Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6, 3441-3456
2024
Publisher: Learning Gate
DOI: 10.55214/25768484.v8i6.2730

Modulatory potentials of nitric oxide in obesity-induced endothelial dysfunction

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Abstract: Obesity is caused by a significant increase in adipose tissue due to excessive caloric intake that exceeds energy expenditure. Obesity has emerged as a significant public health issue in both poor resource and economic developed nations, owing to its increased incidence and links to chronic diseases, such osteoarthritis, hypertension, non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVDs). It is believed that uncoupled eNOS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, xanthine oxidase, lipoxygenase, cyclooxygenase, microsomal P-450 enzymes, and pro-oxidant heme molecules are responsible for the drastic decrease in NO production and the relative increase in reactive oxygen species (ROS) secretion, which are considered as the molecular mechanisms associated with obesity-induced endothelial dysfunction. Vascular endothelium defines a monolayer of cells, which lies between the vascular smooth muscle cells (VSMCs) and the vessel lumen. It performs a number of protective actions facilitated by the release of nitric oxide (NO), a soluble gas that is generated in endothelial cells by the amino acid L-arginine through the action of endothelial nitric oxide synthase (eNOS). The maintenance of vascular homeostasis is facilitated by various biological actions of NO, such as modulation of vascular dilator tone, control of local cell growth, and protection of the endothelium from the harmful effects of cellular components in blood circulation, while maintaining normal endothelial functions. Decreased peripheral arterial endothelium-dependent dilation (EDD) in response to mechanical (intravascular shear) or chemical (acetylcholine) stimuli suggests that decreased NO bioavailability has been recognised as major molecular mechanisms associated with the progress and development of obesity-induced endothelial dysfunction. In this review, the modulatory effects of NO in obesity-induced endothelial dysfunction will be discussed.

Keywords: *Endothelial dysfunction, Endothelial nitric oxide synthases, Nitric oxide, Obesity.*

1. Introduction

The prevalence of various clinical condition associated with obesity-related metabolic conditions has increased significantly, as a result of the exponential increase in obesity incidence. Currently, it is estimated that 1.9 billion people worldwide are obese or overweight, with 50 million of these being children under the age of five [1]. Obesity describes excessive accumulation of body fat, described by the body mass index (BMI), which is computed as weight (kg) divided by height (meters) squared. It is a global issue that affects both developed and low-resource countries. BMI levels higher than 19 and less than 25 kg/m^2 are regarded as normal, whereas BMI values of equal to or higher than 25 kg/m^2 are regarded as overweight, while BMI values of equal to or higher than 30 kg/m^2 are regarded as obese [2].

Increased calorie consumption and physical inactivity are the two main factors contributing tremendously to the progress of obesity. These factors result in a positive calorie balance and a corresponding rise in body fat percentage. Factors, such as tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6), adipsin, angiotensinogen, adiponectin, resistin, and leptin are the active substances

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released by adipose tissue, which are passed to the organ that stores energy. These substances may also promote obesity-induced endothelial dysfunction [3]. Vascular endothelium is extremely dynamic that syntheses various molecules which work in both autocrine and paracrine manner to regulate the normal function of the vascular network. It regulates blood flow in a fluid state, provides fluid and molecules exchange between the blood and surrounding tissues, initiates vascular networks, and regulates vascular resistance in response to changes in vascular blood flow, as well as controlling arterial tone in resistance vessels [4]. The endothelium could achieved these roles by the synthesis of endothelial cells moieties through its paracrine and autocrine activities and many regulatory mediators, including NO [2, 3, 4].

Disturbances in endothelial functions were investigated to facilitate the progress of atherosclerotic endothelial dysfunction, leading to CVDs [5, 6, 7]. NO is the major significant substance secreted by the endothelium, and is crucial for vasodilation, attenuating inflammatory response, and oxidative stress, produced mostly from ROS [8]. Reduced NO bioavailability may lead to coronary artery constriction during physical activity or mental stress, which could provoke myocardial ischemia and ischemic heart stroke in patients with coronary artery disease. Furthermore, decreased NO bioavailability can promote vascular inflammation, which might result in the oxidation of lipoproteins and the development of foam cells, the precursor to atherosclerotic plaque [8].

Impaired endothelium functions have been associated with a growing number of diseases, such as hyperhomocysteinaemia, congestive heart failure, hypertension, smoking, diabetes, hypercholesterolemia, hyperlipidaemia and obesity [2, 6]. Hence, the vascular endothelial wall in these circumstances may enhance inflammation, oxidation of lipoproteins, extracellular matrix accumulation or lysis, deposition of lipid-rich materials, smooth muscle proliferation, activation, adhesion and aggregation of platelet and development of thrombus.

The detrimental effects of ED may influence the progress and development of CVDs, which could be ameliorated by NO molecules [9]. In this review, the functions of endothelium and the molecular mechanisms associated with obesity-induced endothelial dysfunction would be discussed. The chapter also summarized the significant role played by NO as a potential modulator of obesity-induced endothelial dysfunction and the therapeutic approaches to be employed to determine the possibility of reversing ED by facilitating the release of NO from the endothelium.

2. Normal Endothelium

Endothelium is the innermost monolayer lining the blood vessels, that establishes contact between the endothelial lumen and the surrounding tissues [10]. The layer is surrounded by the tunica intima, comprising of endothelial cells, the tunica media, which contains VSMC, and the elastic tunica adventitia, which comprises the terminal nerve fibres in the connective tissues. Physiologically, the vascular endothelium regulates vascular homeostasis by preserving a stable equilibrium between the production of vasodilators and vasoconstrictors, oxidants and antioxidants, prothrombotic and antithrombotic factors, proinflammatory and anti-inflammatory molecules [4], constant normal blood flow, circulation of nutrients and hormones, and migration and proliferation of VSMC [10]. It regulates the activities of coagulation and fibrinolysis, lowers the vascular tone, controls cellular and vascular adhesions, suppresses leukocyte adhesions, controls inflammatory processes and angiogenesis (Fig. 1) [6].

Additionally, it regulates haemostatic processes, including inhibiting the activation, adhesion and aggregation of platelet through interactions with prostacyclin (PCL) and NO by ecto-adenosine diphosphate (ADP)-ases, Von Willebrand factor (vWF), thrombomodulin (TM), anti-thrombin III (ATIII), tissue factor (TF), and tissue factor pathway inhibitor (TFPI), along with CD39 and CD73 exposures, and prostaglandin E2 induced by glycosaminoglycans on the surface of endothelial cells (TFPI). It regulates plasminogen activator inhibitor-1 (PAI-1), tissue-type plasminogen activator (t-PA), urokinase plasminogen activator (uPA)) [11]. Through its paracrine and autocrine activities and other range of regulatory mediators, including NO, prostanoids, endothelin-1 (ET-1), angiotensin II (Ang II), t-PA, PAI-1, vWF, adhesion molecules, and cytokines that have been activated in response to various stimuli, the endothelium produces endothelial cell moieties, to render its normal functions. [2,3,4].

