Endothelial Dysfunction in Cardiovascular Diseases and It's Treatment

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Abstract:

Endothelial dysfunction is described by unbalanced dilation and constriction of blood vessel, elevated reactive oxygen species, and others factors, as well as low level of NO bioavailability. The presence of endothelial dysfunction breaks the barrier permeability that is a portion of inflammatory response in the progress of cardiovascular problems. Acquiring more knowledge into the pathophysiologic mechanisms that fervor atherosclerosis and endothelial dysfunction as well as discovering new biomarkers and treatment approaches to prevent atherosclerosis and endothelial dysfunction and lower the risk of developing CAD and its consequences are all areas of great interest. Novel markers of endothelial activity and dysfunction could have significant therapeutic ramifications. Adhesion molecules of endothelium, cytokines, some reactive proteins, selectin stimulates microparticles, perioxidation of low density lipoproteins, endocan etc are biomarkers of endothelial activation. Endothelial healing can be achieved using pharmacological and nonpharmacological therapy. The former entails lowering body weight, engaging in cardiovascular activity, and limiting salt consumption; the latter involves the use of calcium antagonists, statins, erythropoietin, tetrahydrobiopterin, renin-angiotensin system inhibitors, and certain types of β blockers. These treatments aim to boost NO release and NO synthase activity, prevent NO degradation, and improve endothelial progenitor cell function.

Keywords: Endothelial dysfunction, Nitric oxide, Atherosclerosis, Cardiovascular disease, Mechanism, Biomarkers.

1. Introduction:

Cardiovascular disease is the major cause of death throughout the globe [1]. The most common type is CAD, which is defined by the building up of lipids and cells of immune system in the coronary arteries subendothelial space, also known as atherosclerosis. This process involves the vascular endothelium's inflammatory response [2, 4]. Endothelial cells form a semipermeable unilayer that separates arterial wall from intravascular flow elements. This layer maintains vascular tone, inhibits platelet aggregation, and keeps fluid levels stable. The endothelium generates vasodilator and vasoconstrictor molecules such as NO and endothelin, respectively; an imbalance in the production of these vasoactive substances leads to endothelial dysfunction [3,4,6,7] .This disease is characterized by the imbalance of NO solubility in the blood vessel

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.Endothelial dysfunction contributes to CVD risk factors such as elevated blood pressure, increased blood glucose levels, overweight, abnormal blood lipids, and obesity etc [8,9] .There has been a lot of interest in finding new biomarkers or bioindicators of endothelial dysfunction in CVD. Novel bioindicator have emerged as potential diagnostic risk factors for CVD, as have new pharmacological and non-pharmacological rising therapeutic ways to avoid the endothelial dysfunction.

1.1. Proposed Mechanisms of Endothelial Dysfunction:

The pathophysiology of cardiovascular diseases is strongly correlated with the malfunctioning of endothelial cells in the vasculature [Bounlanger,2016].

1.1.1. NO and Oxidative stress role: It is a complicated and multifaceted process from endothelial dysfunction disease to atherosclerosis. Reduced antioxidant and anti-inflammatory outcome, more permeability to lipoproteins, and increased production of cytokines and adhesion molecules are all the consequences of declining endothelial function, which also impairs vascular homeostasis [10]. The most prevalent mechanism for the development of dysfunction among a variety of intricate pathways seems to be oxidative stress. Most cardiovascular risk factors are typically linked to increased intracellular oxidative stress and ROS. This leads to the promotion of multiple mechanisms, including the activation of the production of peroxy-nitrite, NADPH oxidase, NO inactivation, eNOS uncoupling, endothelin expression stimulation, and so on from Figure 1 [11].

