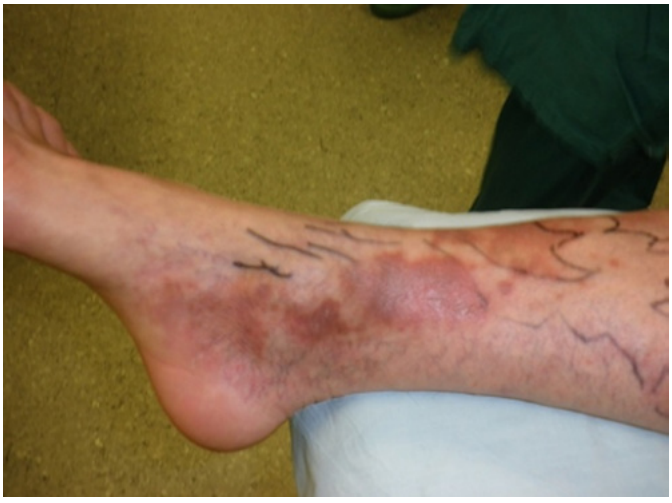

Fig.2: C_4: Changes in skin and subcutaneous tissue secondary to CVD

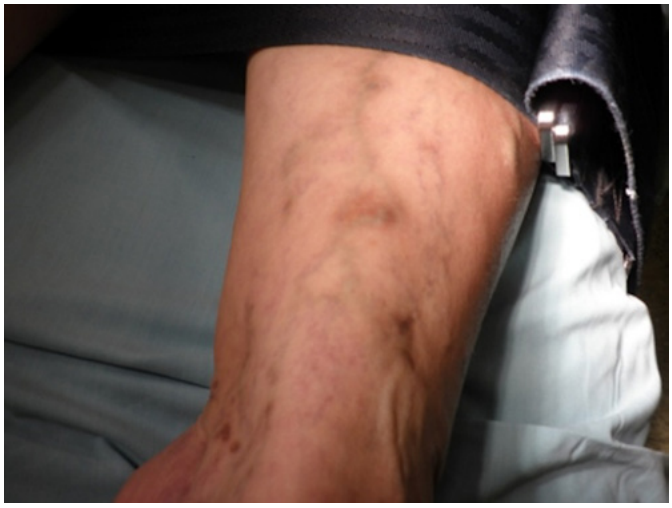

Fig. 3: C_{4a}: Pigmentation/Eczema

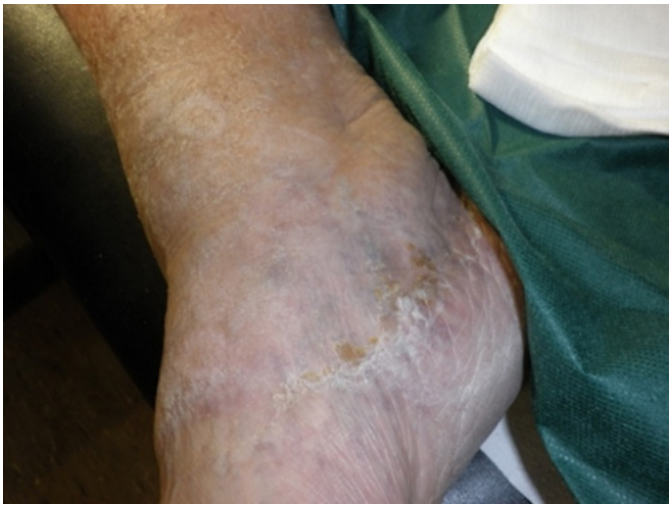

Fig.4: C_5: Healed venous ulcers

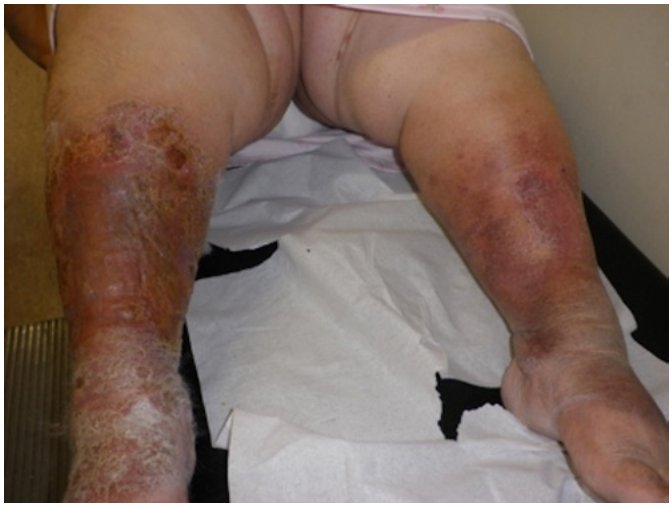

Fig.5: C_5: Healed venous ulcers

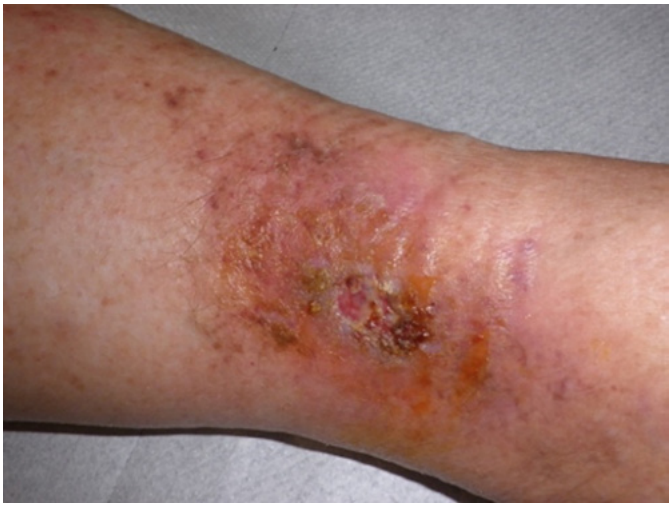

Fig. 6: C_6: Active venous ulcers

RISK FACTORS OF CVD

Several risk factors have been described for the development of CVD[6-12], with the majority of them originating from the modern way of living, as shown in Table 2

Table 2: Risk factors of CVD

1.	Heredity (genetic predisposition)
2.	Obesity
3.	Number of pregnancies
4.	Orally administrative contraceptives (hormone replacement therapy)
5.	Prolonged standing/bed rest
6.	Reduced mobility
7.	Diet low on fibers
8.	Smoking
9.	Garters, "Stiletto heel"
10.	History of venous thrombosis of the lower extremities
11.	Lower extremities trauma
12.	High height

It is widely known that pathological conditions on the venous system of the lower extremities arise after venous hypertension has been established[13]. The causes of venous hypertension are presented in Table 3[14,15,16].

Table 3: Causes of venous hypertension of lower extremities

1.	Incompetence of superficial, perforator and deep venous valves
2.	Venous obstruction
3.	Combination of 1 and 2
4.	Failure of pump mechanisms (From muscle contraction of lower extremities)

Venous valve incompetence of perforator veins "allows" the blood to flow from deep towards superficial venous system due to higher pressure generated by the muscular pump of the gastrocnemius. This venous hypertension can cause great venous dilatation and secondary dysfunction of the valves of the superficial venous system.

In the same manner, venous obstruction of the deep vein system can be attributed to endoluminal causes, such as the deep vein thrombosis with insufficient recanalization and extraluminal vein pressure.

