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International Journal of Pharmaceutical Research & Allied Sciences, 2024, 13(4):12-18
https://doi.org/10.51847/q0gNDdDNSV

Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Beyond the Barrier: The Endothelium's Unsung Role in Physiology & Pathology

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ABSTRACT

Research conducted in recent years has significantly transformed our understanding of the role of the vascular endothelium in maintaining the overall homeostasis of the body. It has been revealed that the endothelium is responsible for synthesizing a wide range of biologically active substances that play a key role in numerous processes both in health and disease - such as hemodynamics, hemostasis, immunological responses, and regenerative processes. This extensive endocrine activity has led to the endothelium being sometimes referred to as an "endocrine tree." The functioning of the endothelium depends on its functional condition, which is shaped by the signals it receives. Endothelial dysfunction understood as an impairment of the vasodilatory, antithrombotic, and anti-inflammatory properties of the cells lining the vessels, is closely linked to cardiovascular diseases - the leading cause of death worldwide. It is considered a key stage in the development of atherosclerosis and one of the major risk factors for hypertension, diabetes mellitus, and cardiovascular incidents. This paper aims to gather and present information that will allow for a better understanding of the structure and significance of this majestic organ in human physiology.

Keywords: *Endothelium, Endothelial dysfunction, Cardiovascular system, Oxidative stress*

INTRODUCTION

Over the past three decades, our understanding of the role of the vascular endothelium has continuously changed, recognizing it as a complex organ that is dynamically controlled and essential for a variety of physiological and pathological processes. Initially perceived as a simple semipermeable barrier—"the cellophane wrapper" of the vascular tree—recent abundant research underscores its critical physiological functions, particularly in regulating vascular tone, blood flow, and platelet activation [1, 2]. Simple squamous cells with a cobblestone-like appearance, endothelial cells (ECs) line the whole cardiovascular system (CVS), including the blood vessels, lymphatic vessels, and walls of the heart, in a continuous, thin, and smooth monolayer [1, 3, 4]. The endothelium is home to numerous receptors for various biologically active substances (BAS), and it also senses the pressure and volume of the moving blood - a phenomenon known as shear stress, which stimulates the synthesis of anticoagulant and vasodilatory substances. Therefore, the higher the pressure and speed of the blood flow (in arteries), the less likely clots are to form. Endothelial dysfunction (ED), which occurs under the influence of damaging factors (mechanical, infectious, metabolic, immune complex, etc.), rapidly reverses the direction of its hormonal activity: vasoconstrictors and coagulants are produced [1-4]. The biologically active substances produced by the endothelium mainly act in a paracrine manner (on neighboring cells) and autocrine-paracrine manner (on the endothelium itself), but the vascular wall is a dynamic structure. Its endothelium is continuously renewed, and as parts become obsolete, they, along with BAS, enter the bloodstream, spread throughout the body, and can affect systemic blood flow. The activity of the endothelium can be assessed based on the concentration

of BAS in the blood. The structure of the vascular wall creates a certain pattern in the distribution of coagulating factors (vasoconstrictors) and anticoagulant factors (vasodilators) [2]. As long as the endothelium remains intact and undamaged, it primarily synthesizes anticoagulant factors, which also serve as vasodilators. They provide a non-thrombogenic surface with highly selective permeability properties, actively regulating molecule exchange in response to endogenous or exogenous signals. Covering an approximate surface area of 4000-7000 m^2, the endothelium is one of the body's largest organs, highlighting the significant impact its dysfunction can have on body homeostasis [2]. Pathologically, the endothelium serves dual roles: it mediates immune responses by amplifying inflammation at injury or infection sites, and as an integral component of the cardiovascular system, its dysfunction can lead to disease [2, 3].

This paper aims to gather and present information that will allow for a better understanding of the structure and significance of this majestic organ in human physiology.

RESULTS AND DISCUSSION

Endothelial dysfunction

There are two types of blood vessels: macrovasculature and microvasculature. Large blood vessels, including arteries and veins, that carry blood to and from organs make up the macrovasculature. The ECs that make up the majority of the microvasculature are tiny arteries, venules, and capillaries. It is crucial for managing the metabolic exchanges between the blood and peripheral tissues as well as local blood perfusion. Arterioles, measuring 10-100 μm in diameter, are highly innervated and respond to sympathetic vasoconstriction, crucial for adjusting vascular peripheral resistance and blood flow volume, thereby influencing capillary fluid exchange. Capillaries and venules are the primary sites for fluid and macromolecular exchanges, with venules also playing a significant role in leukocyte adhesion. This indicates that ED in various locations can disrupt numerous physiological processes within the organism [5].