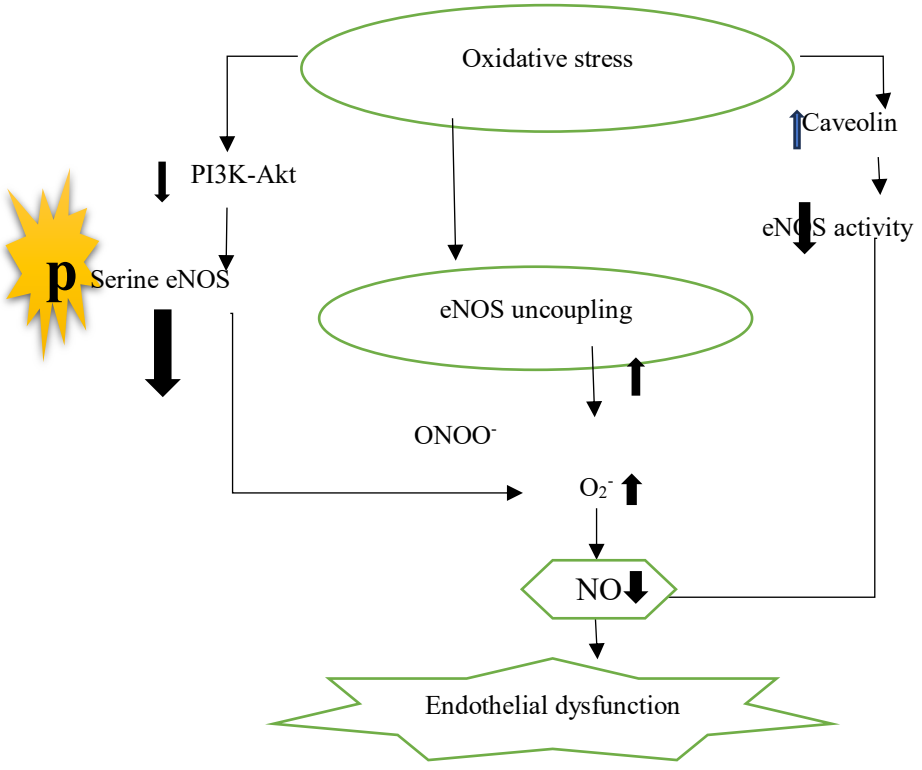

Figure 1: Flow chart of NO and Oxidative stress role

1.1.2. Chronic inflammation: Another fundamental mechanism of Endothelial dysfunction disease is inflammation, and there appears to a causal connection between inflammation and oxidative stress [12]. By producing NO, the endothelium regulates vascular inflammation in a physiological context. On the other hand, an unhealthy endothelium will worsen vascular inflammation and encourage the generation of reactive oxygen species, both of which are harmful to the vascular system. The signalling mechanisms underlying vascular inflammation may be amplified by oxidative stress, and superoxide is released more frequently by inflammatory cells [12] Numerous inflammatory indicators are linked to atherosclerosis and endothelial dysfunction. The protein like CRP is generated in response to many types of inflammation. CRP deposits on the intima prior to monocyte emergence, hence directly contributing to the pre phase of atherosclerosis [13]. Furthermore, CRP has a direct impact on NO bioavailability, which results in endothelial dysfunction, intimal hyperplasia, and oxidative stress. It has been suggested that one potential mechanism for CRP's direct action is through lectinlike oxLDL receptor-1, which is essential for endothelial dysfunction caused by oxLDL in human aortic endothelial cells [14]. The upregulation of interleukin-1 and tumour necrosis factor-alpha, which stimulate leukocyte migration and adherence, is also linked to inflammation [15]. Furthermore, the expression of adhesion molecules by leukocytes and endothelial cells, including VCAM and ICAM, monocyte chemoattractant protein-1, P-selectin protiens, and interleukin-6, is induced by these inflammatory cytokines, which exacerbates ED [16]. Once monocytes have penetrated the intima, they change into macrophages and exhibit receptors that help lipids be taken up and accumulated. This process causes the macrophages to become foaming cells. Some Smooth muscle cells eventually move, and fatty patchs created by vessels of smooth muscle cells and foam cells produced from macrophages the precursor lesions may eventually develop into atheromatous of plaques [17]. Consequently, ED is crucial for the development and advancement of atherosclerotic plaque.

