Journal of Biomedical Sciences
Research Article Peer-review, Open Access

The Role of Vascular Endothelial Dysfunction in the Development of Inflammatory Periodontal Diseases

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Relevance: Insufficient formation of various biologically active substances in the endothelium, leading to an imbalance of these substances, is called endothelial dysfunction (ED). This term describes numerous changes in the functional status of the endothelium that occur in response to external stimuli. However, gradual and permanent disruption of endothelial function occurs with prolonged exposure to damaging factors. ED is considered a condition in which the endothelium is unable to produce nitric oxide (NO) in sufficient quantities. Insufficient NO production is considered the main sign of ED, since NO is the most sensitive factor to damage and plays an important role in the regulation of virtually all endothelial functions. Inflammatory processes and atherosclerosis are among the many pathological conditions caused by this imbalance in NO production. In the modern scientific community, the endothelium is considered dynamic, heterogeneous and widespread. It performs the most important tasks for maintaining the body's homeostasis. The endothelium is involved not only in secretory and synthetic processes, but also in metabolism and immune protection. Its cells can synthesize NO, which regulates vascular tone and blood pressure. The endothelium is also involved in metabolism, regulating lipid and carbohydrate metabolism and promoting the immune response, protecting the body from inflammation and pathogens [2.4.6].

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Currently, a huge amount of experimental data has been accumulated, which allows us to identify a number of basic functions of the endothelium. Firstly, angiogenesis, the process of formation of new blood vessels, necessary for tissue growth and healing, depends on the endothelium. Secondly, the endothelium regulates the level of lipids in the blood and prevents the development of atherosclerosis. Thirdly, the endothelium is responsible for maintaining the balance between the narrowing and dilation of blood vessels, which is necessary to maintain normal blood pressure. Finally, the endothelium regulates the hemocoagulation potential of blood plasma, maintaining the balance of blood coagulation and thinning processes; this is vital for maintaining normal blood circulation and preventing thrombosis.

The endothelium also performs an important transport function, transferring substances from both sides between the blood and other tissues. Transport of substances through the endothelium is carried out using active and passive mechanisms, ensuring the maintenance of homeostasis and the removal of metabolic products. In addition to the transport function, ET plays an important role in the reception of signals regulating various processes in the body. This is due to the fact that endothelial cells have unique receptors for various cytokines and adhesion proteins. Expressing a variety of molecules on their surface, endothelial cells play a key role in the regulation of inflammatory processes and the immune response. These molecules, acting as receptors, provide adhesion of leukocytes to the endothelium, as well as their subsequent transmigration through the vessel wall [3.5].

Inflammation can manifest itself as a small focus or a large area covering large areas of tissue. It can be not only focal, but also spread over a larger area or even the entire organ. In some cases, inflammation can lead to systemic inflammation, such as vasculitis or systemic lupus erythematosus. Even localized inflammation can cause systemic reactions affecting the entire body, which makes it difficult to distinguish systemic inflammation from localized. For example, an increase in body temperature, changes in blood composition, and other systemic manifestations can be caused by local inflammation [1.7.9].

The inflammatory process localized in the histion (connective tissue) is a multi-stage phenomenon characterized by a sequential change of phases, each of which has unique features and mechanisms of development:

Alteration: This is the injury of cells and tissues at the beginning of the inflammatory process. Physical, chemical and biological agents are among the many sources of alteration. Damaged cells release prostaglandins and cytokines, some of the inflammatory mediators that trigger a series of inflammatory reactions. At this stage, the first damage to cellular structure and function occurs. This gives reason to expect further inflammatory changes.

Exudation: The next stage involves the release of blood cells, fluid, and proteins from the vessels into the surrounding tissues. Increased permeability of the vascular wall during inflammation allows immune cells, such as neutrophils and macrophages, to penetrate into the damaged tissues, accompanied by exudation. These cells play a key role in protecting the body by phagocytosis of pathogens and removal of dead cells. In addition, they secrete additional inflammatory mediators, which contributes to an enhanced immune response [6.8.10.12.14].

