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DOI: 10.46903/gjms/16.01.1813

REVIEW ARTICLE

ENDOTHELIAL DYSFUNCTION: A CARDIOVASCULAR RISK FACTOR

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ABSTRACT

Endothelium is one of the largest organ by area and consist of at least one trillion endothelial cells having more than 100 gram weight and covering more than 3000 square meters area in an adult human body. Endothelium interacts with most of the body systems and is implicated in end organ diseases particularly the cardiovascular. The endothelium maintains vascular tone by precisely regulating the vasodilatation and vasoconstriction while effectively providing the adequate supply of blood to the target organs. Factors that affect the endothelium and subsequently cardiovascular system include hypertension, smoking, obesity, hyperglycemia, hyperlipidemia, poor dietary habits and physical inactivity. Endothelial dysfunction is strongly associated with cardiovascular risk factors such as atherosclerosis, elevated level of low density lipoprotein oxidation, cytokine elaboration, up regulation of adhesion molecules, increased cell permeability, platelet aggregation as well as proliferation and migration of vascular smooth muscles. Endothelial dysfunction is a pathophysiological term used to indicate diminished production of nitric oxide and an imbalance in endothelial derived contraction and relaxation.

KEY WORDS: Endothelium; Endothelial cells; Endothelial dysfunction; Atherosclerosis; Hyperglycemia; Hyperlipidemia; Nitric oxide; Reactive oxygen species; Diabetes mellitus; Hypertension.

This article may be cited as: Khan N, Bibi N, Niazi ZR, Shah K, Sherazi SA, Khan S. Endothelial dysfunction: a cardiovascular risk factor [review article]. Gomal J Med Sci 2018 Jan-Mar; 16 (1): 27-30. https://doi.org/10.46903/gjms/16.01.1813

INTRODUCTION

The vascular endothelium is a monolayer of endothelial cells forming the inner lining of all blood vessels including arteries, veins and capillaries as well as lymphatic system. The endothelium is autocrine, paracrine and endocrine organ regulating the vascular tone and maintain the homeostasis.[1,2] The pathophysiological alteration of endothelium results in the endothelium dysfunction, leading to atherosclerosis and plaque formation. It may subsequently lead to imbalance in vasoconstriction and vasodilatation which are associated with an increased risk of cardiovascular disorders.[1,2]

The endothelial dysfunction results in decreased bioavailability of vasodilators, specifically the nitric oxide (NO). It also causes increased level of endothelium-derived contractile factors.[3] This imbalance may lead to the impairments of endothelium-dependent vasodilatation resulting into proliferation, inflammation and coagulation, associated with cardiovascular events.[4]

The cardiovascular risk factors include hypertension, smoking, hyperglycemia, aging, hypercholesterolemia and a family history of atherosclerotic diseases which are concomitant with endothelial dysfunction and cardiovascular disorders[5-7]. These factors are strongly associated with inflammation, thrombosis, vasoconstriction, elevated level of C-reactive protein as well as systemic infections, contributing to cardiovascular events (Figure 1).[8-10]

Keeping in view the direct relationship between endothelial dysfunction and atherosclerosis, the diseased status of endothelium is directly involved in the pathophysiology of various cardiovascular disorders including hypertension, inflammation, generation of reactive oxygen species (ROS), oxidative stress and other vascular abnormalities such as coronary heart disease and pulmonary hypertension. Here in this review we have summarized the literature regarding endothelial dysfunction and cardiovascular disorders.

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Email: zahidscholar1@gmail.com
Date Submitted: 09-01-2018
Date Revised: 29-09-2018
Date Accepted: 02-12-2018

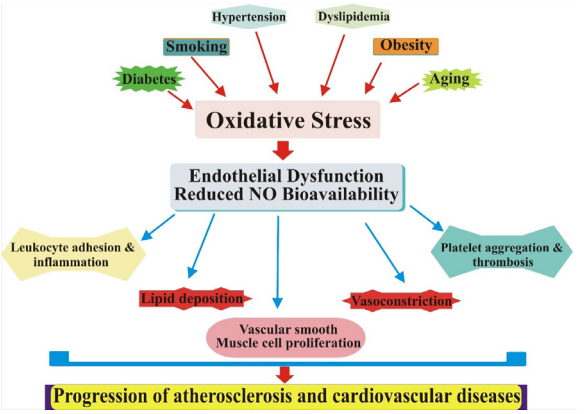

Figure: 1 Different pathological and physiological factors contributing to endothelial dysfunction leading to cardiovascular disorders