1.1.3. Shear stress: Atherosclerotic lesions often develop at particular arterial locations, such as the inner side of curved coronary artery segments, bifurcations, and branching sites. Vascular trees are susceptible to the systemic risk aspect of ED [18]. One of the factors that modulates to atherogenic action and explain the clinical heterogeneity of atherosclerosis is locally disrupted shear stress caused by blood flow [19]. Localized ESS induces vascular responses that compound atherosclerosis and lead to an unstable phenotype. In particular, low ESS causes atherogenic endothelium phenotype and shortly development of atherosclerotic plaque by modifying the expression of endothelial genes through mechanoreception and mechano-transduction pathways [20]. By increasing ET-1 and inhibiting nitrogen oxide, lipid absorption and its breaking process, also inducing plaque infection and oxidation in endothelial cells of BV, low ESS causes atherosclerosis [21]. Higher ESS values are thought to be athero protective due to the up-regulation of eNOS, since low ESS is largely linked to plaque growth and susceptibility. Consequently, the primary mechanisms underlying the positive effects exercise has on the cardiovascular system are thought to be increases in blood flow in blood vessels and shear rate [22]. Nonetheless, there appears to be a connection between plaque vulnerability and overly elevated ESS. Increased shear stress levels have been linked in certain studies to intimal ulcerations or plaque ruptures in the coronary and carotid arteries of body [23].

1.1.4. Atherosclerosis: Chronic inflammation and cholesterol buildup in the arteries are the hallmarks of atherosclerosis, which eventually restricts blood flow to the artery and causes ischemic stroke and heart attacks [24]. Research suggests that endothelial

dysfunction and atherosclerosis are linked to aberrant lipid metabolism, inflammatory responses, and hemodynamic changes [25]. Endothelial cells activate in response to atherogenic insults such as ox-LDL, cholesterol crystals, inflammation, and disrupted blood flow. Impaired endothelial-dependent vasodilation can result from reduced endothelial-derived NO. Endothelial cells activate by expressing adhesion molecules such MCP-1, VCAM-1, and E selectin, attracting some cells like macrophages to penetrate the artery wall [26]. Endothelial cell exposure to diverse stimulation causes oxidative stress, which exacerbates the vessels inflammation and atherosclerosis. Atherogenesis also involves other types of immune cells like tissue mast cells, B lymphiod cells, T cells, and dendritic cells. Increased endothelial dysfunction, as evidenced by increased platelet interactions in blood vessel, renders plaques unstable and vulnerable to rupture due to overproduction of prothrombosis molecules and ineffective anticoagulatory, antithrombotic, and fibrinolytic functions, as well as inflammation resolution [27]. Disruption of endothelial glycocalyx microstructure promotes atherosclerotic plaque formation by affecting mechano-transduction, vascular tone, and stability.

2. Biomarkers of Endothelial Regulation in Heart Diseases:

Endothelial activation biomarkers may offer insights into the development of cardiovascular disease as well as novel therapeutic targets [28]. Given that endothelial activity may promote the formation of atherosclerotic lesions, the quest for marker of endothelial activation is crucial in the atherogenesis [29]. Proinflammatory endothelium activation in atherosclerotic cardiovascular disease leads to the release of endothelial adhesion molecules [34]. Tumour necrosis TNF-α factors and other pro-inflammatory cytokines elicit the production of these adhesion molecules. Additional adhesion molecule inducers could be the acute-phase protein (CRP), which the liver produces in reaction to IL-6 [28].

An author examined patients with incident coronary heart disease, 316 control participants, and 272 patients with carotid atherosclerosis. They discovered that patients with carotid artery stenosis and coronary heart disease had greater levels of ICAM-1 and E-selectin. Furthermore, there was a strong correlation observed between the control group high lipoprotein cholesterol levels and E-selectin levels. The results suggest that E-selectin could play a role in the pre stages of atherosclerosis by leukocytes along with the endothelium. Conversely, the attachment and trans endothelial migration of leukocytes cells are the functions of circulating ICAM-1 that are more nearly linked to atherosclerosis part. Hence, for carotid stenosis and subclinical coronary insufficient disease, Hwang et al. [30] propose that soluble E-selectin and ICAM-1 may function as markers of endothelial activation. Tzoulaki et al. [31] stated a population basis cohort study to investigate the relationship between biomarkers of endothelial activation and peripheral atherosclerosis progression. Significant indicators of lower-extremity atherosclerosis development were identified to be sICAM-1, IL-6, and CRP. They propose that molecular indicators linked to the leading of atherosclerosis include CRP, IL-6, and ICAM-1 [31]. The presence of E-selectin in the circulating blood is interpreted as definitive proof of endothelium activation because it is only expressed on the activated endothelium of blood vessel. Although elevated levels of ICAM-1 and VCAM-1 were thought to be a consequence of endothelial activation to an disease [32,33]. One potential major source of IL-6 production would be the proinflammatory stimulation of endothelial cells. Nowadays, it is thought that endothelial-derived IL-6, which measures hsCRP, is a reliable and

practical biomarker for determining risk factors for atherosclerotic cardiovascular diseases [34].

