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Endothelial Dysfunction: Association with Age, Diagnosis, Treatment

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Abstract

Age is one of the key risk factors for the development and progression of many chronic non-communicable diseases, the most common of which are cardiovascular disease. It is believed that Endothelial Dysfunction (ED) underlies premature aging and the development of associated with age diseases. Despite the large number of studies in this area, it is still unclear when exactly it is necessary to start screening patients for ED and what data should be used to select and prescribe therapy to improve ED. In this review, we will briefly present up-to-date information that may be useful in physician clinical practice for identifying and managing patients with ED.

Keywords: Endothelial dysfunction; Oxidative stress; Proinflammatory state; Diagnostic tools; Treatment; Cardiovascular disease; Aging; Reactive oxygen species; Antioxidant therapy; Type 2 diabetes mellitus

Abbreviations: ACE: Angiotensin Converting Enzyme; CAM: Cell Adhesion Molecules; CVD: Cardiovascular Disease; CVR: Cardiovascular Risk; EC: Endothelial Cell; ED: Endothelial Dysfunction; eNOS: Endothelial Nitric Oxide Synthase; FMD: Flow-Mediated Vasodilation; ICAM-1: Intercellular Adhesion Molecule-1; Nrf2: Nuclear Factor Erythroid-2 Related Factor 2; OS: Oxidative Stress; ROS: Reactive Oxygen Species

Background

Endothelial Dysfunction (ED) is an imbalance between the systems of homeostasis regulation, vascular tone, mediators of anti and procoagulation, that characterized by decreased vasodilation, proinflammatory state and prothrombotic manifestations. All these changes lead to vascular inflammation, impaired tissue perfusion, decreased vascular function and subsequently to aging rates acceleration and the development of age-related diseases, which mainly include Cardiovascular Disease (CVD) in general population, and frailty and sarcopenia in older patients [1]. On the other hand, speed-up in aging and the emergence or progression of mentioned diseases contribute to the severity of ED, which creates a vicious circle. Such close links between ED, CVD and aging are due to common Cardiovascular Risk (CVR) factors, such as bad habits, insulin resistance, hyperglycaemia, dyslipidemia, high blood pressure, etc., and common key pathogenic mechanisms, namely development of Oxidative Stress (OS) and pro-inflammatory state.

CVR factors against the background of physiological aging processes contribute to the violation of redox balance and the development of low-grade inflammation in blood vessels. Affected Endothelial Cells (ECs) release inflammatory mediators and become prothrombotic, that contributes to the development of ED. ECs are particularly long-lived, so in addition to the deterioration of these cells, there may be an accumulation of damage to both genomic and mitochondrial DNA during their lifetime, which contributes to even greater dysfunction [2]. Since ED can be reversible, early detection and timely treatment of such pathology can prevent the development of accelerated aging rates and age-related diseases, especially CVD. Therefore, in order to increase the effectiveness of ED detection and its elimination in clinical practice it is necessary to understand which category of patients needs screening for ED, which ED markers can be used and which therapy may be the most appropriate.

Risk Factors for Endothelial Dysfunction as Screening Criteria

There are currently no clear search criteria for a category of patients who are at increased risk of ED developing. However, a number of factors can be identified among those that may contribute to the emergence and deterioration of ED such as:

- CVR factors, including the presence of endocrine disorders, CVD, liver and kidney diseases;

- Increased levels of OS markers;
- Increased levels of pro-inflammatory markers;
- Violation of the gut microbiota composition.

The latter mentioned risk factor for ED, namely gut microbiota disturbances, has become relevant in recent years due to improved diagnostic methods. G it is associated with ED indirectly through the development of redox balance disorders and low-grade inflammation, for example, due to bacterial endotoxins [3-4].

Various CVR factors, including behavioral, can cause the development of ED directly or due to the development of OS and inflammation. Thus, smoking was shown to cause oxidative damage, generalized vascular inflammation and ultimately violation of endothelial integrity according to the review found that adverse childhood experiences, psychosocial stressors that occur during sensitive developmental windows, can cause ED in young women [5-6]. A large study of 7682 Asian men found that overweight and obesity compared to normal weight were associated with an increased risk of low-quartile Flow-Mediated Vasodilation (FMD), a marker of ED. Interestingly, the risk of ED was higher in obese young adults than in older obese adults [7].