The irreducible venous hypertension may result in skin manifestations with hyperpigmentation, subcutaneous fibrosis (lipodermatosclerosis) and possibly, ulcer formation. The degenerative skin manifestations have been initially attributed to fibrin deposition via fibrinogen infiltration around venous capillaries, preventing oxygen diffusion[17].

Recent studies[3] could not clearly elucidate whether the inflammatory manifestations of the vein and valvular wall precedes the venous incompetence, or they are generated by it. Changes in shear stress play a fundamental role in the development of inflammation of the vessel wall. Evidence that normal shear stress exhibits anti-inflammatory effects has been previously presented, while low shear stress or several other hemodynamic disorders (reflux) seem to cause an increase of pro-inflammatory mediators and vasoactive substance from the endothelium[18,19]. This effect results to elevated expression of adhesion molecules (E-selectin, Intercellular Adhesion Molecule-1: ICAM-1), chemokines and inflammatory mediators. Additionally, the glycocalyx of the endothelial cells [which consists of polysaccharides chains (glycosaminoglycan)] has been shown to be damaged, and concomitantly contributes to shear stress transmission and leukocyte adhesion inhibition[20]. On the contrary, increased ICAM-1 expression reinforces leukocyte adhesion, which leads to local inflammatory responses. Monocyte and macrophage infiltration of venous vessel and valves is also associated with the adhesion molecule ICAM-1. Increase of collagen on vessel wall and decrease of elastin and laminin has also been demonstrated[3].

In a recent study[21] the importance of the integrity of the glycocalyx has been emphasized, as damage or loss of it results in the dysfunction of endothelial cells and the expression of adhesion molecules that attract leukocytes and cause an inflammatory reaction. The dysregulation of the glycocalyx is considered responsible for:

a. Mechano-transduction of acute and chronic stimuli,
b. Increased permeability of the vascular barrier,
c. Increased adhesion of blood leukocytes, lymphocytes, and platelets and
d. Extravasation of blood cells that cause inflammatory reaction and proteolysis in the microenvironment of blood vessels[21].