In patients with coronary disease problem, circulating microparticles of BV are also linked with IL-6 and C-reactive proteins [31]. Thirty patients with unstable angina, twenty with stable angina, and twenty healthy people had their circulating endothelium microparticles examined by Cui et al. [35]. The study demonstrated a significant increase in endothelial microparticles in myocardial infarction and unstable angina. Additionally, there was a correlation found between the raised levels of endothelial microparticles and CRP or IL-6. According to their findings, endothelial microparticles may encourage vascular inflammation and contribute to the development of thrombosis [35]. Endothelial microparticles were reported to be elevated in individuals with acute coronary syndrome, diabetes mellitus, and hypertension etc, suggesting that they could be employed as a marker in CVD patients [29]. Endothelial micro-vesicles are emerging as a promising diagnostic for CVD [34,36,37,38]. Endothelial micro-vesicles, which are ripped from an active endothelium due to cell detachment and death, it should be biomarker for atherosclerosis [34]. According to Rabelink et al. [36], The levels of endothelium microparticles serve as a marker of prolong endothelial activity. In addition to this suggestion, Berezin proposed that circulating endothelial-derived microparticles are indicators of cardiovascular risk [37]. Endothelial microparticles have membrane proteins on their surface, including tissue factor, P-selectin etc. In this setting, circulating endothelium microparticles could be used to detect endothelial activity. On the other side the surface microparticles can express annexin V to phosphatidylserine nature, implying that are the microparticles could be a marker of the endothelial abnormality condition. Pathologically [34,32,33], activated endothelium-derived microparticles are showing the progression of endothelial cells from early moderate disturbance to high injury. high CD62E+ - Circulating endothelial microparticles with high CD62E+ levels were observed in patients with prior of ischemic stroke and attack problems [35]. As compared to the healthy subject group, the CAD patient had a greater mean proportion of CD62E+microparticles, as demonstrated by Hu et al. The sensitivity and specificity of the cutoff value of 1.35 percent were 76.9% and 88.9%, respectively, according to the ROC curve analysis for CD62E+ microparticles. Our results suggest that endothelial activation uses the E-selectin molecule to participate in the pathophysiology of coronary artery disease [18]. According to recent findings by Landers-Ramos et al. [39], there were more CD62E+ endothelium microparticles in coronary artery disease patients (265.66 ± 96.1 particles/μL) than in healthy individuals (1676.6 ± 32.1 particles/μL), though not to a statistically significant degree. The possible causes of this difference could be attributed to the study's smaller sample sizes and the notable distinction in the total drugs used by patients with coronary artery disease and healthy controls (4 ± 1.1) [39]. In addition, peripheral vascular illnesses such as Takayasu arteritis, polyarteritis nodosa, and microscopic polyangiitis have also been linked to endothelial microparticles [33,28]. The collective findings suggest that endothelial microparticles may function as a marker for endothelial activity. The disease activity and treatment effectiveness could be tracked by measuring the increased or decreased levels of endothelium microparticles.

Numerous other chemicals that are comes from activated endothelium been suggested as potential markers of endothelial activation for disorders related to cardio-metabolism, such as hypertension, diabetes mellitus, coronary artery disease, etc [29,36]. ADMA, endocan, and Ox-LDL are three of these suggested biomarkers that are particularly interesting. Endothelial activation is a result of perioxidized low-

density lipoprotein [28]. Ox-LDL, a biomarker of oxidative stress, has been recognized as a high risk for coronary artery disease [29]. Lectin-like oxidized LDL receptor is the primary receptor for oxidized LDL, which is expressed on endothelium cells. Oxidized LDL stimulates endothelial cells via interacting with LOX-1. In combine, oxLDL activates the CD40/CD40L signalling pathway via LOX-1, reinforcing inflammation [32].