ED is identified as a pathological state marked by an imbalance between vasodilating and vasoconstricting substances, a loss of anti-thrombotic properties, and increased permeability. It encompasses any form of abnormal endothelial activity. Most cardiovascular (CV) risk factors are associated with ED, and their therapeutic modification can lead to improvements in vascular function [3, 4]. A common manifestation of ED is impaired nitric oxide (NO) bioavailability, resulting from either reduced production by endothelial nitric oxide synthase (eNOS) or increased degradation by reactive oxygen species (ROS) [4].

A summary of the interactions and mechanisms of action of various endothelium-derived factors on endothelial cells is presented in **Figure 1**.

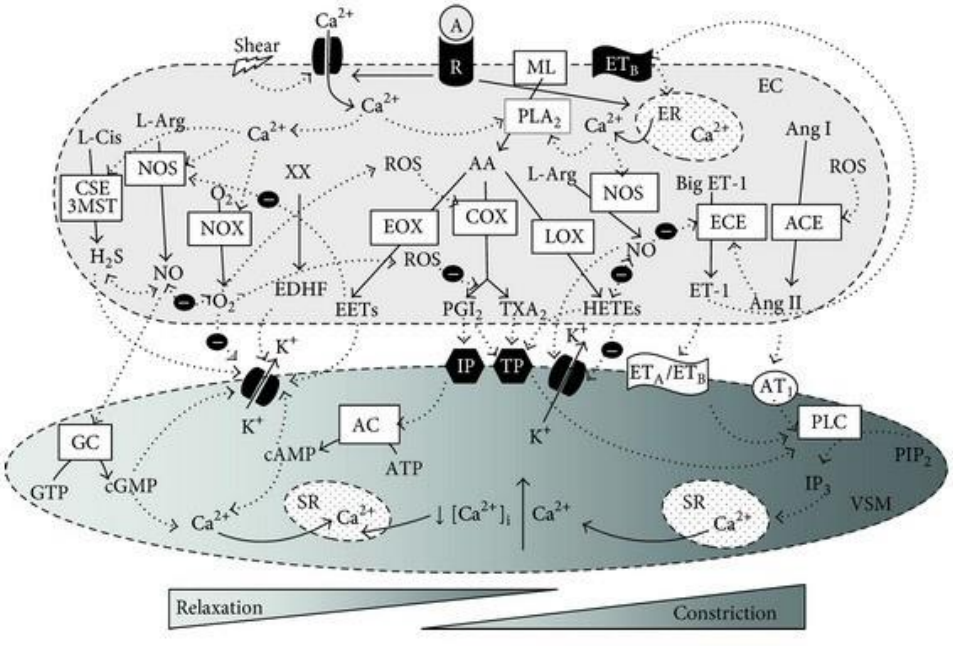


Figure 1. A summary of the interactions and mechanisms of action of various endothelium-derived factors on endothelial cells. The image adopted from Bernatova [6]

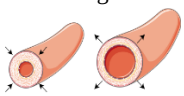
ED is a hallmark of cardiovascular disease and arteriosclerotic vascular disease, commonly known as atherosclerosis, where it has been consistently documented. The dysregulation of endothelial cells plays a pivotal role in a multitude of pathological conditions including vasculitis, hypertension, cardiomyopathy, retinopathy, neuropathy, and cancer. ED is not limited to hypertensive individuals but is also observed in normotensive subjects with a family history of hypertension, as well as among active and passive smokers, and conditions like aging, obesity, diabetes mellitus, dyslipidemia, hyperhomocysteinemia, and in patients with inflammatory or infectious diseases. Often, these conditions are linked to an overproduction of ROS leading to oxidative stress, which interacts with nitric oxide reducing its availability and potentially causing direct cellular damage through the production of peroxynitrite. Thus, oxidative stress is a critical mechanism in the development of ED, if not its primary cause [5-7].