Edelweiss Applied Science and Technology
ISSN: 2576-8484
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The secretions of TM, heparin sulphate proteoglycan (HSPG), and TFPI are linked to endothelial anticoagulant activities. When protein C is activated by the interaction of TM and thrombin, both FVIII and FV activites are subsequently suppressed. The TM is a heparin-like molecule that acts as a co-factor to ATIII, while the FXa and TF-FVIIa complex activities are attenuated by TFPI. Endothelial t-PA improves the fibrinolytic system, while PCL and NO are produced to maintain endothelial antiplatelet properties [12]. NO is unquestionably recognised to achieve a significant role in maintaining normal vascular endothelium through various ways, such as inhibiting platelet aggregation, monocyte adherence to endothelial cells, and aberrant VSMC proliferation [13].

Endothelial nitric oxide synthase (eNOS) converts L-arginine to NO in the presence of cofactors such tetrahydrobiopterin. When NO is produced, it diffuses to the VSMC and enhances guanylate cyclase, which causes vasodilation mediated by cyclic guanosine monophosphate (cGMP) (Fig. 1). Additionally, NO is linked to various endothelium-protective processes, such as the suppression of vascular inflammation, growth of VSMC, platelet aggregation, and the release of tissue factors [3]. Hence modifications to the regular endothelial physiology might lead to endothelial dysfunction, associated with a reduction in the bioavailability of vasodilators, particularly the NO [13].

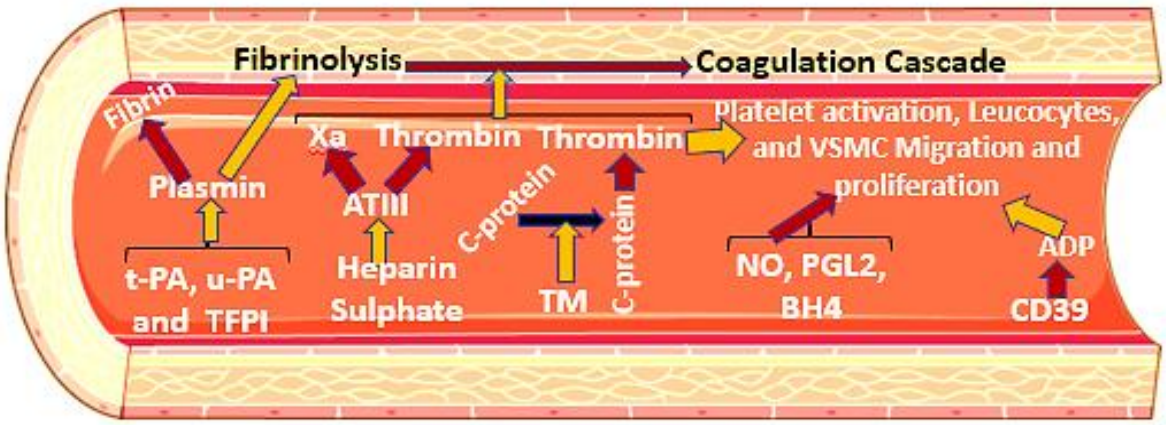

Figure 1.
Some protective functions of the normal vascular endothelium.

t-PA; tissue-type plasminogen activator, u-PA; urokinase plasminogen activator, ADP; adenosine diphosphate, ATIII; antithrombin III, TFPI; tissue factor pathway inhibitor, FXa; factor X activated, NO; nitric oxide, PGI2; prostacyclin, BH4; tetrabiopterin.

2.1. Mechanisms of Obesity-Induced Endothelial Dysfunction

The endothelium is an extremely dynamic tissue that serves several essential activities, which differ from one vessel segment to another and from one system to another. The vascular endothelium secretes molecules which control the functions and vascular network in an autocrine and paracrine manner [4]. Under normal physiology, endothelium functions to maintain a balance between oxidants and antioxidants, vasodilators and vasoconstrictors, proinflammatory and anti-inflammatory molecules, prothrombotic and antithrombotic signals and secretion of endothelial-derived vasodilating and vasoconstricting factors.

However, in obesity the endothelium could lost this tightly controlled equilibrium and exhibits oxidant, vasoconstrictor, proinflammatory, proatherogenic, and prothrombotic properties, which promotes the progression and development of vascular endothelial dysfunction and end-organ damage [1, 13]. A dysfunctional endothelium is associated with leukocyte adhesion, platelet activation, pro-oxidation of mitogens, impaired PGI2, coagulation, decreased NO synthesis and released, decreased secretion of EDHF and vasoconstriction factors, such as Ang II and prostaglandin (PGH2), as well as atherosclerosis and thrombosis [14]. The development of vascular diseases starts with endothelial

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dysfunction, which has negative impacts on other vascular cells, such as VSMC and immune cells, which may ultimately result in vascular failure. Inflammation is a term associated with oedema, transmigration and infiltration of leukocytes, blood vessel and connective tissue proliferation. Inflammation is recognised as the first stage of vascular dysfunction [4, 14].

Several fundamental mechanisms, such as increased concentrations of LDL and triglycerides, elevated oxidative stress radicals, inflammatory agents, and unbalanced hemodynamic activity, are hypothesised to be responsible for the progression of endothelial dysfunction. Adipose tissue-associated inflammation, reduced NO bioavailability, oxidized low-density lipoprotein (oxLDL), and insulin resistance (IR) are the main contributing factors for endothelial dysfunction [14, 15]. Other participating agents of endothelial activation and deregulation included reduced tetrahydrobiopterin (BH4) bioavailability, increased eNOS uncoupling, generation of ROS and arginase, increased glycation, and secretion of the receptor for advanced glycation end products (RAGE). Increasing asymmetric dimethylarginine, activating nuclear factor kappa-light-chain enhancer of activated B-cell (NF-kB), suppressing Kruppel-like Factor-2 [16], and phenotypic changes in perivascular adipose tissue leading to mild inflammation and higher leptin with a corresponding decrease in adiponectin secretions are other associated factors [6].

The molecular mechanisms for obesity-induced endothelial dysfunction are mostly caused by defective NO production and enhanced ROS secretion through uncoupled eNOS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, xanthine oxidase, lipoxygenase, cyclooxygenase, microsomal P-450 enzymes, and pro-oxidant heme molecules [17]. Furthermore, the synthesis of angiotensinogen of the renin-angiotensin-aldosterone system (RAAS) through defective adipocytes may result in its increased secretion in the RAAS system and a successive increase in the secretion of ROS. Defective eNOS genes facilitate endothelium dysfunction by reducing NO production [17].