ADMA is an endogenous inhibitor linked to vascular endothelial activation. In hypertensive childs and adults, elevated plasma ADMA is associated with elevated VCAM-1. When NO from the endothelium is blocked, vascular ECs become activated. In this sense, increased plasma NO inhibitor ADMA suggests that eNOS inhibition induces endothelial activation. In this sense, ADMA may serve as a particular biomarker of endothelial activation to an disease, indicating a risk factor for CVD like hyper-lipidaemia, hypertension, coronary artery disease, unstable angina, and stroke etc [29]. Reduced ADMA plasma levels after coronary intervention, on the other hand, may indicate a reduced risk of cardiovascular disease. [29] An intriguing new biomarker of endothelial activity in CVD is endocan [29,40]. In hypertensive patients receiving amlodipine, a Ca-channel blocker, A man Tadzic [40] investigated the impact of blood pressure reduction on the endocan and soluble cell adhesion molecules during inflammation. Important findings include: (1) significantly lower serum levels of sICAM-1 and sVCAM-1 following treatment; (2) significantly lower serum endocan concentration following amlodipine therapy, with the decrease in endocan levels tending to decrease with pressure of blood reduction (3) significantly positive correlation between significantly lower levels of endocan and lower levels of ICAM-1. Based on these results, it is possible that endocan, which can compete with ICAM-1 for LFA-1, is secreted by active endothelium in critical hypertension. On the other hand, a drop in blood pressure is linked to the deactivation of endothelial cells. Thus, a lower risk of developing atherosclerosis can be indicated by lower levels of endocan [40] in Table 1.

Table 1: Endothelial activation indicators in cardiovascular disease that circulate as soluble and cell components.

Biomarkers Or Indicators	Other names	Cellular origin	Conceivable Use	Family
CRP	C-reactive protein	Activated endothelium	A sensitive and reliable indicator of endothelial activity that is non-specific.	Acute phase protein
EMPs	CD62E+ endothelial microparticles	Activated endothelium	A marker for endothelium activation	The proteoglycan
ADMA	Asymmetric dimethyl arginine	Activated endothelium	new marker for endothelial activation	An endogenous family

IL-6	Interleukin-6	Activated endothelium	Consistent marker for endothelial activation, which is nonspecific.	Cytokine family
E-selectin	CD62E, ELAM-1	Activated endothelium, as evidence of endothelium activation	A sensitive and consistent marker for endothelial activation	Selectin family
P-selectin	CD62P, GMP-140, PADGEM	Weibel-Palade dies of activated endothelial cells of endothelium	A marker for endothelial activation	Selectin family
ICAM-1	CD54, intercellular adhesion molecule	Activated endothelium	A sensitive and consistent indicator for endothelial activation	IgG gene superfamily
VCAM-1	CD106, vascular cell adhesion molecule	Endothelium activation	A consistent biomarker for endothelial activation	IgG gene superfamily
Endocan	Endothelial cell-specific molecule	Activation of endothelium	A new marker for endothelial activation of cells	The proteoglycan
LOX-1	Lectin-like oxidized LDL receptor-1	Activated endothelium	A potential new marker for endothelial activation	A receptor for oxidized LDL
CD 40L	CD ligand, CD154, TNF-related activation	Activation of endothelium	A potential new biomarker for endothelial activation	TNF superfamily

3. Endothelial Dysfunction And Cardiovascular Risk Factors:

3.1. Hyper lipidaemia: Both inflammation and ED are crosslinked with high amount of low-density cholesterol and low levels of high-density cholesterol in the body [41]. The enhanced ROS-mediated NO degradation in persons with dyslipidemia and CAD has been proposed as the reason why partial normalization of the impaired coronary endothelial function was observed upon infusion of L-arginine, the NO substrate [42]. There are three potential pathways that could be responsible for dyslipidemia-induced ED: (1) increased O2 generation, oxidative stress, and NADPH oxidase up-regulation; (2) elevated levels of ADMA of a plasma; and (3) LDL oxidation. eNOS inhibitor ADMA competes with an L-arginine for the same eNOS binding site, causing eNOS uncoupling. O2 – production rises as a result, but NO production falls [43].