Moreover, the available data suggest that the patient's age in the presence of CVR factors is not a limiting factor. ED screening may be required not only for patients with pre-existing chronic diseases in the middle-aged or the elderly, but also for relatively healthy young patients, adolescents and even children with certain CVD risk factors. Numerous evidence suggests that CVR factors begin to develop early in life, for example, 57% of today's children are expected to be obese by the age of 35 years, and the prevalence of hypertension among children and adolescents increased by 75% between 2000 and 2015 years [8]. In a study, found that obese 6-9 year old children had elevated levels of ED markers, namely soluble intercellular adhesion molecule-1 (ICAM-1) [9]. Metabolic syndrome was associated with a risk of ED marked by ICAM-1 according to the data of children aged 13-15 years from the Ewha Birth and Growth Cohort Study [10]. In another recent study, healthy non-smoking student volunteers aged 23-27 years were diagnosed with acute significant ED (based on FMD measurements with high-resolution ultrasound) due to consumption of energy drinks [11].

Markers of the inflammatory process include acute phase proteins (C-reactive protein, fibrinogen, serum amyloid A) and cytokines, among which tumor necrosis factor alpha, CD40 ligand, interleukin-1, interleukin-6, interleukin-8 and interleukin-18, monocyte chemotactic protein 1 have a proven role in inflammatory response enhancing, induction of adhesion molecules expression in ECs and deterioration of ED [12]. Moreover, a recent study found that exactly coronary blood flow disorders in patients with chronic systemic inflammatory diseases, namely rheumatoid arthritis, systemic lupus erythematosus and psoriasis, were associated with worse cardiovascular events and all-cause mortality, which further indicates the need for ED screening in patients with prolonged pro-inflammatory conditions [13].

OS is not a pathological condition in case the balance between redox processes is maintained. It is believed that normal levels of circulating free radicals ensure the maintenance of homeostasis, and in the elderly they help with the timely activation of immune, inflammatory reactions of the body to protect against existing damage. Excessive number of free radicals, on the contrary, stimulates the acceleration of aging and the development of new disorders. The function of cells is affected by Reactive Oxygen Species (ROS) which modify proteins through oxidation, sulfenylation, nitrosylation, glutathionylation, carbonylation and phosphorylation. Proteins that are particularly sensitive to redox effects include ion transporters, receptors, signaling molecules, transcription factors, cytoskeletal structural proteins and matrix metalloproteases, all of which are involved in the regulation of vascular function.

There is currently no standard set of OS markers that increase equally in all patients with redox disorders. The known research results indicate a connection between the increase of some specific markers with the presence of certain pathological changes or conditions in the body. But no markers that are always elevated in ED and are associated only with it have been identified. Therefore, any of the OS markers can be an indicator of the probable development of ED. Such markers of OS include:

- High levels of prooxidant pathway components, namely ROS that affect the vascular wall, various sources of ROS such as NADPH oxidase, xanthine oxidase, uncoupled Endothelial Nitric Oxide Synthase (eNOS), myeloperoxidase and lipoxygenase;
- Oxidation products of proteins, lipids, carbohydrates, ribonucleic acids, such as oxidized low-density lipoproteins;
- Low levels of antioxidants (vitamins C and E etc), transcription factor Nuclear factor erythroid-2 Related Factor 2 (Nrf2) or antioxidant enzymes, namely superoxide dismutases (MnSOD, CuZnSOD, EcSOD), superoxide dismutases (MnSOD, CuZnSOD, EcSOD), catalases, glutathione peroxidases, paraoxonases, thioredoxin peroxidases and heme oxygenases [2].

Methods of Endothelial Function Assessment

Modern methods of ED diagnosing can be divided into instrumental (invasive and non-invasive) and biochemical. The most complete information on instrumental diagnostic methods is currently presented in the consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis (2021) [14]. Instrumental diagnostic methods allow to assess the vasomotor function of blood vessels by assessing coronary or peripheral circulation. The gold standard of ED assessment is the determination of coronary epicardial function in both epicardial

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and resistance vessels based on angiographic evaluation of vasodilatory reactions to administered vasoactive substances such as acetylcholine or nitroglycerin. In addition to being invasive and expensive, this method is only employed in patients requiring cardiac catheterization for indications other than ED evaluation. Therefore, currently the most common methods are brachial arterial Low Flow Mediated Constriction (L-FMC), FMD and their composite endpoint vasoactive range, that belong to non-invasive methods that assess peripheral circulation. The technique quantifies the ability of larger conduit arteries to dilate in response to reactive hyperaemia after a brief (5 min) suprasystolic occlusion of the brachial artery using a blood pressure cuff.