Activation of NF-kB signalling molecules of endothelial cells leads to pro-adhesive and procoagulant phenotypes, which are associated with impaired vascular barrier functions. Additionally, NF-kB target genes, including adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, which interact with inflammatory cytokines of the vascular wall to facilitate extravasations, which progres to endothelial dysfunction [5]. Changes in the endothelium intercellular matrix can impair endothelial integrity, disrupt normal endothelial function, and promote vascular permeability. These promote vascular failure and enhance the progress and development of vascular diseases, including atherosclerosis. Endothelial dysfunction is associated with atherogenesis.

The contributing agents that enhance atherogenesis together with ox-LDL, Ang II, and hyperglycaemia, which activate the functions of NF-kB and mitogen-activated protein kinase (MAPK) of the endothelium. These also activate proinflammatory cytokines, iNOS, chemokines, causing an increase in the production of ICAM-1 and VCAM-1, enhance the activities of growth factors, and other enzymes [10]. Stimulation of proinflammatory signalling complexes of the inflammasomes and oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) promotes the synthesis of interleukins, such as IL-1β and IL-18, which activate the inflammatory processes [18]. During atherosclerosis, proinflammatory signals activate endothelial cells (ECs), which facilitate the secretions of adhesion molecules and disrupt the endothelial barrier [19]. These stimulate the movement of leukocytes such as neutrophils, T-lymphocytes, and monocytes, and helps them to stick to the endothelium lumen. Once in the endothelium layer, the leukocytes infiltrate the endothelial intima. While in the intima, leukocytes begin the proatherogenic inflammatory process.

Atherosclerosis has been demonstrated to originate from vascular injury, excessive deposition of lipids, VSMCs migrations and proliferation, apoptosis, necrosis, fibrosis, and localized inflammation [20]. Immune and inflammatory responses have been implicated in various phases of atherosclerosis [20, 21]. A high blood concentration of apolipoprotein B–containing lipoproteins, at which LDL is the predominant lipoprotein, has been recognised as the main cause of atherosclerosis in obesity, as demonstrated in inherited hyperlipidaemias (monogenic disease) [22, 23]. However, the condition can occasionally develop even at lower concentrations when coincidentally existed with other known causes of atherosclerosis (a multifactorial disease), including smoking, hypercholesterolemia, hypertension,

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hyperglycaemia, obesity, chronic inflammation, diabetes mellitus, and other complexes of genetic factors (a familial tendency) [24].

During atherosclerotic progression, the configuration of the extracellular matrix underneath the endothelium and alteration of the endothelial permeability allow small LDL particles to enter the endothelial lumen and bind to proteoglycans through apolipoprotein B-100 and remain in the sub-endothelium [25, 26]. The ROS produced from reactive radicals oxidizes LDL in the endothelium to ox-LDL. This activates many pro-inflammatory processes through lectin-like oxidized LDL receptor-1 (LOX-1). Ox-LDL particles facilitate endothelial and VSMC cells to produce a monocyte chemotactic protein (MCP-1), and monocyte colony-stimulating factor (M-CSF) that facilitates monocyte recruitment [21]. Retention and activation of macrophages, along with macrophages, encourage ox-LDL absorption through the macrophages, which results in the development of foam cells (Fig. 2).

Additionally, the ox-LDL interacts with healthy platelets to enhance platelet activation and aggregation. Activated platelets express LOX-1, which facilitates adherence of platelets to endothelium and triggers endothelin-1 release. These lead to decreased endothelial NO secretion, increased prostaglandin secretion, and impaired endothelial function. Rupture of the fibrous cap of the plaque initiates an interaction between blood coagulation factors and thrombogenic plaque, leading to the production of thrombi [20, 25, 26]. Endothelial dysfunction is associated with impairment of blood flow or agonist-induced vasodilation or a decrease in the essential endothelium-derived vasodilator. The fundamental basic of vascular endothelial dysfunction is the impairment of the endothelial cells, which was investigated as the predictive future of CVD events [4]. The dysfunction of the endothelial vasodilation has been demonstrated in several situations, such as hypercholesterolaemia, smoking, hypertension, diabetes mellitus, heart failure and post-ischaemic reperfusion [8]. Due to complexity of endothelium-derived relaxing factors, many sites may be impacted. These include endothelial membrane receptors, which bind to an agonists or physiological stimuli to secrete NO, decrease concentrations or suppress the utilization of L-arginine; the substrate of eNOS, decrease eNOS activity or amount of eNOS; the enzyme involves with the conversion of L-arginine to NO. These altered the secretion of NO from the endothelium, and promote the production of NO by oxygen free radicals, impaired diffusion of NO from endothelium to VSMC, reduced NO binding to guanylate cyclase, which limits the increase in intracellular cyclic GMP level, altered NO transport from endothelium to VSMC, and generally reduced VSMC sensitivity to vasodilators [8].

Endothelial dysfunction is associated with pathological condition that affects endothelium on a systemic level. It has been associated with a decline in the bioavailability of vasodilators, primarily the NO, which affects endothelium-dependent vasodilation and upsets the balance between the metabolism and function of vascular walls. Additionally, one of the primary reasons of endothelial dysfunction is excess ROS, which also plays a role to the progress of hypertension, atherosclerosis, diabetes, cardiac hypertrophy, heart failure, ischemia-reperfusion injury, and stroke. Because of its crucial involvement in the emergence of clinical coronary, cerebrovascular, and peripheral arterial disorders, vascular endothelial dysfunction is identified as the main therapeutic target for inhibiting the progress to CVD morbidity and mortality [5, 11]. Therefore, therapeutic drugs that alter this condition are of clinical relevance, since decreased endothelial function has been considered to play a significant causative function to the pathophysiology of vascular abnormalities [13].

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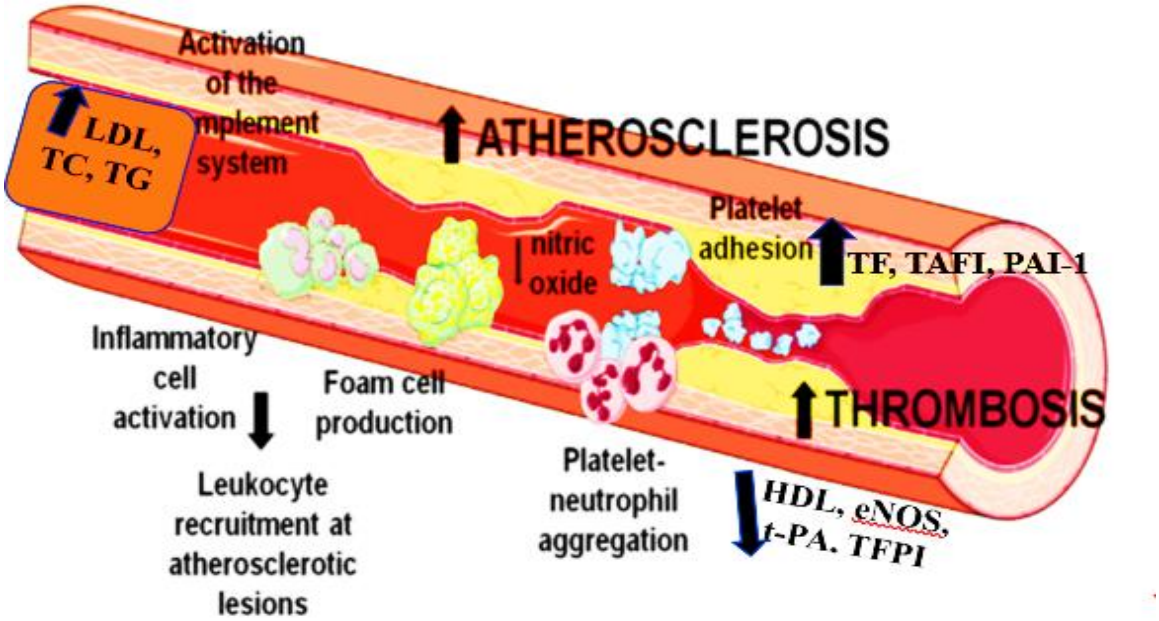

Figure 2.
Mechanisms of obesity-induced endothelial dysfunction.

