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Endothelial Dysfunction: The Physiological Gateway to Heart Disease

Aqsa Shahid, Alishbah Roobi, Wania Nasir*, Hina Pervaiz, Ayesha Waris and Rida Sarwar

Department of Physiology, The University of Faisalabad, Pakistan

*Corresponding Author: wanianasir.physio@tuf.edu.pk

ABSTRACT

The physiological basis of endothelial dysfunction has long been understood as an early physiological derangement which lies at the root of cardiovascular disease (CVD) progression. It aimed to understand the physiology, clinical implications, and treatment of endothelial dysfunction. It had been found that deficits in nitric oxide (NO) availability, oxidative stress, and inflammation and eNOS dysfunction had been part of the process leading to vascular injury, atherosclerosis and arterial stiffness. Clinical evidence has revealed endothelial dysfunction prior to the development of CVD and its association with a high risk of CHD, stroke and cardiovascular incidents. These diagnostic techniques, such as flow-mediated dilation and endothelial biomarkers, had helped in identifying early risks, and lifestyle and pharmacologic approaches had helped enhance endothelial function.

Keywords: Endothelial dysfunction, Cardiovascular Disease, Nitric oxide, Oxidative stress, vascular health, Atherosclerosis

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Introduction

Dysfunction of endothelium is one of the early manifestations of vascular diseases before any other manifestations appear. It used to be regarded as a simple physical barrier that separates the blood from tissues. Nowadays, it is perceived as an endocrine organ performing regulation of functions like vasodilation, inflammation, platelets' activation and vascular remodeling. Endothelium of a vessel performs the function of maintaining homeostasis of vascular system by producing certain substances which provide protection of vessels – in particular, NO which causes vasodilation, anti-inflammatory action and antithrombotic effects. Occurrence of endothelial dysfunction becomes the major physiological gate through which cardiovascular risk factors like hypertension, diabetes, obesity, smoking and dyslipidaemia influence the vascular system [4]. Production of ROS in excessive amounts, occurrence of inflammation and decline in the activity of eNOS result in the inflammation of vessels and further in their atherosclerosis and stiffness [5]. Modern scientific advances highlight the importance of endothelial dysfunction as an essential pathogenetic pathway between metabolic syndromes and serious cardiovascular diseases like coronary artery disease, stroke, heart failure and peripheral vascular disease [6, 7].

Physiological Mechanisms and Causes of Endothelial Dysfunction

Endothelium, known as a metabolically active organ, regulates the functions of cardiovascular system controlling vascular tone, inflammatory response, coagulation, and arterial remodeling [8]. In the physiological state, endothelial cells support vascular integrity because of their ability to produce NO, prostacyclin, and other vasodilators. The interruption of these processes results in endothelial dysfunction and, therefore, causes NO unavailability, oxidative stress, and vascular inflammation that become pro-thrombotic [9]. Nowadays, it is known that the process of eNOS uncoupling plays the role of molecular mechanism of endothelial dysfunction because due to the absence of such cofactors as tetrahydrobiopterin (BH4), eNOS is not able to synthesize NO but superoxide radicals [10]. Heo et al. discussed in their 2025 article that decreased NO signaling, ROS overproduction, chronic inflammation, and abnormal blood flow patterns play the role of important mechanisms linking endothelial dysfunction with atherosclerosis, hypertension, heart failure, and stroke [11]. Despite all progress in medicine, cardiovascular disorders remain the leading cause of mortality in the world taking 17.9 million lives per year and accounting for 32% of deaths [12].