But the existence of various protocols (cuff position, duration-magnitude of occlusion, time stamps for post-deflation measurements), as well as significant inter and intra-observer variability, cardiac output dependence and limited quantitative data remain important limitations. Other known non-invasive methods of ED also include venous plethysmography, finger plethysmography and retinal endothelial function. Determination of venous ED in comparison with arterial function evaluation is almost not carried out. Firstly, such an assessment is more complex: the available methods are invasive and have limited reproducibility. Secondly, the assessment of arterial ED provides enough information to get an insight of the different areas of the arteries and the functional state of the veins, because ED is a systemic disorder. Finger plethysmography based on the recording of finger arterial pulse amplitude by pneumatic probes after reactive hyperemia induction similarly to the FMD technique and the index between the examined and the control arm is calculated. Retinal endothelial function assessment via provocation with flicker light has been recently proposed since vasoreaction is partially dependent on NO. A number of studies have also used the measurement of epicedial fat thickness, carotid-intima media thickness, arterial stiffness, peripheral arterial tonometry, laser doppler flowmetry, pulse wave velocity and anklebrachial index as non-invasive methods of assessing endothelial function [14-16].

As endothelial functions are diverse, there are many biomarkers that reflect dysfunction of various endothelial properties. Despite the high potential of such biomarkers, there are still no standardized chemical tests and protocols for the evaluation of ED. Therefore, biochemical markers of ED are currently used only in clinical trials. In general, the endothelial proinflammatory phenotype, which indicates the development of ED, is characterized by increased expression of soluble Cell Adhesion Molecules (CAMs), which include E-selectin previously referred to as endothelial-leukocyte adhesion molecules-1, P-selectin, ICAM- 1 and vascular cell adhesion molecule-1. CAMs are the most common markers of ED in clinical trials. However, because most of these CAMs are produced not only by the endothelium due to inflammation but also by leukocytes and platelets, these molecules are not specific biomarkers of endothelial damage and have limited diagnostic value as stand-alone markers of ED. One of the classic markers of ED is also molecules involved in blood clotting, especially von Willebrand factor and soluble thrombomodulin.

Procoagulant marker of endothelial activation can be the ratio between tissue plasminogen activator and its endogenous plasminogen activator inhibitor-1. Potential markers of ED also include asymmetric and symmetric dimethylarginine, endothelial progenitor cells, endothelin-1, circulating microRNAs, as well as increased levels of monocytes and circulating endothelial microparticles released from different plasma cells. as erythrocytes, leukocytes, platelets and endothelial cells. New circulating biomarkers of ED include endoglin, or CD105, and endocan, or endothelial cell-specific molecule-1 [16-18]. The sensitivity and specificity of the determination of individual markers of ED may also depend on the age of the patient. Thus, it was found that miR-122 expression was significantly lower in young patients (up to 40 years) compared to patients ≥40 years and was associated with the risk of ED [19].

Therapeutic Strategies for the Treatment of Endothelial Dysfunction

Existing therapeutic approaches for the correction of ED can be divided into recommendations for lifestyle adjustment and the appointment of drug therapy. Lifestyle adjustments include excluding bad habits, especially smoking, avoiding a sedentary lifestyle, dietary correction, which in addition to a balanced diet and adherence to the regime also includes recommendations for the inclusion of food products rich in antioxidants such as vitamin C, E, flavonoids [2,12,17]. According to the data of recent studies, special attention among flavonoids is paid to quercetin because of its high potential for eliminating ED, due to its beneficial effects on the cardiovascular system, antioxidant effect and proven senolytic activity [18].

Drug therapy is usually secondary, as there are currently no drugs whose primary purpose is to improve endothelial function. Therefore, the existing drugs are aimed at eliminating or reducing the ED risk factors, namely at the prevention of CVR factors or their elimination/reduction; oxidative state reduction; gut microbiota function improvement. The first group of drugs can be distinguished in lipid-lowering therapy, antihypertension drugs, anti-diabetic drugs, anti-inflammatory treatment of patients with systemic inflammatory disorders, antiplatelet drugs.

Thus, it was found that the use of statins, fenofibrates and PCSK9 inhibitors may improve function among lipid-lowering therapy. Statin-induced improvement in both peripheral and coronary endothelial function is independent of lipid-lowering effect and based on the anti-inflammatory and antioxidant properties. Fenofibrate (peroxisome proliferator-activated receptor alpha agonist) may improve endothelial function through

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the increase of NO production, decrease of superoxide anion levels, and activation of eNOS and adenosine monophosphate-activated protein kinase phosphorylation [12]. PCSK9 inhibitors (namely evolocumab) also have antioxidant properties and may improve ED [2].