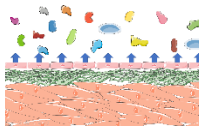
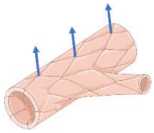
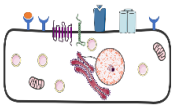
The significance of endothelium in physiology and pathology – molecular mechanisms

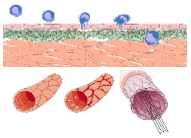
Besides the abovementioned facts, the endothelium plays a crucial role in the innate immune system, acting as a barrier to prevent the intrusion and systemic spread of pathogens Tight joints, which quickly mend after a vessel burst, preserve the integrity of this barrier. Additionally, the endothelium exerts a significant paracrine function, secreting chemokines, interleukins, interferons, and growth factors, and it facilitates the recruitment and extravasation of immune cells at inflammation sites. Critical to this process are adhesion molecules such as E-selectin, P-selectin, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM), present on ECs surface. It has been observed that the four classical signs of inflammation - calor (heat), rubor (redness), tumor (swelling), and dolor (pain) - are regulated by EC responses to stimuli [5, 6, 8]. Furthermore, the endothelium forms the lymphatic vessels, essential components of the peripheral immune system. These blind-ended tubules, equipped with valves, facilitate the drainage of interstitial fluid containing CD45+ cells and potential pathogens. Although ECs are integral to the immune system, they do not possess the classical immune cell functions such as killing, phagocytosis, or antibody production. Nonetheless, they are an essential part of the body's defense system, and their dysfunction can lead to dysregulation of immune processes, a common occurrence in numerous diseases.

Table 1 depicts the fundamental functions of endothelium that are key in the maintenance of the body's homeostasis. All those processes could be impaired in ED, which could lead to serious issues that impact the entire body.

Table 1. The main functions played by endothelial cells (ECs) are illustrated by Servier Medical Art.

1. Vasoregulation 	By preserving the balance of vasodilative and vasoconstrictive impulses, the endothelium contributes significantly to the regulation of vascular tone, allowing BP and blood flow to adjust to the demands of the moment. By delivering paracrine signals to the smooth muscle cells encircling the arteries, ECs regulate their vasoregulation by either contracting or relaxing them. The most potent vasoconstrictor is endothelin, a 21aa peptide existing in three isoforms – mainly produced by ECs, whereas its main counterplayer is a gasotransmitter – NO. Under normal conditions, eNOS provides NO to adjust vascular tone to alter BP and blood flow. In ED, NO bioavailability is impaired which leads to the development of atherosclerosis and CVD.
2. First aid kit - role in hemostasis 	During the coagulation process, ECs play a crucial role in providing the proper hemostatic balance. Besides the principal role of providing a non-thrombogenic inner layer of the vascular wall, ECs also provide some of the substances essential to the process. Weibel-Palade bodies (WPB) are rod-shaped subcellular organelles considered endothelial-specific first aid kits, equipped to provide an efficient response to the damage sustained by the vasculature, without losing time on the translation process. Their major constituent is vWF whose base role is to recruit the platelets in the place of injury. The remaining content is P-selectin which recruits leukocytes to guard the wound, IL-8 to boost inflammation and recruit neutrophils, ET for vasoconstriction in the affected area, angiopoietin-2 which helps in tissue repair and tPA which prevents excessive fibrin formation. WPB exocytosis is triggered by fIIa, VEGF, or epinephrine. Intense exocytosis of WPB likely promotes vascular inflammation and atherosclerosis. WPB is thought to be the most active promoter of platelet and leukocyte adhesion.
3. Angiogenesis	Angiogenesis is required during growth and development as well as in tissue repair and restoration of oxygen and metabolite supply. During angiogenesis, activated ECs undergo mitosis and migrate out from a preexisting vessel towards a gradient of VEGF. It is a growth factor that is produced autocrinally by ECs or paracrinally by inflammatory cells under hypoxic conditions and stimulates