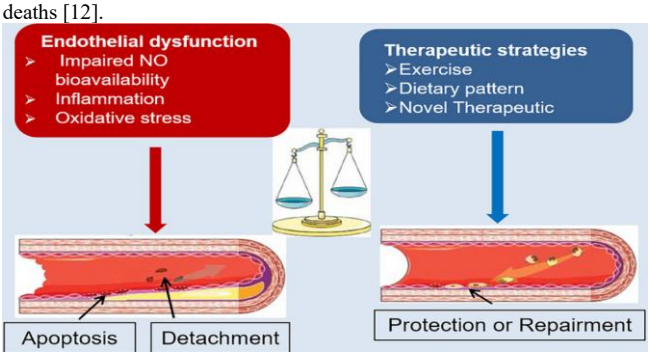

Fig. 1: Endothelial Dysfunction Mechanism Source: [13]

As seen in Figure 1, endothelial dysfunction is caused by a combination of deficiency of nitric oxide, inflammation, oxidative stress, and attempts for vascular protection and endothelial healing [13]. Main cause of this phenomenon is an oxidative stress, which happens because of mitochondrial dysfunction, NADPH oxidase activity, and antioxidant defense system inhibition, resulting in excessive production of ROS. These reactions result in destruction of nitric oxide, which is being turned into toxic peroxynitrite [14]. There are newly found effects of oxidative stress, which affect the activity of key antioxidants such as SOD, GPx, and thioredoxin [15]. The reduction of antioxidant potential, in combination with the activation of NLRP3 inflammasome, causes damage to the endothelium and maintains the inflammation [16]. The findings of the study conducted within the 2025 African-PREDICT trial among 1,196 healthy young people aged 20-30 show strong associations between cardiovascular risk factors and markers of endothelial activation, oxidative stress, and inflammation [17]. Moreover, metabolic disorders have also a great effect on this condition because there are more than 800 million of people suffering from diabetes and therefore the cardiovascular disease risk increases in them two to four times [18]. In addition to the above cellular mechanisms, classical risk factors such as hypertension, obesity, smoking, dyslipidaemia, and aging have been identified as potential contributors to endothelial dysfunction [19]. Hypertension can affect endothelial function through mechanical stress, shear force alteration, and increased ROS production [19]. Over 1.28 billion individuals between the ages of 30 and 79 have been diagnosed with hypertension, which is one of the primary causes of impaired vasculature [20].

Endothelial Dysfunction as a Driver of Cardiovascular Disease Development

The contribution of the endothelial dysfunction in the development of cardiovascular diseases is considerable owing to the fact that the vascular endothelium becomes the barrier leading to the inflammatory and oxidative stress rather than to the barrier against them [22]. Endothelial cells typically play the part of regulating the vasomotor tone and protecting from the thrombotic effects through the synthesis of NO. However, the reduction of NO, increased permeability of the endothelium, oxidative stress, and inflammation cause atherogenic processes and contribute to the vascular damage [23]. The injured endothelial cells enable the entrance of ox-LDL into the vascular wall; as a result, the monocyte adhesion takes place and foam cells emerge. In the study carried out in the context of the Multi-Ethnic Study of Atherosclerosis (MESA) including 6,814 adults it was found that FMD as the sign of endothelial dysfunction is the independent predictor of higher coronary artery calcification, which confirms the role of the endothelial dysfunction in the development of cardiovascular diseases [24]. The same results were received in the Framingham Heart Study of 2024 involving 3,119 participants [25].

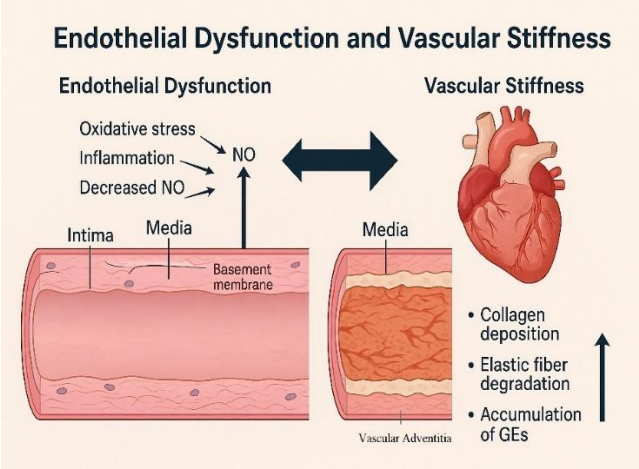

Figure 2: Endothelial Dysfunction and Vascular Stiffness Source: [26]