Endothelial dysfunction involved leukocyte recruitment at atherosclerotic lesion and atherothrombotic formation through platelet activation, adhesion and aggregation., reduced NO bioavailability. eNOS; endothelial nitric oxide synthase, LDL; low density lipoprotein, PAI-1; Plasminogen activator inhibitor-1, TAFI; thrombin activatable fibrinolysis inhibitor, TC; total cholesterol, TG; triglycerides, TF; tissue factor, TFPI; tissue factor pathway inhibitor t-PA; tissue plasminogen activator [Modified 26].

3. Modulation of Endothelial Dysfunction by NO

3.1. Mechanisms of NO Synthesis and Release

NO is among the family of endogenous gasotransmitters associated with the modulation of different metabolic processes, including blood flow and platelet activation, adhesion and aggregation, which are crucial in maintaining vascular haemostasis. It is constantly secreted from the endothelium by the synthesized eNOS. Previous report has also investigated that NOcan be produced in the human placenta, platelets, some neurons, cardiomyocytes and kidneys [8]. Expression of eNOS following Ca^{2+} (calmodulin) complex generates NO through L-arginine and other cofactors, including NADPH, tetrahydrobiopterin and flavin adenine nucleotides as substrates.

Constitutive nitric oxide synthase (cNOS; type III) and inducible nitric oxide synthase (iNOS type II) are the two forms of eNOS. While NO, which is produced by cNOS, is crucial for controlling blood pressure [8], the iNOS is another type of NOS that is Ca^{2+}-independent and stimulated by immune factors. Endocardial endothelial cells produce the constitutive type of eNOS, which has been identified to modify myocardial contraction and coronary tone. Most of the NO in the blood arterial wall is thought to be produced by endothelial cNOS [13, 27]. Exposure of VSMC to cytokines and other stimulators of eNOS activation after endothelium injury may have significant physiological effects on the blood vessel. After endothelial denudation, medial VSMCs undergo rapid proliferation, leading to endothelial regrowth. Many agonists, including acetylcholine, histamine, thrombin, serotonin, ADP, bradykinin, norepinephrine, substance P, and isoproterenol, might facilitate the secretion and release of NO by the endothelium. Additionally, endothelial bradykinin receptors and other vasoactive substances can promote NO release through autocrine and paracrine actions. However, it has been postulated that

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the fundamental physiological stimulus for NO production and release by the endothelium is shear stress of the blood flowing across the vessel by a non-receptor-dependent process [8, 28].

NO as a gas activates soluble guanylyl cyclase, that promote the production of a high amount of cGMP. Cyclic GMP binds to three different intracellular receptor proteins, including cGMP-dependent protein kinases (PKGs), cGMP-regulated ion channels, and cGMP-regulated cyclic nucleotide phosphodiesterases (PDEs). These indicated that cGMP could modify cells activity through protein phosphorylation or other related proteins phosphorylation. Considering several functions of cGMP in the physiological regulation, such as smooth muscle relaxation, visual transmission, intestinal ion transport, and platelet activity, the combination of NO and cGMP might represent a remarkably extensive signal transduction system.

For instance, increased cGMP in VSMC beneath the endothelium facilitates GMP-dependent kinase, which could reduce intracellular calcium, further promoting relaxation, whereas elevated levels of cGMP in platelets caused by NO released into the blood vessel lumen, reduces platelet activation and adhesion to the endothelium [9]. These demonstrated that either cGMP-dependent or cGMP-independent pathways mediate the effects of NO. NO also controls cellular activity in the vessel wall by suppressing the release of growth factors from both platelets and cells around the vessel wall [8]. More specifically, it is now believed that the mechanism of cGMP-induced relaxation involves a decrease in intracellular free Ca^{2+} levels, which serves as a cue to activate myosin light-chain kinase (MLCK) and cause smooth muscle to contract [30]. These reduced intracellular Ca^{2+}, while calcium channel blockers naturally result in vasodilation.

Agents that promote cAMP like-2 agonist, might lead to relaxation of smooth muscle by inhibiting MLCK and promoting the removal of calcium from the cell [30]. Controlling cGMP levels, and hence the function of the NO-cGMP pathway needs effective controlling phosphodiesterase activity. NO exhibits anti-inflammatory activities, which are accomplished by suppressing the production and secretion of cytokines and cell adhesion molecules, which mobilized inflammatory cells to the endothelium and promote their recruitment to the endothelial lumen. The suppression of NF-kB activity, can bind to the promoter regions of genes encoding pro-inflammatory proteins [8]. NO also controls the baseline tone of the systemic, coronary, and pulmonary arteries by an increase in cGMP in smooth muscle, suppression of the potent constrictor peptide endothelin-1, and attenuation for the release of norepinephrine from sympathetic nerve terminals [13].

Additional mechanism that is involved in the generation of eNOS-derived NO is the activation of β-adrenoreceptors in response to high concentration of catecholamine that are enhanced at higher amount in oxidative stress linked to endothelial dysfunction [8]. Additionally, the VSMC could absorb NO, which interacts with a heme-iron group of guanylate cyclase to generate cGMP. This promotes a cGMP-dependent protein kinase, raises the Ca^{2+} level in the VSMC's cytosol, and subsequently inhibit vasoconstriction, while facilitating vasodilation [13]. Also, NO interacts with Kruppel-like factor-2 and endothelium-derived hyperpolarizing factor (EDHF) to promote arterial vasodilation [31]. It suppresses the synthesis of NF-kB by inhibiting the secretion of VCAM-1 and MCP-1 activities [3]. It is also an effective endothelium-derived vasodilator that exhibits antiplatelet, antiproliferative and anti-inflammatory properties, and decrease endothelial permeability[8].