A number of antihypertensive drugs have already been tested in clinical settings to assess changes in endothelial function. Angiotensin Converting Enzyme (ACE) inhibitors (namely perindopril) can diminish the inactivation of bradykinin, thus leading to an augmentation of NO release, and prevent pathological vasoconstriction of the coronary arteries. Calcium channel blockers, β-blockers, and thiazide diuretics are less effective in improving ED than ACE inhibitors. Among β-blockers nebivolol is the only one known to reverse ED by inducing vascular production of NO. Renin inhibitors (namely aliskiren) also significantly improve ED through the increasing plasma NO bioavailability [17].

Most drugs for the type 2 diabetes mellitus treatment affect vascular function either by acting directly on the endothelium or indirectly by improving blood glucose level, insulin resistance and OS. For example, sulfonylureas have a neutral or moderate effect on the vascular system, probably due to improved glycemia; metformin improves endothelium-dependent vasodilation, restores femoral artery blood flow and insulin-mediated microvascular perfusion, as well as decreases blood concentrations of inflammation markers; thiazolidinediones activate the peroxisome proliferator-activated receptor gamma, thereby enhancing NO-dependent endothelial function; glucagon-like peptide-1 receptor agonists vasodilate conduit arteries and increase microvascular perfusion, but it is still unknown whether the effects of this group of drugs on oxidative stress and inflammation are expected; dipeptidyl peptidase-4 inhibitors reduce ROS and inflammatory cytokine expression, show inconsistent NO-dependent vasodilation; sodium glucose cotransporter-2 inhibitors provide indirect or off-target endothelium benefits, namely improve endothelium-dependent vasorelaxation and microvascular perfusion, restore NO bioavailability, abolishe increased ROS, preserve glycocalyx integrity, increase heparan sulphate synthesis and restore mechanotransduction response of endothelial cells with damaged glycocalyx [12,19].

Among anti inflammatory tofacitinib, imatinib and zafirlukast was found to ameliorate ED. Although while increasing lipid levels tocilizumab was found to increase endothelial glycocalyx thickness and to reduce arterial stiffness. Antiplatelet drugs that were proved to prevent endothelial include vorapaxar (antagonist and Protease Activated Receptor 1 (PAR-1) inhibitor), ticagrelor (P2Y12 inhibitor) [12].

Antioxidant therapy includes mitochondrial-targeted therapies aimed at antioxidants (as ubiquinol or α-tocopherol) to the mitochondria; enzymatic systems or cell-permeable cationic peptides (Szeto-Schiller peptides) directed to the mitochondria, mitochondrial protein p66Shc; as well as Nrf2 activators; Nox inhibitors and recouplers of eNOS. Other drugs that can potentially reduce ED mainly due to improved redox balance are serotonin, sanguinarine (selenoprotein P inhibitor), cell-permeable peptides mimicking the kinase inhibitor region of Cytokine Signaling Suppressor-1 (SOCS1) regulatory protein, plant-derived compounds such as polyphenols (known to inhibit arginase activity), resveratrol and Phyllanthus emblica fruit aqueous extracts [2, 12]. According to the review, therapies that can reduce ED due to exposure to intestinal microbiota include probiotic interventions for a minimum of 4 weeks and other compounds such as Berberine, Curcumin, Chlorogenic acid, Luteolin and Sulforaphane [4].

Summary

In summary,

1) The emergence and deepening of ED is associated with the aging acceleration and the development of age-related disorders due to the common risk factors and pathogenetic mechanisms of development;

2) Early detection and timely correction of ED can reduce its manifestations, thereby reducing the speed of aging and the risk of age-related diseases;

3) Screening for the presence of ED is not limited to the age of the patient and is necessary in case of the detection of CVR factors, prolonged pro-inflammatory state, severe redox disorders and disorders of the intestinal microbiota in patients;

4) A set of non-instrumental methods of diagnosis in combination with biochemical markers of ED can be used for the assessment of ED; patient's age and existing pathological disorders must be taken into account when choosing evaluation methods;

ED can serve as an additional criterion for the need of lifestyle adjustment recommendations and appointment of the appropriate drug therapy (antilipidemic, antihypertensive, etc.) in patients with various pathological conditions.

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