Proliferation: Active proliferation of cells, more often hematogenous and histiogenic, less often parenchymatous and epithelial, characterizes the final phase of inflammation. Proliferation improves the healing of damaged tissues and eliminates inflammatory foci. The following processes occur at this stage: active cell division, synthesis of matrix proteins and creation of a new vascular network. Proliferative processes contribute to the completion of the inflammatory process, restoring the structure and function of damaged tissues.

The endothelium plays an important role in the regulation of vascular tone, blood clotting, inflammatory reactions, and other processes. Endothelium-dependent vascular relaxation is a mechanism by which endothelial cells release substances such as NO, prostacyclin, and endothelial hyperpolarizing factor (EDHF), which cause vasodilation and a decrease in blood pressure. In hypertension, ED is observed, i.e., a violation of its ability to produce a sufficient amount of vasodilators and / or excessive production of vasoconstrictors. This leads to an increase in vascular tone, an increase in peripheral resistance and, as a result, an increase in blood pressure [1.5.7].

One of the mechanisms leading to ED in hypertension is an increase in intracapillary pressure, which occurs following an increase in systemic arterial pressure. This creates additional mechanical stress on endothelial cells, which leads to their damage and dysfunction. The damaged endothelium produces fewer vasodilators and more vasoconstrictors, such as ET -1, which contributes to a further increase in arterial pressure and the formation of a vicious circle.

Further studies have shown that ED is not only a consequence, but also a cause of the development and progression of hypertension. In patients with metabolic syndrome, which is characterized by obesity, insulin resistance, and dyslipidemia, there is a violation of endothelial function even before the development of hypertension. This violation contributes to the development of atherosclerosis, thrombosis, and other cardiovascular complications.

The formation of radicals, especially superoxide anion, stimulates the increase in intramural pressure. This radical bond binds to endothelium-produced NO and leads to the formation of peroxynitrite, which has a cytotoxic effect on endothelial cells and stimulates mitogenesis of smooth muscle cells. As a result of this radical bioavailability, it was pulled out. NO and prostacyclin lead to the formation of vasoconstrictor factors. Thus, in ED, the formation of these components increases, in particular ET-1, thromboxane A2 and prostaglandin H2. In addition, increased formation of angiotensin II promotes vasoconstriction and an increase in the synthesis of ET-1.

The key function of the endothelium of postcapillary venules is to initiate and ensure the migration of leukocytes from the bloodstream into tissues to the site of potential damage or infection. However, when the endothelial layer is damaged, leukocyte migration is disrupted, which leads to platelet activation. Platelets, using adhesion molecules, attach to exposed collagen fibers of the vascular wall, forming aggregates called "rosettes". These "rosettes" are able to penetrate through the damaged endothelium into the site of inflammation, performing their protective functions. This process is necessary to enhance the inflammatory response and the participation of platelets in the body's immune reactions. The formation and migration of such cellular complexes increases the efficiency and rate of healing of damaged tissues, ensuring the delivery of necessary cells and substances to the site of inflammation.

Moreover, normal functioning of the endothelium and its interaction with platelets and other blood cells plays a critical role in protecting the body from infectious agents and various damaging factors. In addition, endothelial cells are indispensable in the process of inflammation and tissue repair after injury, because they play an important role in the regulation of vascular tone, coagulation and maintenance of homeostasis. Endothelial damage causes a protective reaction of the body, including activation of blood coagulation and vasospasm to prevent blood loss. However, under pathological conditions, this reaction can cause or worsen the course of the disease. Several main factors determine the prevalence of aggregation and vasoconstriction. The first step is a decrease in the secretion of substances that prevent aggregation, coagulation and vasoconstriction. Secondly, under such conditions, the endothelium increases the release of aggregants, coagulants and vasoconstrictors. Interaction of ET-1 with ET-B receptors suppresses apoptosis of mature dendritic cells. Blockade of these receptors leads to increased sensitivity of dendritic cells to apoptosis, which impairs their ability to present antigens and produce IL-12.