Moreover, the oxygenase domain of NO proteins is a homodimer that transfers electrons from NADPH to the haem, where they are utilized to decrease O_2 and oxidize L-arginine to L-citrulline and NO. Other binding sites in this domain include those for BH4, oxygen, and L-arginine. Importantly, when there is increased oxidative stress, eNOS could lose its physiological functions in a situation known as "eNOS uncoupling" [32]. In such a situation, NO binds to superoxide O_2^- to form peroxynitrite (ONOO), a potent inducer of apoptosis, while eNOS instead may produce ROS, primarily O_2 (Fig 3). Hence, eNOS uncoupling not only causes a reduction in NO bioavailability but also promotes preexisting oxidative stress. The oxidation of BH4 to the deactivated form BH3 by O_2^- and ONOO, as well as the depletion of L-arginine, has been proposed as one of several mechanisms to explain eNOS uncoupling [33].

In particular, the increased production and function of the arginase isoforms (Arg I and Arg II) are responsible for the decrease in L-arginine. Alteration of the eNOS phosphorylation status and

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ISSN: 2576-8484
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oxidative stress linked with eNOS uncoupling are the common characteristics of clinical conditions linked with CVDs, including DM, hypertension, atherosclerosis, and cerebral ischemia (Figure 3) [9].

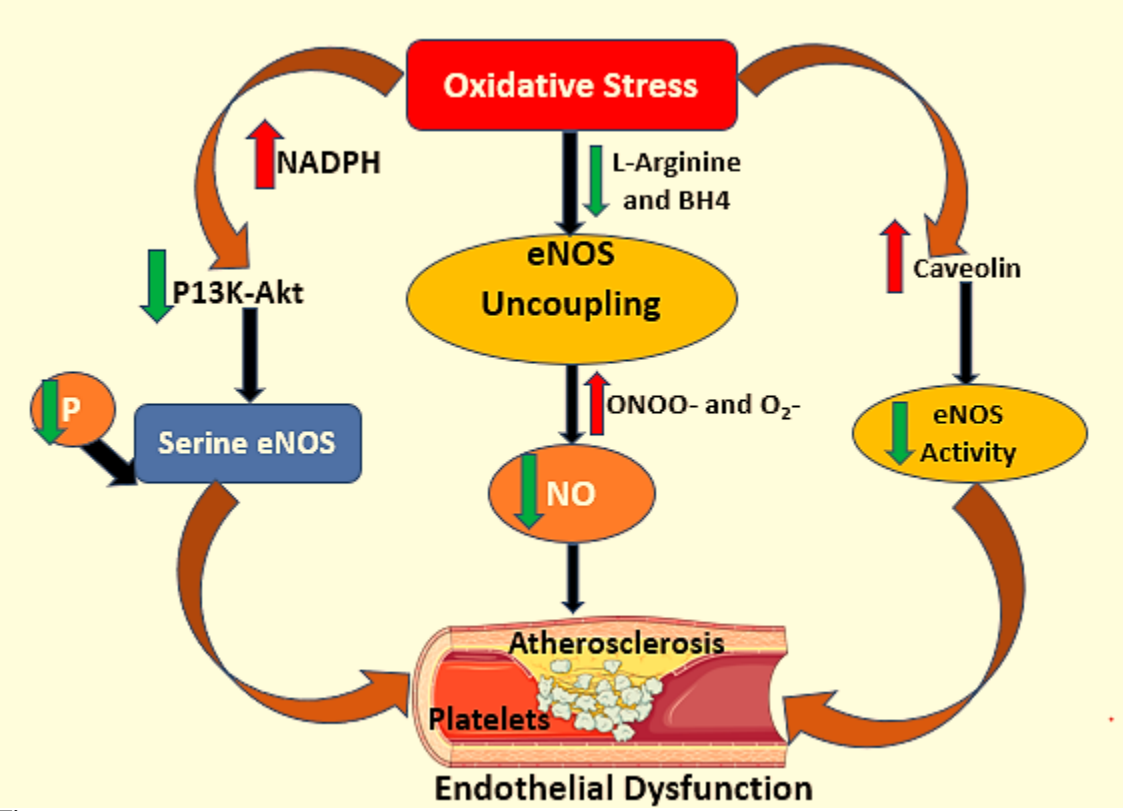

Figure 3.
Mechanism of oxidative stress-induced endothelial dysfunction.

Increase in the oxidative stress caused eNOS to lose its physiological activities, a process termed "eNOS uncoupling". During this situation, NO reacts with superoxide to form peroxynitrite ($ONOO^-$), a potent inducers of cell death, while eNOS produces ROS, mostly O^-_2, rather than NO. Hence, eNOS uncoupling leads to decrease NO bioavailability and participates to further progress the initiated oxidative stress. Several mechanisms have been recognised to describe eNOS uncoupling, including oxidation of BH_4 to the inactive form by $ONOO^-$ together with depletion of L-arginine are also involved. ROS; reactive oxygen species, eNOS; endothelial nitric oxide synthase, NO; nitric oxide.

3.2. Dysfunctional Endothelium and the Roles of No

The pathophysiology of various CVDs, such as essential hypertension, atherothrombosis, and pre-eclampsia, appears to be profoundly associated with dysfunctional endothelial NO pathway. The eNOS catalyses the conversion of NO from the substrate L-arginine in the vascular endothelium. This mediator affects the function of circulating cells and underlying smooth muscle to support the endothelial tonic vasodilator, thromboresistant, and atheroprotective effects [4].

3.2.1. NO and Inflammation

One of the primary signs of inflammation is vasodilation, which is basically triggered by a NO-dependent mechanism. Many inflammatory mediators, including bradykinin and histamine, stimulate endothelial NO release to cause vasodilation. NO can diffuse from the endothelial progenitor cells (EPCs) luminal and abluminal sides [9]. The NO which enters the VSM facilitates soluble guanylate cyclase, resulting to an increase in intracellular cGMP levels, causing smooth muscle relaxation [8],

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while the NO which enters the blood vessel is rapidly deactivated by the interaction with oxyhaemoglobin. Superoxide dismutase (SOD) can greatly extend the lifespan of NO in the blood, which shows that NO is also inactivated through interaction with O^2 [9], since the half-life for NO in the blood is typically recognised within a few seconds.

The endothelium not only transmits vasodilatory signals but also functions as a barrier to prevent materials from being transported between the interstitial and lumen of blood arteries [34]. NO plays a role in regulating the permeability of this barrier, that is essential for homeostatic equilibrium. Because NO reduces endothelial permeability, its effects on vascular permeability seem as primarily anti-inflammatory [35]. Initially, for the mobilization of a leukocyte to the site of injury or infection, the leukocytes must be "trapped" to establish contact with endothelium. This is achieved by up-regulation of P-selectins, a family of adhesion molecules, which is located in Weibel-Palade bodies in the cytoplasm of ECs.