3.2. Diabetes mellitus: Diabetes is typically a separate factor for the onset of CVD and atherosclerosis. Furthermore, endothelial function is known to be compromised by hyperglycemia [44]. It's interesting to note that during an oral glucose test, ED was seen in normoglycemic individuals who are at a high risk of developing diabetes in the body [45]. Reduced NO synthesis and increased generation of vasoconstrictor chemicals were the processes behind ED in the diabetic individuals [46]. Guzik et al. observed that oxidative stress, NADPH oxidase, and eNOS uncoupling were significant factors in the cause of endothelial dysfunction in patients with diabetes condition [47]. AGEs are produced when non-enzymatic glycation of proteins and component of lipids occurs. These end products accumulate takes place in the vessel inner surface, change the structure of the endothelium and the basement membrane of the endothelial vessels, and can obstruct NO activity. These factors significantly contribute to ED. Furthermore, AGEs bind to certain receptors shows on cells like monocytes, macrophages etc. This binding amplifies the inflammatory action and increases vascular permeability and oxidative stress [36,40].

3.3. Elevated blood pressure: It has been demonstrated that some findings in hypertension patients, like activation of the inflammatory system and the endothelial system, contribute to ED [49]. Patients with hypertension have also been shown to produce more ROS and have worse NO bioavailability [50]. Recent reports, inflammation has a causal role in the cause of hypertension in blood vessel. It has also been discovered that blocking inflammatory pathways can delay the onset of high blood pressure and ED linked to atherosclerosis condition [51]. This implies that anti-inflammatory strategies may offer ways to lessen ED brought by hypertension.

3.4. Smoking: Free radicals are abundant in cigarette smoke and are transferred straight to the blood vessel wall. Cigarette smoke produces free radicals, but it also makes it easier for the body to release ROS by triggering the activation of immune cells [52]. Consequently, smoking has been linked to circulating variables linked to endothelial injury and ED, as well as oxidative stress and inflammation [53]. Moreover, it has been observed that smoking lowers HDL cholesterol levels, and enhance endothelial function [54].

3.5. Obesity [Overweight]: Obese patients are more likely to develop atherosclerosis [55]. Multiple cardiovascular risk factors may cause endothelial cells to be injured more severely. Obesity causes endothelial injury, which includes decreased endothelial-dependent vasodilation, increased ET-1 vasoconstriction, increased vasoconstriction and inflammatory activation [56,57]. Obesity was found to be an predictor of coronary ED disease condition in 397 patients with normal CAD [58]. Obesity treatment typically improves or normalizes insulin resistance, hypertension, and erectile dysfunction [59].

3.6. Aging: Age is also factor for cardiovascular disease condition formation in both men and women, and it is linked with increased risk of erectile dysfunction [60]. As we age, we experience deterioration in balance, including reduced NO bioavailability and increased synthesis of cyclooxygenase-derived vasoconstrictor factors. Older animals exhibit activity of eNOS, as well as NO activity [61]. Endothelial contracting factors, including ET-1 and cyclooxygenase-derived prostanoids elements, and ROS generation increase. ADMA levels in plasma seem to increase with age [62].

4. Evaluation of Endothelial Function:

To evaluate endothelium activities takes in vivo, a single, universal test does not exist. Since the endothelium controls a number of vascular functions, evaluating each one separately may be one approach to gauge its integrity. Since Ludmer and colleagues originally described endothelial failure in atherosclerotic coronary arteries in the year of 1986, blood flow and vascular reactivity have been measured as a typical method of assessing endothelial function [63].'Gold standard' for an evaluation parameters of endothelial function testing is the invasive evaluation of coronary endothelial function utilizing for angiography examine, Doppler flow measurements method, and graded intracoronary infusions of endothelium-dependent vasodilators such as acetylcholine etc. In recent years, non-invasive techniques such as stain gauge forearm plethysmography, Arterial infusion of vasodilators like methacholine or acetylcholine substance, and high external vascular ultrasound techniques have been used to assess endothelial function during reactive hyperaemia. Endothelial dysfunction is a condition that affects vascular beds such as arteries and small resistance vessels in the extremities, not just the coronary arteries [65]. To assess endothelial activation, markers such as VCAM, ICAM, ET-I, PAI-I, VWP, and C-reactive proteins can be measured. Identification and measurement of CECs is a new indicator of endothelial function. This approach corresponds with other endothelial function markers, including flow-mediated dilation, and tissue plasminogen activator. Less numbers, irregular morphology, and a lack of consistency in the currently employed methods make it challenging to quantify CECs. In contrast to endothelial progenitor cells, CECs seem to constitute a distinct cell population [66,67] in Table 2.