DISCUSSION

Under normal physiology, the endothelium maintains the vascular homeostasis by regulating the balance between vasodilation and vasoconstriction. Furthermore the endothelium responds to the numerous intrinsic factors including temperature, sheer stress and transmural pressure as well as extrinsic factors such as mental stress, medication and neurohumoral responses. The vasodilatory response of the endothelium results from the release of nitric oxide (NO) synthesized by the amino acid L-arginine by the enzyme endothelial nitric oxide synthase (eNOS) resulting in the generation of intracellular cyclic GMP in response to sheer stress.[11]

At the site of injury and inflammation, reactive oxygen species (ROS) are generated. These reactive species acts as signaling molecules at low concentration and participate in the regulation of basic cellular activities including cell growth and adaptation. At higher concentration due to increased oxidative stress as a result of several disorders as indicated in figure 1, these reactive species cause the injuries and death of various cells. The vascular endothelium regulates the flow of molecules from the blood stream to tissues, and is the prime victim of the oxidative stress playing critical role in the pathophysiology of several cardiovascular disorders. The oxidative stress enhances the endothelium permeability resulting in leukocyte adhesion, linked with the alteration of endothelial signaling as well as transduction and redox-regulation of transcriptional factors.[12]

Numerous studies report that systemic hypertension as well as salt-sensitive hypertension are associated with endothelial dysfunction due to impairments of L-arginino NO pathway.[13] The impairment of endothelium-derived vasodilatation in primary/ essential hypertension as well in reno-vascular hypertension showed that cyclooxygenase dependent vasoconstriction mechanism is involved in attenuation of endothelium-derived vasodilatation.[14]

Another group of researchers investigated that the patients of essential hypertension have deficits both with increased vascular resistance and impaired response towards endothelial dependent vasodilatation.[15] The same research group further investigated that the patients with endothelial dysfunction in essential hypertension are not only restricted to the muscarinic receptors but also do not respond in the restoration of endothelium by the existing antihypertensive therapy.[16] These investigations revealed that even in primary hypertension, the endothelial dysfunction become irreversible after the establishment of hypertension.[17]

Endothelial dysfunction plays a vital role in the pathogenesis of acute coronary syndrome[18]. Intact endothelium is involved in the plaque destabilization with a complex anticoagulant pathway. The endothelial dysfunction is also associated with the oxidative stress which results in the synthesis of reactive oxygen species (ROS), a central promoter of inflammatory processes.[19] For the diagnosis of coronary endothelial functioning, the noninvasive tests such as Doppler echocardiography (ECHO), phase-contrast magnetic resonance imaging (PMRI) and positron emission tomography (PET) are used. Moreover the gold standard and invasive test is the quantitative coronary angiography which accurately examines the alteration in diameter of coronary arteries in response to intracoronary infusion of acetylcholine which is an endothelium dependent vasodilator. Functioning of the coronary endothelium can be examined by the intracoronary Doppler techniques to measure the coronary blood flow in response to a physiological or pharmacological stimuli.[4,20,21]

The diabetes induced endothelial dysfunction is also associated with an increased risk of cardiovascular events in hyperglycemia. The intracellular depletion of NADPH occurs as a result of redox reaction. In diabetes the overexpression of growth factors have also been reported which results both in the proliferation of endothelial cells and vascular smooth muscles, probably promoting the neovascularization. The non-enzymatic glycation of the macromolecules including proteins are also associated with chronic diabetes.[22]

The diabetic patients have an increased tendency towards oxidative stress resulting in increased level of oxidized lipoprotein particularly the low density lipoprotein (LDL). In case of hyperglycemia and high level of fatty acids, oxidation of phospholipids and proteins has also been reported that may result in the platelet aggregation and prothrombotic tendency. Insulin resistant diabetes are implicated with endothelial dysfunction, supported by the hypothesis “insulin and/ or insulin precursor may be atherogenic.[22]

Thoroughly investigating the literature, it has been

revealed that the diminished concentration of NO synthase to produce NO has been associated with endothelial cells when placed in an in vivo diabetic environment.[23-27] Most of the experimental studies reported that endothelial dysfunction is closely related with atherosclerosis and microangiopathy in diabetes.

CONCLUSION

Dysfunctioning endothelium is the leading cause of various cardiovascular events including hypertension, coronary heart diseases, atherosclerosis, platelet aggregation and so many similar events.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
GRANT SUPPORT AND FINANCIAL DISCLOSURE
None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	NK, NB
Acquisition, Analysis or Interpretation of Data:	NK, NB, ZRN, KUS, SK
Manuscript Writing & Approval:	NK, ZRN, KUS, SAS, SK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.