	mentioned processes in the endothelium. Other factors act angiogenically such as the large family of angiopoietin peptides or chemokines, e.g., IL-8 that induces the proliferation of ECs in ischemic myocardium or different cancers. New vessels' formation begins as outgrowing sprouts of tip and stalk cells. Tip cells equipped with many filopodia and VEGF receptors to sense the growth factor gradient are highly migratory leading cells behind which follow the stalk cells. Among three receptors for VEGF-A: VEGFR1, VEGFR2, and VEGFR3, belonging to the tyrosine kinase family, VEGFR2 seems to play first fiddle in this process even though VEGFR1 has greater affinity for VEGF. VEGF-C and VEGF-D interacting with VEGFR3 on the surface of lymphatic ECs leads to lymphangiogenesis.
4. Secretion 	ECs secrete chemokines, interleukins, interferons, growth factors, and vasoactive substances, all of which can play a role in metabolic homeostasis. Galley and Webster grouped the factors depending on their function: vasodilating factors – NO and prostacyclin, and the vasoconstricting compounds such as TXA2, free radicals, leukotrienes, or ET. Other emphasized substances mentioned in this study are factors acting on the hemostasis process: procoagulants e.g., vWF, TXA2, fV, thromboplastin, PAF or PAI-1 and antithrombotics including prostaglandins, thrombomodulin, antithrombin, as well as uPa. In turn, ECs are also involved in the production of the substances that constitute the extracellular matrix, mostly fibronectin, laminin, collagen, and proteoglycans. Moreover, endothelium produces growth factors like IGF; HGF; CTGF/CCN2; TGF-β; colony-stimulating factors, or VEGF. Lastly, it is worth mentioning that PRR stimulation leads to the production of inflammatory mediators including IL-1β, IL-6 and IL-8, TNF-α, and leukotrienes. The WBP has a vital role in EC secretion, but its content remains situation-dependent.
5. Glucose and lipid transport. 	By modifying transendothelial access and local blood flow, glucose transport is controlled. The primary GLUT in ECs, the GLUT-1 transporter, plays a crucial role in the energy-independent transport of glucose across the cellular membrane. It is noteworthy that certain mediators, such as the HIF-1α factor, cause an increase in GLUT-1 expression. However, insulin signaling does not control glucose transport in human micro- and macrovascular ECs. Another important organ in the control of lipid transport in the body is the endothelium. It is not necessary for fatty acids (FA) with medium (6–12 carbons) and short (< 6 carbons) chains to actively traverse the cell membrane. Compared to long-chain FA (> 12 carbons), which require a specific transporter to get across the cell membrane, they are less common in diets. Before the mAspAT/FABPPM transporter was identified in rat aortic ECs in 1991, it was believed that all lipids could enter the cells by diffusion. Since then, more types of FA transport proteins (FATPs) have been identified, such as intracellular FABPs (FA-binding proteins), FATP1-6, and FAT/CD36 (FA translocase). When VEGF-B, for example, is produced by nearby cardiomyocytes, it causes the expression of FATP3 and FATP4, which helps ECs absorb FA, which is necessary for the synthesis of ATP. Very relevant is the fact that lipoproteins are transported across endothelium via coordinated receptor-mediated endocytosis and exocytosis. All LDL receptors, scavenger receptors, and VLDL receptors can take up the LDL, acetylated LDL, oxidized LDL (oxLDL), or VLDL. CD36 is a key scavenger receptor that is required for the internalization of oxLDL in ECs. In turn, HDL transport is possible thanks to SR-B1 and ABCG1 proteins.
6. Receptor and marker organ 	As endothelium is one of the biggest body organs, it is equipped with an abundance of surface proteins for various purposes. ECs express several PAMP receptors including the TLR family. TLR1-TLR6 and TLR9 are found in all different kinds of tissue-specific ECs in rest, whereas TLR7, TLR8, and TLR10 are normally absent but could be induced under inflammatory activation. Their activation stimulates the production of cytokines by endothelium. Another characteristic feature of ECs is the presence of membrane-bounded receptors for numerous ligands including proteins, lipid-transporting particles, metabolites, and hormones. The junctional proteins that provide cell-cell and cell-matrix interactions are also widely expressed among ECs. In inflammation, the expression of adhesion molecules is increased and more E-selectin, P-selectin, ICAM and VCAM molecules provide easier leukocyte migration. ECs also form tight junctions between themselves thanks to several proteins including claudin-5, and its reduction in junctions leads to elevation of vascular permeability. ECs also express on their membranes the blood group AB antigens which should always be considered in transplantations.