Increased activity of Matrix Metalloproteinases (MMPs), especially of MMP-2, has been reported in patients with chronic inflammatory conditions of CVD, exhibiting lipodermatosclerosis and active venous leg ulcers[22]**.** In the aforementioned patients, the levels of Tissue Inhibitor MMP-2 (TIMP-2) have been reported to be decreased[23,24]. The aberrant activity of MMPs can contribute to the degradation of connective tissue, promoting the development of venous ulcer, therefore affecting its healing rate.

In lipodermatosclerosis, skin capillaries become elongated and tortuous, while in more advanced skin changes, they can adopt a glomerular appearance via endothelial cell proliferation[25]. Vascular Endothelial Growth Factor (VEGF), which can be involved during this process, increases microvascular permeability[26] whereas VEGF levels have been found to be elevated in venous hypertension-induced short-term standing in CVI patients compared to their normal counterparts. Additionally, transforming Growth Factor-β1 levels (TGF- β1) have been found to be increased in biopsies of skin lesions, unlike healthy skin biopsies of the same patients in which the levels of TGF-β1 are found to be significantly lower. TGF-β1 has been located in leukocytes, fibroblasts and collagen fibrils, but it has also been reported that activated leukocytes that extravasate, release TGF-β1 that concomitantly promotes collagen formation through dermal fibroblasts, leading to dermal tissue fibrosis[27, 28, 29].

Recently, the role of fibronectin (FN), a high-molecular glycoprotein of the extracellular matrix (ECM), in patients with lipodermatosclerosis and venous ulcers has been studied[30]. Fibronectin plays a major role in the healing process, as it participates in the ECM formation. Plasma FN interacts with fibrin to form the provisional matrix, which is replaced by the mature ECM consisting of high levels of cellular FN. Fibronectin interacts with collagen, tenascin, transglutaminase, and other proteins facilitating their integration in the ECM. Therefore, Fibronectin contributes significantly to ECM formation and stabilization, processes disturbed in CVD. Hence, FN metabolism could be a target for the design of novel therapeutic approaches for CVD.

The elucidation of the sequence of inflammatory responses led to drug development, such as sulodexide, a highly purified mixture of low molecular weight heparin (80%) and dermatan sulfate (20%). Sulodexide results to venous ulcer healing and the improvement of symptoms, such as pain, the feel of heaviness on the extremity and edema, while exerting a systemic action through the inflammatory chemokines[21, 31].

Skin hyperpigmentation in CVD patients having dermatosclerosis, has been attributed to extravasation of red blood cells, which subsequently leads to increased levels of ferritin and iron in the affected areas. The elevated ferritin and iron levels may cause oxidative stress, activation of MMPs and create the conditions that augment tissue damage and delayed healing[32]. The case of the C282Y mutation of the hemochromatosis gene, which is a common genetic disorder of iron metabolism, could be included in the same context. In this case, the risk of developing venous ulcer is seven times higher compared to CVD patients not having this mutation[33].

ULTRASONOGRAPHY IN CHRONIC VENOUS DISEASE

The color-flow duplex ultrasound represents the "gold standard" method[3] for detecting CVD, as it provides the ability to control the morphological and functional status of the venous system. Apart from its contribution in diagnosis, color-flow duplex ultrasound has a partial prognostic ability in cases of incompetence of the perforator veins, as those are associated with the severe skin manifestations of C_4, C_5 and C_6 stages, according to CEAP classification[3,34]. Additionally, with the extended use of intravenous therapeutic methods (intravenous laser therapy, radiofrequencies vein ablation) in the recent years, ultrasonography gained a partially therapeutic role, since locating the incompetent perforator veins is of paramount importance for the treatment of venous ulcers (C_4 - C_6)[21, 35, 36].

C4-C5 THE CRUCIAL STAGES OF THE CEAP CLASSIFICATION

Epidemiological data concerning the frequency of CVD and its severe stages (C_4, C_5, C_6) have been extensively presented in the beginning of the current manuscript. However, some of these data were considered to be originated from old studies or studies being methodologically flawed[37].

Today, the epidemiological data of C_4-C_6 stages are considered significantly modified in the last 10-20 years and according to accumulating data from current studies, more modifications are expected in the future. There is a lot of evidence supporting considerations such as the established correlation between age and CVD frequency. The increase of survival may increase the number of C_4-C_6 cases[38], while -on the contrary-the improved methods for prevention and treatment of venous thromboembolism are expected to decrease the number of patients that will develop the severe manifestations of post-thrombotic syndrome.

All the evidence and the particularities presented for the stages C_4-C_6 of CEAP classification have led some researchers[39] to suggest that these stages should become a separate CVD group entitled "skin changes of CVI" with the following characteristics:

a. C_4 stage is considered as a venous ulcer that has not yet developed, but probably will appear after a local injury or insect bite.

b. C_5 stage is considered as a healed venous ulcer that can relapse, unless treatment to decrease AVH is continued.

c. C_6 stage is considered a venous ulcer that is likely to heal with the appropriate treatment that will aim in the reduction of venous ambulatory hypertension (AVH).