The leukocytes move continuously in the blood vessel because of the relatively low-affinity binding, which has been explained as "rolling" within the endothelium. The momentum of the leukocyte is drastically decreased to interact with the endothelial integrins, such as ICAM-1 through the CD11/CD18 family of adhesion molecules. The expression of P-selectin appears to be significantly regulated by NO [8]. P-selectin expression is increased by inhibitors of NO synthase, while P-selectin expression is decreased by NO, which results in increased leukocyte adhesion to the endothelium [36]. Leukocyte infiltration at the site of injury or infection is a defining characteristic of inflammation that could lead to endothelial dysfunction induced by obesity and is significantly influenced by NO. Leukocyte adhesion to the endothelium is intensely increased when NO generation is inhibited, which promotes endothelial dysfunction [36], whereas NO can significantly reduce leukocyte adhesion to the vascular endothelium in response to stimulation through a chemotactic agent (Fig. 4).

Furthermore, NO may inhibit neutrophil aggregation and generation, preventing it from injury-induced by the potent reactive oxygen metabolites [4]. In response to contact with antigens, bacterial products, or several factors, mast cells secrete a variety of chemical signals, such as histamine, serotonin, platelet-activating factor (PAF), leukotrienes, TNF, heparin, and prostaglandins. These indicated that mast cells are crucial in regulating inflammatory responses. Mast cells serve to send a signal to the immune system when foreign pathogens or toxic substances are present [37]. The activities of mast cell appear to be controlled by NO, which comes either from another cellular source or mast cell itself, while interleukin-1β (IL-1β) activation can significantly increase the amount of NO secret from mast cells [9]. The secretion of several inflammatory mediators from these cells, such as histamine, PAF, and TNF, appears to be down-regulated by the NO secreted through the mast cell, which is an interesting finding. Also, the synthesis of NO by mast cells can lead to a decrease in the propensity of these cells to degranulate [38].

NO could prevent macrophages from producing a range of immunomodulatory cytokines, including IL-12 and IL-1 and it can also control how macrophage-derived cytokines affect target cells. According to a previous study, administering aspirin to rats led to TNF-dependent apoptosis of cells in the stomach mucosa. It has been investigated that an aspirin derivative that releases NO can significantly lower apoptosis and protect gastric chief cells from TNF-induced injury triggered by cGMP-dependent and independent mechanisms [8]. Platelets are essential for inflammatory processes, blood clotting and thrombosis. Serotonin, thromboxane, and lipoxins, are among other proinflammatory mediators that can be released by platelets. Vascular endothelial growth factor (VEGF) and endostatin are among the substances present in platelets that can regulate the angiogenesis (development of new blood vessels) process.

One of the strongest pro-angiogenic agents is VEGF, while endostatin is a potent inhibitor of angiogenesis [34, 38]. Many soluble mediators, including NO, regulate platelet adhesion and aggregation to the vascular endothelium. Therefore, NO exhibits a significant role in downregulating inflammatory processes by down-regulating platelet aggregation and adhesion (Fig. 4). The pro-angiogenic effects of VEGF are also partially mediated by NO, which has an impact on tumour growth and repair [8].

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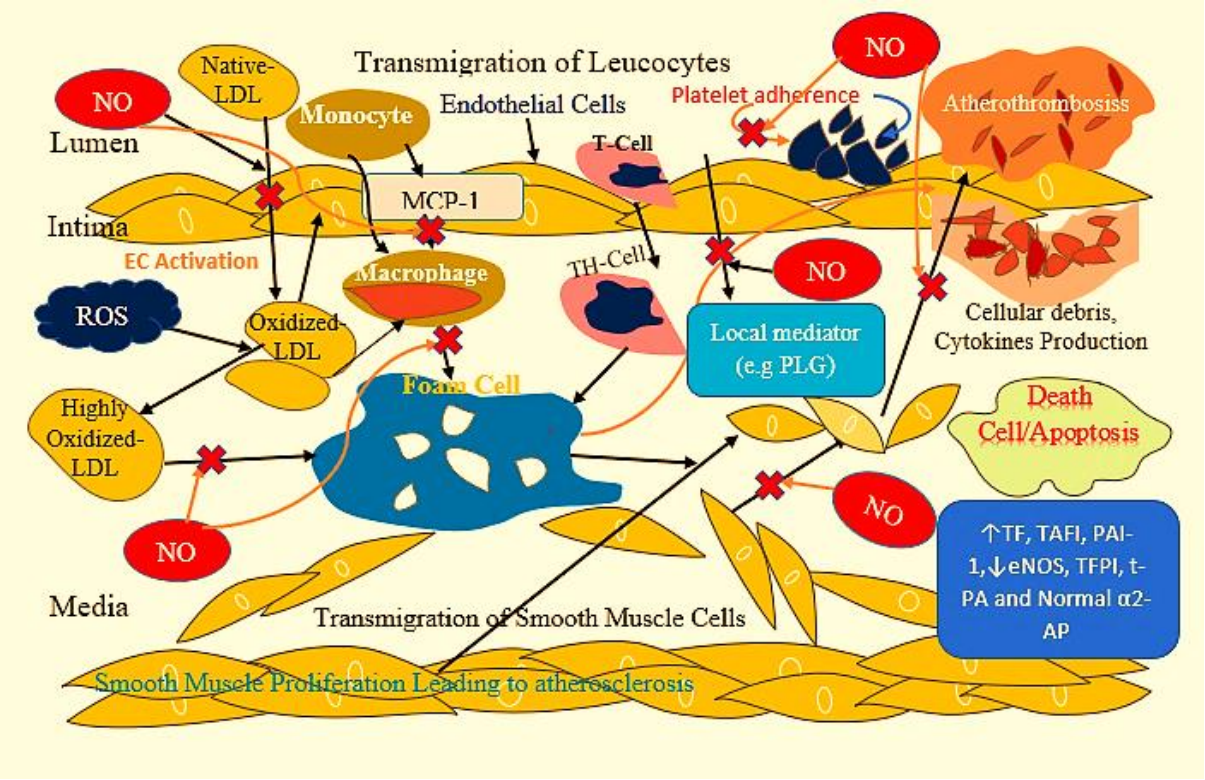

Figure 4.
Possible mechanisms of action of no on obesity-induced endothelial dysfunction.

During atherothrombosis, monocytes are attached to the endothelium. The endothelial permeability allows the LDL particles to penetrate and enter the arterial wall. Within the endothelium, mature monocytes transform into macrophages and engulf the LDL particles to generate foam cells. The SMCs transmigrate to the tunica intima. The rupture of the plaque fibrous cap leads to the generation of atherothrombosis. TF; tissue factor, PLG; prostaglandin, TFPI; tissue factor pathway inhibitor, TAFI; thrombin activatable fibrinolysis inhibitor, eNOS; endothelial nitric oxide, PAI-1; plasminogen activator inhibitor, t-PA; tissue-type plasminogen activator, α_2-AP; α_2-antiplasmin, MCP-1; monocyte chemoattractant protein-1.