7. Leukopheresis and cell migration barrier 	Leukapheresis is the first step of the multistage process of extravasation of leukocytes to the site of inflammation or infection, and its regulation is one of the most crucial functions of ECs during inflammatory response. For ECs, it is a major challenge to maintain the balance between tightly sealing the vessel walls to prevent leakage of transported fluid on the one hand and facilitating extravasation of immune cells on the other. Transendothelial migration (TEM) takes place in several stages (1) tethering, (2) rolling (3) firm adhesion, (4) crawling, and eventually (5) diapedesis. The main group of adhesion molecules is constituted by Ca^{2+} dependent lectins: E-selectin that must be synthesized de novo after IL-1 or TNFα induction, P- selectins that are stored in WPBs, whereas L-selectin is synthesized constitutively by leukocytes. The key role is also played by chemokines such as CCL2 that elicits a rapid surface presence of L-selectin, PSGL-1, and CD44 crucial for the neutrophil recruitment process and induces E-selectin expression to attach to monocytes. Arrest and crawling are mediated by stronger anchoring through integrin and their ligands: ICAM-1 and LFA-1; VCAM-1 and VLA-4 which provide the cell-cell and cell-ECM interaction supporting the crawling process even against the flow direction. The passage of leukocytes is paracellular in 90% of cases, however, 10% of TEM is happening transcellular directly through ECs. It additionally implies why the non-disturbed function of ECs is essential in leukocyte migration.

Abbreviations used in **Table 1**, not explained in the text: CCL2 – chemokine C-C motif ligand 2, CTGF/CCN2 – connective tissue growth factor, ET – endothelin, fIIa – active factor II – thrombin, FATP – fatty acid transport proteins, fV – factor V, GLUT-1 – glucose transporter 1, HGF – hepatocyte growth factor, HIF-1α – hypoxia-inducible factor 1-alpha, ICAM – intercellular adhesion molecule 1, IL – interleukin, IGF – insulin-like growth factor, LFA-1 – lymphocyte function-associated antigen 1, LDL – low-density lipoproteins, mAspAT/FABPPM – mitochondrial aspartate aminotransferase/fatty acid binding protein (pm – plasma membrane), oxLDL – oxidized LDL, PAF – platelet-activating factor, PAMPs – pathogen-associated molecular patterns, PRR – pattern recognition receptors, PSGL-1 – P-selectin glycoprotein ligand-1, SR-B1 – scavenger receptor class B, type 1, TGF-β – transforming growth factor β, TLR – toll-like receptor, TNFα – tumor necrosis factor α, tPA – tissue plasminogen activator, TXA2 – thromboxane A2, uPA – urokinase, VLA-4 – very late antigen-4 (integrin α4β1), VEGFR1/2/3 – VEGF receptor 1/2/3, VLDL – very low-density lipoproteins.

Increased oxidative stress, primarily due to an overproduction of ROS, is recognized as a key mechanism in the development of ED. The aberrant synthesis of vasoactive molecules caused by this oxidative stress further raises the risk of CV disease and impairs vasoregulation [9]. Vessel constriction results from an imbalance brought on by decreased secretion of vasodilatory factors and a predominance of vasoconstrictive ones. If this imbalance persists for a long time, total peripheral resistance may rise, raising blood pressure (BP) throughout the body [10]. This assertion is supported by studies in animal models that examined the consequences of eNOS gene deletion and chronic inhibition of NO synthesis with Nω-nitro-L-arginine methyl ester, both of which were found to induce arterial hypertension [11-13]. However, the relationship between ED and hypertension is complex, potentially forming a vicious cycle where high BP exacerbates ED through increased shear stress on endothelial cells, thus highlighting the importance of antihypertensive therapy to mitigate this process [11].

Virchow's triad is a renowned concept in medicine regarding the formation of thrombosis. It is a combination of three factors that underlie the development of blood clots within the blood vessels. Those three primary factors are endothelial dysfunction or damage, altered blood flow, and intrinsic hypercoagulability. In ED, the balance between prothrombotic and antithrombotic factors is often disrupted, necessitating pharmacological intervention to restore homeostasis [14, 15]. Initiated by the unpacking of a vascular emergency kit, the release of Weibel-Palade bodies (WPB) occurs. WPB are secretory organelles found in endothelial cells lining the intima of arteries, capillaries, veins, and the endocardium. WPB store factors regulating vascular hemostasis—the release of WPB leads to an increase in local serum levels of von Willebrand factor (vWF) and elevated presence of P-selectin on the surface of activated ECs [15, 16]. An increase in vWF levels is implicated in thrombotic events, whereas P-selectin facilitates the initial recruitment of leukocytes to sites of injury or inflammation [17, 18]. P-selectin also plays a significant role in the development of arteriosclerotic vascular disease [17, 19], though the direct link between WPB exocytosis and atherosclerotic plaque formation requires further elucidation.