ET-1 promotes adhesion and rolling of leukocytes along the walls of blood vessels, which is the initial stage of their migration to the site of inflammation. This process is ensured by the interaction of ET-1 with two types of receptors on the surface of endothelial cells: P-selectin receptors and ET-B receptors. P-selectin binds to carbohydrate ligands on the surface of leukocytes, ensuring their primary adhesion to the vessel wall. ET-B receptors, in turn, are G-protein-coupled receptors, the activation of which leads to a number of intracellular signaling cascades that enhance the expression of P-selectin and other adhesion molecules.

Studies have shown that blocking P-selectin receptors or ET-B receptors with specific antibodies or antagonists results in a significant reduction in leukocyte rolling and adhesion. For example, animal experiments have shown that administration of antibodies against P-selectin prevents the development of an inflammatory reaction in vessels after ischemia-reperfusion.

ET, a potent vasoconstrictor peptide ten times more potent than angiotensin II, plays an important role in regulating vascular tone. However, its effect on the body is ambiguous and concentration-dependent.

Normally, at physiological concentrations, endothelin performs an important function of maintaining vascular homeostasis. By binding to endothelial receptors, it stimulates the production of vasodilators, promoting vasodilation and lowering blood pressure. This helps maintain normal blood flow and ensure adequate blood supply to organs and tissues.

However, in pathological conditions accompanied by endothelial damage, such as atherosclerosis, inflammation or trauma, endothelin levels can increase significantly. Under such conditions, ET begins to interact not only with endothelial receptors, but also with receptors of vascular wall smooth muscle cells. This leads to activation of signaling pathways that cause smooth muscle contraction and vasoconstriction, which in turn contributes to increased blood pressure and impaired blood supply to organs and tissues [1.4.7.9.13.14].

ET-1 plays an important role not only in the regulation of vascular tone, but also in the modulation of inflammatory processes. It is able to affect lymphocytes, changing their ability to produce cytokines, which are key mediators of inflammation. ET-1 production is enhanced by a variety of factors, including proinflammatory cytokines such as TNF-α and IL-1, as well as thrombin, vasopressin, and angiotensin II. This leads to increased expression of endothelin mRNA and its receptors, which in turn enhances the inflammatory response. It is interesting to note that inflamed gums are also characterized by high immunoreactivity to ET-1, which indicates its active participation in the pathogenesis of inflammatory periodontal diseases.

Although ET-1 has the ability to attract neutrophils and monocytes to the site of inflammation by acting as a chemoattractant, its effect on the migration of these cells is significantly weaker compared to other chemokines such as IL-8 and MCP. They are produced by various cells in response to inflammation or infection and create a concentration gradient that directs leukocytes to the site of injury. In contrast to these chemokines, ET-1 exhibits a weaker chemotactic effect on leukocytes. Activation of these receptors leads to a number of intracellular signaling cascades that can have both a stimulatory and inhibitory effect on leukocyte migration.

Thus, ET, being one of the key regulatory peptides, plays a multifaceted role in the body, participating in various physiological and pathological processes. In the context of periodontal diseases, ET acts as an active participant in the complex interaction between pathogenic microorganisms, periodontal defense mechanisms and the immune system.

In particular, in periodontal diseases, ET is an active participant in the complex interaction between pathogenic microorganisms, periodontal defense mechanisms, and the immune system. Periodontopathogenic bacteria, such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans, produce a variety of virulence factors that can damage periodontal tissues and activate the immune response.

Conclusion. In response to bacterial invasion, innate and adaptive immune cells migrate to the site of inflammation and begin to produce proinflammatory cytokines such as IL-1, TNF-α, and IL-8, as well as lytic enzymes such as matrix metalloproteinases. These molecules play an important role in protecting the body from infection, but their excessive production can lead to damage to the periodontal tissues. ET, in turn, enhances the inflammatory response by stimulating the production of proinflammatory cytokines and chemokines, which attract additional immune cells to the inflammation site. In addition, endothelin contributes to the disruption of microcirculation in periodontal tissues, which leads to hypoxia and disruption of tissue trophism, aggravating the inflammatory process.

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