3.2.2. NO as an Antioxidant

Both *in vitro* and *in vivo* studies have shown that NO is a free radical scavenger similar to O_2^- [8]. It was discovered that administering NO increased the antioxidant capability of the plasma by twofold. Furthermore, these NO concentrations reduced the reperfusion-induced mucosal damage, which has been demonstrated to be mediated by reactive oxygen metabolites. The exact method by which NO scavenges O_2 is not known. It is probable that when NO production is greater than local O_2-generation, ONOO may decompose faster to nitrate and nitrite, decreasing tissue exposure to $ONOO^-$ and to the OH^- that could be produced by $ONOO^-$. The O_2^- is a potent modulator of mast cells, that facilitates activation and degranulation in this content [39, 40].

In the previous studies, administering the superoxide scavenger superoxide dismutase significantly reduced the intestinal epithelial permeability, facilitated by the suppression of NO production. Thus, it was proposed that an accumulation of O_2^- occurred due to decreased NO after NO synthase inhibitor has been administered. Additionally, the presence of O_2 may promote mast cell activity or function, increase epithelial permeability, and act as a precursor to the formation of the potent reactive oxygen metabolites. Also, NO acts as a superoxide scavenger and might potentially inhibit the formation of O_2.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 3441-3456, 2024
DOI: 10.55214/25768484.v8i6.2730

Previous studies have suggested that NO may prevent neutrophils from producing O_2 by directly blocking NADPH oxidase [8].

3.2.3. NO Regulates Vasomotor Tone of the Endothelium

Recent study has shown that endothelium releases NO to counteract the intrinsic constrictive properties of acetylcholine on the VSM. Endothelial dysfunction is initiated by several pathophysiological conditions, mostly through a reduction in the endothelium-dependent vasodilation [8]. Endothelial dysfunction resulting from a block in NO secretion, may lead to agonistic activate smooth muscle receptors to cause vasoconstriction rather than endothelium-dependent vasodilation. Increased intracellular free Ca^{2+} in VSMC may cause their contraction. The substantial vasorelaxant action of NO blocks this latter effect when the endothelium is normal. Numerous agonists, including acetylcholine, bradykinin, serotonin, adenosine, ADP, ATP, histamine, and thrombin, are potent in this regard. Even angiotensin II induces macrovascular endothelium to release NO, which potentially modulates the vasoconstrictor effects of angiotensin II on VSMC [9, 41]. This advantageous effect might be negated by the concurrent formation of peroxynitrite ($ONOO^-$), which might contribute to various pathophysiological activities in the vascular endothelial wall.

Experimental evidence has shown the significance of NO as a modulator of endothelial vasomotor tone by suppressing its generation, while the L-guanidino arginine group can be chemically altered to produce substances that block NO synthase. NG-monomethyl-L-arginine (L-NMMA), NG-nitro-L-arginine (L-NA), and NG-nitro-L-arginine methyl ester (L-NAME) are all inhibitors of NO release from ECs and aortic rings, demonstrating that NO is continually released from these tissues, which maintain the vasodilator tone. Evidence has shown that the blood pressure of rats and rabbits increases *in vivo* by around 30 mm Hg after receiving short-term doses of L-NMMA or L-NA [8]. Therefore, under typical circumstances, NO can prevail over constrictive forces. In another animal model, it was shown that L-NMMA was administered systemically to an awake dog at dosages, which elevate systemic blood pressure by inhibiting NO secretion in the systemic circulation and by increasing coronary vascular resistance. This study raises the possibility that NO release, particularly at the arterioles (resistance arteries) in the vascular distributions, may be physiologically important in the modulation of basal systemic and coronary tone.

Numerous studies have examined the function of NO in human basal vascular tone [40]. When L-NMMA was infused intravenously, NO secretion in the forearm was inhibited, and the blood flow in the arm was measured using strain gauge plethysmography before and after this event. Because of the vasoconstrictor effects of L-NMMA, it is possible that NO had a substantial role in the forearm's resistance to the arterial basal dilator tone. Furthermore, L-NMMA decreased the vasodilatory activity to intra-arterial infusion of acetylcholine, signifying that this agonist enhances NO generation from endothelium. Also, following the injection of L-NMMA into coronary arteries of indivivuals with normal coronary angiograms, who have no associated risk to develop coronary atherosclerosis, it was discovered that the epicardial coronary diameter and coronary blood flow were reduced by 14% and 19%, respectively [8].

This demonstrated that NO may contribute to basal epicardial and arteriolar dilator tone in the normal coronary circulation. L-NMMA dramatically reduced the acetylcholine-induced vasodilator response in these healthy patients at the epicardial and microvascular levels of coronary circulation, suggesting that acetylcholine may facilitate the secretion of NO from the coronary endothelium [1, 6].

3.2.4. The Key Modulators of NO Pathways

Currently, the used of NO to restore homeostasis has been improved by many treatment approaches. The most effective approach at this time is requires the administration of some drugs to trigger the downstream eNOS/NO effectors and inhibit eNOS uncoupling, improve BH4 and L-arginine bioavailability, and control eNOS post-translational modifications [43]. There are numerous therapeutic strategies available, which target the production and oxidative inhibition of NO in the human vascular. It is commonly acknowledged that inhibiting the renin-angiotensin-aldosterone pathway is an effective treatment for obesity-induced endothelial dysfunction related to CVDs [44].

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 3441-3456, 2024
DOI: 10.55214/25768484.v8i6.2730

Angiotensin-converting enzyme inhibitors (ACE-I) and AT1 receptor blockers (ARBs) can increase BH4 bioavailability, decrease eNOS uncoupling, and prevent cerebral ischemia by increasing eNOS activity in the middle cerebral artery, while decreasing the size of cerebral infarcts as investigated in animal models [9]. The renin-angiotensin system blockers also have NO-dependent antithrombotic actions. In addition to this, a study has shown that angiotensin 1-7, a part of the renin-angiotensin system, enhanced the generation of NO, which helps to reduce thrombosis in rats. Additionally, the antioxidant, anti-inflammatory, and anti-atherosclerotic potentials of statins, help to lower cholesterol and promote endothelial functions by increasing NO bioavailability. Previous study has reported that fluvastatin treatment improved endothelial vasodilation by increasing NO production in hypercholesterolemic individuals [9]. In an experimental MI rat model, statins have been found to decrease eNOS uncoupling by decreasing vascular O^2 and BH4 oxidation.

Also, statins were discovered to prolong longevity by restoring EPCs mobility, neovascularization of the heart, and enhancing NO bioavailability. Improved endothelium homeostasis can also be achieved by stimulating β--adrenoreceptor subtype 3 ($\beta 3$), that causes eNOS activation and ultimately increases NO bioavailability [45]. A prospective medication that can improve NO pathways is nebivolol, a third-generation β--adrenoreceptor blocker, since it can inhibit β-1 and activate β-3 receptors. Existing studies have reported that nebivolol increases the production of endothelial NO in the conductance and resistance of rat arteries in a calcium-dependent way. The same researchers examined the heart production of the NO in mice after iNOS enhanced activity and activation of the $\beta 3$ receptor. Hence, nebivolol can be considered as a therapeutic target for CVDs associated with obesity-induced endothelial dysfunction.