Many studies have shown increased levels of inflammatory mediators, such as interleukins, tumor necrosis factors (TNFs) and C-reactive protein in venous ulcer microenvironment. It has not been elucidated yet if these inflammatory factors are on the causal basis of tissue injury, or can be considered as indicators of the healing process, or if they are an uncommon complication of skin changes in CVD, in combination with microbial contamination[34, 37].

Today it is widely accepted that the longer a venous ulcer remains, the more difficult it is to be cured and remain in complete remission. However, the question is whether these venous ulcers exhibit distinct features from the start or these differences result after a specific time point?

Moreover, it has been established that the healing process of chronic ulcers is affected by many different mechanisms associated with distinct phases of the process. The above can justify the fact that many theories have been formulated for the explanation of these mechanisms. The role of **"**chronic inflammation**"** in skin changes of CVD has already been highlighted. Here, it is also underlined that poor healing in ulcers may be a consequence of premature fibroblast senescence, as a result of stress caused by chronic and non-receding inflammation[40]. The accumulation of more than 15% prematurely senescent fibroblasts in venous ulcer is an indication of the hardships in the healing process. Therefore, the ratio of senescent to non-senescence fibroblasts is a potential prognostic marker that can determine the therapeutic response [**37**]. Moreover, therapeutic maneuvers and novel strategies that would affect this ratio in favor of the non-senescent fibroblasts, could contribute in the improvement of the healing rates of ulcers. Towards this direction, there was a study that intended to enhance the healing process by applying biotechnologically prepared skin substitutes[37]. Prematurely non-senescent fibroblasts can be entered in the ulcer through these substitutes, releasing growth factors that could potentially

reverse the anti-proliferative capacity of the chronic ulcer exudate. However, besides the great cost that was required, this effort was not successful in justifying the use of these skin substitutes in the everyday clinical practice[37].

Another factor that has attracted scientific attention was the inability of ulcer to epithelialize, despite of the good perfusion of scar tissue inside the ulcer. Biopsies from non-healing edges of ulcers revealed skin hyperkeratosis with high proliferative rates of keratinocytes, advocating for an incomplete activation and differentiation of keratinocytes[41].

Additionally, the abnormal expression of early (keratins K1/K10) and late (filagrin, involucrin and transglutaminase1) indicators of differentiation and activation (K_6, K_{16}, K_{17}), as well as the dysregulation of the components of intercellular connections, are included in the above clinical and histopathological cases[41].

OPTIONS FOR TREATMENT OF SKIN MANIFESTATIONS

There are a variety of treatment options -conservative and invasive- aiming at the improvement of symptoms, the prevention of complications, and the promotion of ulcer healing. However, the key to therapeutic success lies in the reduction of venous hypertension[21].

Conservative treatment of CVD consists of compression therapy (stockings and bandages), physical therapy, manual lymphatic drainage, phlebotonics, and sulodexide. Compression therapy in early- stage CVI improves edema and the feeling of heaviness in the legs, and contributes in the treatment of leg ulcers. Physical therapy can help improve muscle pump function, while manual lymphatic drainage followed by compression bandaging can be used to reduce chronic leg edema[3].

Natural or synthetic phlebotonics (diosmin, rutin, grape seed extract, hydrosmin, ruscus and Indian chestnut) are considered the first pharmacological line for symptomatic treatment for varicose veins but did not show advantages in ulcer healing. Phlebotonics reduce symptoms such as pain, heaviness, paresthesia and improve skin change[21].

Conservative measures such as physical therapy, manual lymphatic drainage, and phlebotonics may improve symptoms and promote ulcer healing but they are not substitutes for compression bandaging or surgery[3].

Sulodexide is a useful venoactive treatment as this drug is contributing to ulcer healing. However, in a systematic review and meta-analysis of large series there was found a high degree of heterogeneity in almost all of theme, suggesting that additional randomized trials should be performed to attain conclusive evidence[31].

CONCLUSION

Varicose veins of the lower extremities are defined as a disease that affects large part of the population, associated with a poor quality of life. The skin manifestations of the disease have been classified and updated to meet the graded severity and to influence, -to some extent- therapeutic manipulations.

The investigation of the factors involved in dermatological manifestations has been the object of research for several years and continues to concern clinical scientists, but it has not provided any conclusive results until now. Alongside, at the clinical laboratory level, color-flow duplex ultrasound remains the "golden standard" method for the evaluation of the majority of CVD manifestations, indirectly contributing to treatment selection, which has gradually shifted to "more conservative" methods (intravenous laser treatment, radiofrequencies).

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