Angiogenesis disruption is another consequence of ED. Age-related ED may cause endothelial apoptosis in the microvasculature, impair the function of endothelial progenitor cells (EPCs), and downregulate vascular endothelial growth factor (VEGF), a crucial regulator of angiogenesis across various tissues [20]. Cardiovascular diseases (CVDs), such as coronary artery disease, can diminish the function and number of circulating EPCs. Moreover, disruptions in angiogenesis within the context of CVD pose significant risks, as they may hinder the formation of compensatory circulation, thereby limiting blood supply to cardiac muscle cells. The impact of angiogenesis disturbances is also pronounced in cancer, where hypoxic or damaged cancer cells release VEGF in a paracrine manner. It is believed that the majority of EPCs originate from the CD133+ hemangioblast stem cell

population, mobilized into circulation in response to VEGF or granulocyte-macrophage colony-stimulating factor [21].

ED serves as a foundational step in the progression of arteriosclerotic vascular disease, playing a pivotal role in its development. Conditions such as hypertriglyceridemia, dyslipidemia, and diabetes mellitus are well-established contributors to ED. In the context of ED, the increased surface expression of adhesive molecules due to inflammation and oxidative stress amplifies the influx of immune cells, exacerbating atherogenesis [21]. This process is characterized by chronic dysregulation of adhesion molecules, allowing immune cells to bypass the cell migration barrier. Additionally, receptor dysregulation and secretion imbalances are implicated in the onset of metabolic disorders, including obesity, insulin resistance, dyslipidemia, cognitive impairment, diabetes, and fatty liver disease [7]. The consequences of ED are illustrated in **Figure 2**. In inflammatory conditions, ED arises from a complex interplay among the endothelium, pro-inflammatory cytokines, circulating lipids, platelets, and traditional CV risk factors. Endothelial cells can be activated by these substances directly or indirectly, which compromises their functionality and promotes a pro-atherogenic state. Subclinical vascular damage and the development of clinically evident cardiovascular disease are the final results of this state.

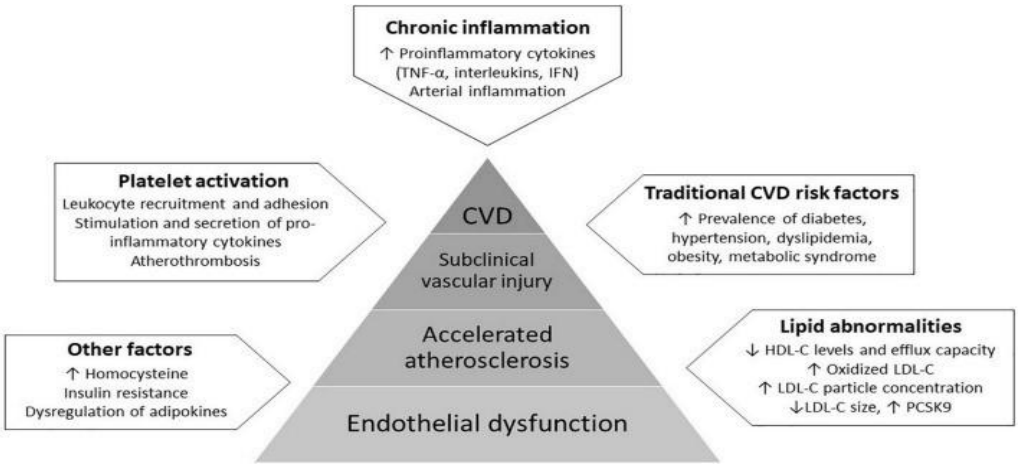


Figure 2. Outline of the clinical and pathophysiological repercussions of endothelial dysfunction. The image is sourced from Anyfanti *et al*. [22]

CONCLUSION

The relationships highlighted indicate that in ED, the processes described above are compromised to varying extents. Atherosclerosis, hypertension, dyslipidemia, and altered coagulation system characteristics are all significantly linked with CVD. Consequently, addressing ED through pharmacological therapy indirectly targets these conditions, enhancing the quality of life and survival rates of affected individuals. ED not only represents a CV risk in itself but also maintains strong associations with other CV conditions. The endothelium is thought to be one of the most significant organs in the human body, and almost any illness may cause it to malfunction. It is impossible to overestimate the importance of this organ in preserving physiological homeostasis, and researchers, health professionals, and non-health professionals alike ought to pay it greater attention.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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