Table 2: Evaluation of endothelial function

A. Computation of vascular activity	B. computation of blood flow	C. Computation of markers of endothelial activation
Endothelial dependent vasodilators	Invasive estimation	Estimation of markers coagulation and fibrinolysis
Endothelial independent vasodilators	Less/Non-invasive assessment	Estimation of markers of low-grade inflammation

5. Treatment:

5.1. Pharmacological therapy:

5.1.1. β blockers: Beta blockers often have a weak protective impact on endothelial cells. Nonetheless, it has recently been noted that NO plays a role in the vasodilatory mode of action of several β blockers. The mechanism of nebivolol-induced NO release has been proposed to involve an increase in intracellular Ca2+ through phospholipase C activation and an increase in NO release via the endothelial cells' oestrogen receptor [68]. With regard to celiprolol, it has been suggested that serotonergic receptor stimulation causes an increase in intracellular calcium, which in turn causes NO release [69]. In addition, celiprolol promoted the liberate of NO through triggering the PI3K or Akt pathway system [70]. However, due to their anti-oxidant properties, certain β blockers, such carvedilol, have been demonstrated to have an endothelial protective effect.

5.1.2. Calcium antagonists: The injection of bradykinin (BK) receptor antagonists, guanylate cyclase inhibitors, NOS inhibitors, or endothelial cell removal results in a reduction in the vasodilatory impact of calcium antagonists. It has been reported in several studies that calcium antagonists enhance the synthesis of NO. Long-term delivery of these agents improves endothelial-dependent FMD in clinical patients. Proposed mechanisms of action include blood pressure reduction, blood flow enhancement, antioxidant impact, VEGF rise, superoxide dismutase (SOD) increase, and BK boosting effect.

5.1.3. ACE inhibitors: Administration of ACE inhibitors has been shown in multiple papers to significantly improve endothelial function. First, the following was given as the explanation for how ACE inhibitors shield the endothelium: They solely stimulate BK type 2 receptors on endothelial cells to produce NO, enhance BK, and block the degradation of BK. But the generation of ROS by AII is elevated in a number of cardiovascular disorders. It is therefore thought that when ACE inhibitors lower AII, ROS generation falls and NO activity rises.

5.1.4. ARBs: In several illnesses of the arteriosclerotic plaque, ARBs enhance endothelial function. Table II provides a summary of irbesartan's effects, which are commonly documented in human studies. After receiving irbesartan for an extended period of time, endothelial-dependent FMD improved in cardiovascular disease, diabetes mellitus, and essential hypertension. ARBs primarily function through an antagonistic action on AII receptors, which causes local and blood levels of AII to rise and activate AII type 2 receptors. This is thought to be the NO release mode of action because it causes vasodilation and an antiapoptotic impact. Similar to this, there is an increase in AII (1–7), an active metabolite that is known to cause NO release. ARBs simultaneously have anti-inflammatory and antioxidant properties while also improving endothelial function in a comparatively short amount of time in a number of arteriosclerotic disorders. Additionally, it has been observed that people with type 2 diabetes who take ARBs have higher EPC [71,72].

5.1.5. Statins: Many large-scale clinical trials have shown that statins (HMG CoA reductase inhibitors) are cholesterol-lowering medications that prevent the development of ischemic heart disease and cerebral stroke. Statin administration for six months is known to enhance endothelial-dependent vasodilation in patients' forearm or

coronary arteries who have high cholesterol. Considered a pleiotropic effect, the improvement in the endothelium-dependent vasodilation of the forearm arteries occurs in a timeframe of 2-12 weeks and is not correlated with a reduction in LDL cholesterol. But since endothelial function is also enhanced by LDL apheresis or cholesterolestyramine, the drug's ability to decrease cholesterol must also takes role in the enhancement of endothelial function. Statins increase NO release by activating the PI3-K/Akt pathway, decreasing caveolin-1, increasing eNOS and Hsp90 interaction, stabilizing eNOS mRNA through Rho/Rho kinase inhibition, and decreasing adhesion molecules. Statins can also increase EPCs in patients with heart failure [73]. Statins may increase NO levels, as this effect on EPC is not detected when NOS is not present.

