

Review Article

The role of inflammatory reaction in chronic venous disease of the lower limb

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Received: 27 March 2019

Revised: 12 April 2019

Accepted: 13 April 2019

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ABSTRACT

Chronic venous disease is the problem which is assuming alarming proportions in subjects whose occupation involves prolonged sitting or standing. The exact mechanism by which the venous system gets damaged continues to be a subject of endless research. The role of inflammation is a significant factor in the evolution of chronic venous disease. Awareness of this mechanism can help in both prevention and treatment of this complex vascular disorder. The paper reviews inflammatory mechanism underlying the pathogenesis of chronic venous disease in lower limbs.

Keywords: Chronic, Venous, Disease, Inflammation, Leukocytes

INTRODUCTION

Chronic venous disease (CVD) is an insufficiency of the peripheral veins caused by either partial or total obstruction, endothelial distention or alteration of routine venous function.¹⁻³ The disease traditionally was more prevalent in individuals who were involved in an occupation involving prolonged standing. However, the disease now affects even those individuals whose occupation involves prolonged hours of sitting. CVD if left untreated can lead to a multitude of complications which at times can even be lethal as in deep vein thrombosis. A large number of articles have been published which postulate various hypothesis for etiopathogenesis of CVD.³⁻⁷ Significant number of articles stress on inflammatory reaction underlying CVD affecting the lower limbs.⁸⁻⁹

FEATURES OF CVD

Chronic venous disease of lower limb can present in a variety of ways. The symptoms are subtle to start with but may progress rapidly eventually leading to severe

incapacitation. This may interfere with daily functioning of these individuals. These features include telangiectasis, pedal edema, varicosities, pigmentary changes and chronic leg ulceration.¹⁰⁻¹² Chronic venous insufficiency (CVI) is a combination of edema, skin changes and ulceration. Various classifications have been proposed. However the CEAP classification created by the American venous forum is the one widely used. This classification officially recognized CVD and thereby helping in managing such cases at a very early stage.³

PATHOPHYSIOLOGY

The clinical features seen in CVD are an end result of venous hypertension.^{13,14} Venous wall abnormalities including valvular incompetence constitutes the basis of CVD. Significant pathological changes occur in the venous wall which lead to functional damage.¹⁵⁻¹⁷ The damage is in both the wall as well as the valve. This leads to reversal of flow or reflux which is seen at all levels that is superficial vein, perforator, and deep veins. The smooth muscle and connective tissue fibers which are abundantly found in tunica media, are the first to get

affected.¹⁸⁻²⁰ There is significant alteration in composition of intracellular matrix. It is the composition of the intracellular matrix that is responsible for maintaining integrity of venous wall. The intracellular matrix is predominantly glycosaminoglycans.^{21,22} Its interaction with smooth muscles and elastic fibers is responsible for the venous wall to endure high pressures. Even collagen and elastin in venous wall adds to the resilient and endurance of the venous wall.^{23,24}

In CVD patients there is alteration of elastic fibers which gets separated from smooth muscle fibers.^{25,26} There may be a deficiency of various types of collagen in such patients (especially type III).^{27,28} Various enzymes may be released by stagnant inflammatory cells thereby contributing to CVD. Release of matrix metalloproteinase (MMP) followed by its activation can cause dissolution of collagen in intracellular matrix.^{29,30} This leads to significant weakening of the venous wall. Furthermore, activation of endocrinal cells releases Beta transforming growth factor (B-TGF) which causes migration of muscularis cells with accompanying proliferation in intimal layers.^{24,27}

The long-lasting secretion of B-TGF induces both MMP and tissue inhibitor of metalloproteinase (TIMP) release. This alteration of balance between MMP and TIMP leads eventually to significant damage of extracellular matrix.²⁸

In addition to this superimposed but altered blood flow pattern and hemodynamics add to valvular damage. Persistent reflux leads to extension of valvules, atrophy of cusps and hemodynamic alteration. All the aforementioned factors perpetuate the process of chronic inflammation.³¹

Several cellular events contribute in a large way to the inflammatory process.³¹ Extensive leucocyte infiltration mainly macrophages and lymphocytes are seen in CVD patients. Other cells which are found to increase are granulocytes, monocytes, macrophages and lymphocytes.³² Continuous high intravascular pressure leads to increase in sheering stress and perpetuates increased endothelial cells and leucocyte activation.³³ Lymphocytes adhere to the endothelial cells, leading to a series of effects such as endothelial cell constriction, selectin expression, release of Von Willebrand factor, cytokines, adhesion molecules and tissue factors.³³

Extravasation of leucocytes takes place in stepwise manner. Initially leucocytes stick to endothelial wall by selectin molecules which eventually tethers leucocytes to endothelial cells. This leads to further activation of leucocytes there by compounding the inflammatory process.^{31,33} Besides leucocytes, RBCs also extravasate due to venous hypertension. The degradation products of RBCs are potent chemo attractants and are presumed to serve as the initial signal for leucocytes. Hypoxia which is a common accompaniment can lead to increased production of platelet aggravating factor (PAF).³⁴ PAF in

turn further activates leucocytes. Plasma levels of selectin are very high in CVD patients. Besides selectin, a variety of other molecules are quite high in CVD patients. These add symbiotically in bringing about a conformational change in basic structure of integrin molecules.

Leucocyte sequestration due to stasis in valve cusps add to the damage caused to the venous wall.³⁰ As per white cell trapping hypothesis there is massive leucocyte activation in micro-circulation followed by their migration into the subcutaneous tissue. These activated leucocytes release cytotoxic molecules which are instrumental in causing extensive damage of valve cusps and venous wall eventually leading to breakdown of the skin.^{31,33,35}

CONCLUSION

Of the various theories proposed, leucocyte activation theory is the most commonly accepted theory to explain the sequelae seen in CVD. Targetted therapy towards control of the inflammatory process may perhaps help in preventing disastrous complications of CVD.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Vagholkar K, Garima S, Kripalani Y. The role of inflammatory reaction in chronic venous disease of the lower limb. *Int Surg J* 2019;6:1835-7.