Endothelial dysfunction leads to vascular stiffness whereby reduction in nitric oxide bioavailability, oxidation, and inflammation lead to the modification of the vessel wall structure as shown in figure 2 below. Deposition of collagen, degradation of elastic fibers, and accumulation of advanced glycation end products lead to stiffening of the vessels. Endothelial dysfunction is not only associated with atherosclerosis, but also leads to other pathologies such as hypertension, thrombosis, myocardial infarction, heart failure, and ischemic stroke. Reduced production of NO and endothelin-1 leads to increased vascular resistance and blood pressure, while inflammatory mediators and adhesion molecules (VCAM-1 and ICAM-1) cause plaque instability and plaque formation [26]. In a longitudinal study done on the UK biobank among over 10,000 adults, biomarkers of endothelial dysfunction have been found to be significantly related to coronary heart disease and stroke, independent of cardiovascular risk factors [27]. A meta-analysis of more than 35,000 individuals showed endothelial dysfunction to be strongly associated with cardiovascular events such as myocardial infarction, stroke and cardiovascular death [28].

Diagnosis, Prevention and Therapeutic Approaches Targeting Endothelial Dysfunction

Early detection of endothelial dysfunction is vital because vascular dysfunctions usually develop several years before the appearance of clinical symptoms of cardiovascular disorders and allow intervention on time [29]. Detection of vascular dysfunctions includes both functional and molecular assessments which are used for diagnosing vascular abnormalities without doing harm to patients. Brachial artery flow-mediated dilation is currently used more frequently than other noninvasive methods of diagnosing because it measures NO-dependent vasodilation of blood vessels [30]. The systematic review and meta-analysis of 35 articles with 17,280 participants showed that low values of FMD independently predict cardiovascular disorders as each additional percent in FMD decreases cardiovascular risk by 12% [31]. Moreover, another meta-analysis involving nine studies and 943 participants demonstrated that patients with coronary heart disease have significantly lower values of FMD in comparison with control group [32].

Prevention and treatment of endothelial dysfunction rely on restoring endothelial equilibrium using both behavioral and pharmacological approaches. Exercise has been shown to benefit eNOS function, stimulate NO production, decrease oxidative stress and enhance vascular function. [33]. Additionally, the PREDIMED study was conducted in 7,447 people at high risk for developing cardiovascular disease and the results revealed a 30% reduction in the risk of major cardiovascular events in the Mediterranean diet which included extra virgin olive oil or nuts [34]. Giving up smoking, losing weight, improving glycemic control and lowering blood pressure reduce inflammation and damage to endothelial cells. Pharmacotherapy is a key component of lifestyle modification. Statins have been shown to improve endothelial function due to their ability to improve nitric oxide production and reduce inflammation, while ACE inhibitors and ARBs are protective against oxidative damage and vascular remodeling [35]. Other positive actions that can be offered by SGLT2 inhibitors and GLP-1 receptor agonists include. For example, according to the EMPA-REG OUTCOME study, which was conducted in 7,020 people with type 2 diabetes, empagliflozin decreased cardiovascular mortality by 38% [36].

Conclusion

The physiological mechanism which plays a key role in the relationship between heart disease risk factors and heart diseases is endothelial dysfunction. One may notice that according to the information provided above, endothelial dysfunction, which takes place due to a decrease in nitric oxide level, oxidative stress, inflammation, and metabolic disorders, leads to such consequences as atherosclerosis, blood vessel disorders, and thrombosis What makes the mentioned evidence important is the fact that the dysfunction of endothelium occurs much earlier than heart diseases do, which makes it a very good target for diagnosis and prevention.

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