The relationship between the adrenergic pathway, NO bioavailability, and oxidative stress is another aspect that requires attention. This context shows that the significant effects of nebivolol are due to its antioxidant potentials, that were thought to be another factor that causes an increase in the NO bioavailability [46]. Nebivolol has also been proven to improve mortality and morbidity in elderly individuals with CVDs. It has been shown to inhibit platelet aggregation by increasing NO bioavailability, which indicates the antithrombotic effects of this β-blocker [47]. However, it is very essential to know that adopting a normal lifestyle is a useful strategy for the prevention and attenuation of obesity-induced endothelial dysfunction linked with CVDs. In this regard, physical activity and certain diets, including diets rich in polyphenols, were identified to activate NO pathways.

Physical activity (PE) is crucial for lowering the risk of CVDs, oxidative stress linked to ageing, preventing and attenuating endothelial dysfunction, as shown by several experimental and epidemiological findings [48]. Recent research has demonstrated that regular exercise reduces oxidative stress and activates the production of nitrite and eNOS in spontaneously hypertensive rats [48]. It has been proposed that the enhancement of NO function might be associated to the decrease in oxidative stress brought by PE. Previous studies demonstrated that water-based exercises boosted NO metabolism by enhancing endothelial function and cardiorespiratory capacity in individuals with chronic heart failure and coronary artery disease [48]. PE has cardioprotective effects, as shown by the increase in NO metabolite concentrations and decrease in MI following high-intensity interval training in ischemic rats [43].

The impacts of PE on NO generation have been attributed to several molecular processes, including the phosphorylation state and eNOS transcription rate. For instance, it was discovered that eNOS mRNA levels were elevated in rats that underwent both acute and long-term aerobic training. Previous studies have shown that exercise might enhance cardiac function in ischemic rats through the $\beta 3$ adrenoreceptor by raising the eNOS phosphorylation [9]. Some researchers have emphasized the involvement of the $\beta 3$ adrenoreceptor in mediating the activities of PE on the NO generation. In this regard, other investigators suggested that a significant amount of eNOS uncoupling might be needed for exercise-induced myocardial cardio-protection in ischemia-reperfusion [49].

Finally, vascular endothelium is perhaps the most crucial body defence mechanism against obesity-induced endothelial dysfunction, which can result in atherothrombotic CVDs, as shown by the aforementioned sources [6]. Determination of the obesity-induced endothelial function in humans,

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 3441-3456, 2024
DOI: 10.55214/25768484.v8i6.2730

appears to be predictive, and therapeutic interventions that boost the bioavailability of vascular endothelial NO may enhance long-term outcomes in normal individuals, high-risk subjects, or those who have endothelial dysfunction that leads to obesity-induced atherosclerotic CVDs [50]. Insulin sensitizers, novel antioxidant compounds, or combinations of classic antioxidant agents, as well as drugs that target endothelial NO synthase "coupling" are some of the more recent therapeutic strategies that target endothelial dysfunction in certain disease conditions. The identification of prospective responders to therapies that target particular intracellular pathways in the vascular endothelium may one day be aided by genetic profiles [6, 51].

4. Conclusion

It is very clear that NO plays a key role in mediating several endothelial regulatory functions. It is also becoming certain that several conditions which are thought to be "risk factors" for obesity-induced endothelial dysfunction, leading to atherothrombotic CVDs may be associated with the reduction in NO bioavailability. Obesity-induced endothelial dysfunctions have been linked to an increasing number of diseases, such as hypercholesterolemia, hyperlipidaemia, systemic hypertension, smoking, DM, and congestive heart failure. Therefore, under these conditions, the vascular endothelial wall may promote inflammatory processes, such as lipoprotein oxidation, smooth muscle proliferation, extracellular matrix accumulation or lysis, deposition of lipid-rich material, platelet activation, and thrombus generation. These obesity-induced related endothelial dysfunctions could influence the onset and clinical manifestation of atherosclerosis, progressing to CVDs. New treatment approaches for various CVDs are anticipated to result from the interactions that boost endogenous NO production, function or complement it with exogenous NO. Additional research is required to confirm the validity of various treatments that appeared to be helpful in restoring endothelial function.

Funding:
This review was sponsored by the Universiti Putra Malaysia (UPM), Faculty of Medicine and Health Sciences, under IPS (UPM/800-3/3/1/GP-IPS/2020/9686500) Grant, office of the Vice-Chancellor (Research and Innovation), UPM, Malaysia.

Acknowledgement:
The hard work of the School for Postgraduate Studies, UPM, and the management of UPM, for admission offer and encouragement to write this little manuscript with the automatic grantee to pay for its publication charges, are highly appreciated.

Abbreviations:

ICAM-1	Intercellular Adhesion Molecule-1
VCAM-I	Vascular Cell Adhesion Molecule-1
JNK–c-	Jun N-Terminal Kinase
TF	Tissue Factor
IL-10	Interleukin-10
ROS	Reactive Oxygen Species
VEGF	Vascular Endothelial Growth Factor
TNF-α	Tumour Necrosis Factor-α
PGL2	Prostacyclin
IL-6	Interleukin-6
CCL	Chemokine (C-C Motif) Ligand,
EC	Endothelial Cells
ET1	Endothelin-1
FGF	Fibroblast Growth Factor
H2S	Hydrogen Sulfide
PGH2	Prostaglandin H2
PGI2	Prostacyclin
t-PA	Tissue Plasminogen Activator
VSMC	Vascular Smooth Muscle Cells

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 3441-3456, 2024
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SO_2	Superoxide
uPA	Urokinase Plasminogen Activator
EPCR	Endothelial Protein C Receptor
TH	T-Helper
NO	Nitric oxide,
IKK	Inhibitor of K- Kinase
PKR	Protein Kinase-R
CRP	C-Reactive Protein
HGF	Hepatocyte Growth Factor
IGF-1	Insulin-Like Growth Factor-1
MMP2	Matrix MetalloProteinase-2
TAFI	Thrombin-Activatable Fibrinolytic Inhibitor
TFPI	Tissue Factor Pathway Inhibitor
CAMs	Cells Adhesion Molecules
EDHF	Endothelium-Derived Hyperbolizing Factor
EGF	Epidermal Growth Factor
HSPG	Heparan Sulfate Proteoglycans
PAF	Platelet-Activating Factor
PAI-1	Plasminogen Activator Inhibitor-1
PDGF	Platelet-Derived Growth Factor
TGF-β	Transforming Growth Factor-β
TXA2	Thromboxane A2,
vWF	vonWillebrand Factor
H_2O_2	Hydrogen Peroxide
TM	Thrombomodulin,
α_2-AP	α_2-Antiplasmin

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ISSN: 2576-8484
Vol. 8, No. 6: 3441-3456, 2024
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Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 3441-3456, 2024
DOI: 10.55214/25768484.v8i6.2730