5.1.6. Renin inhibitors: A renin inhibitor, like the other two medicines, improves endothelial function in experimental mice. In Watanabe hyperlipidaemic rabbits, aliskiren, a renin inhibitor, increased blood NO concentration after ACh treatment and decreased NO release after L-NMMA treatment, similar to valsartan. It also reduced plaques in the aorta. Combining aliskiren and valsartan increased these effects, indicating that aliskiren acts independently of AIIs [74]. The impacts on people are predicted soon.

5.1.7. Insulin-resistance improving drugs: In addition to being insulin resistant, patients with hypertension, diabetes, obesity, and dyslipidemia also suffer endothelial damage. Insulin-induced decrease of endothelial-dependent vasodilation could account for this. NO release triggered by insulin as a result of NOS activation via the PI3-K/Akt pathway. Thiazolidinediones promote endothelium-dependent vasodilation in diabetic patients, decrease CRP and ADMD levels, and enhance insulin sensitivity. In largescale clinical research, these medications also stopped cardiovascular events from happening.

5.1.8. Therapies that impact EPC count: Risk factors contribute to endothelial dysfunction, which serves as a trigger for increased endothelial cell mobility, accumulation at the site of damage, and angiogenesis. In humans, exercise improves EPC number and function. When ADMA and low-density cholesterol levels are high, high density lipoprotiens cholesterol levels are low, hypertension, diabetes mellitus, smoking, and hyperhomocysteinemia are present, the number of EPCs falls. Risk factors contribute to endothelial dysfunction, which serves as a trigger for increased endothelial cell mobility, accumulation at the site of damage, and angiogenesis. In humans, exercise improves EPC number and function. When ADMA levels are disturbances takes place hypertension, diabetes mellitus, smoking, and hyperhomocysteinemia are present, the number of EPCs falls.

5.1.9. Erythropoietin: EPO encourages the release of NO by activating the PI3-K/Akt pathway. Additionally, a data suggests that in individuals with coronary artery disease, the blood EPO concentration is strongly correlated with the number of EPC [75]. Moreover, the number of EPC rose when EPO was administered. These results imply that endogenous EPO might be crucial to the synthesis of EPC.

5.2. Non pharmacological therapy:

5.2.1. Loss of body mass: Obese people with coronary disease who reduce weight have been demonstrated to improve their endothelial function [76] It is assumed that concurrent improvements in a range of risk variables are involved, but decreases in circulating cytokines, particularly inflammatory cytokines generated from visceral fat, may also play a role.

5.2.2. Limitation of salt intake: Consuming sodium raises blood pressure, and endothelial damage is notable in salt-dependent hypertension. It was recently demonstrated in vitro that when extracellular sodium concentration was raised from 135 mM to 145 mM when aldosterone was present, the stiffness of cultivated endothelial cells increased [77]. In other words, because endothelial cells have less ability to undergo transformation, there is a drop in NO emission. By reducing salt consumption, the vasomotor protective benefits of NO are shown regardless of the drop in blood pressure.

5.2.3. Exercise: Exercise improves endothelial function even in human coronary arteries, as has been demonstrated. Increased shear stress on the vascular walls brought on by increased blood flow during exercise causes an increase in NO release. Moreover, studies have shown that exercise increases EPC and lowers oxidative stress.

6. Conclusion:

Endothelial dysfunction has a significant part in the progression of CVD. Endothelial dysfunction, characterized by decreased NO bioavailability, elevated oxidative stress, and chronic inflammation, plays a role in atherogenesis and other cardiovascular problems. Recognizing the pathophysiological pathways underlying this illness is critical for timely diagnosis and therapy.

The identification of biomarkers associated with endothelial dysfunction, such as inflammatory cytokines and adhesion molecules, has shown promise in the early identification and monitoring of cardiovascular risks. By enabling tailored therapy strategies, these biomarkers can enable more individualized treatment plans.

Therapeutic approaches include pharmaceutical alternatives that improve endothelial function and promote NO availability, as well as lifestyle alterations such regular physical exercise, diet, and weight control. Endothelial health can be successfully restored by drugs that target the renin-angiotensin systems like calcium channel blockers, statins, and other medicines.

To summarize, treating endothelium dysfunction offers a technique to enhance cardiovascular health and may also be a tactic to stop cardiovascular disorders from developing in the first place. Our capacity to control and reduce the risk of CVD will be significantly improved by ongoing research into novel therapies and biomarkers.

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