

# Clinical and Humoral Aspects of Endothelial Dysfunction in Impaired Renal Function in Patients with Chronic Heart Failure

Zakirova G. A., Masharipova D. R., Tagaeva D. R.\*

Republican Scientific and Practical Medical Center of Specialized Therapy and Medical Rehabilitation, Tashkent, Uzbekistan

**Abstract** The endothelium is a dynamic, functionally complex organ that modulates a variety of biological processes, including vascular tone and permeability, inflammatory responses, thrombosis, and angiogenesis. Endothelial dysfunction poses a threat to the integrity of the vascular system and plays a key role in the pathogenesis of atherosclerosis and cardiovascular diseases. Decreased nitric oxide (NO) bioavailability is a hallmark of chronic kidney disease (CKD), with this impairment occurring almost universally in patients who have reached the most advanced phase of CKD, end-stage renal disease (ESRD). Low bioavailability NO in CKD depends on several mechanisms affecting the expression and activity of endothelial NO synthase (eNOS). Accumulation of endogenous eNOS inhibitors, inflammation and oxidative stress, glycosylation products (AGEs), bone mineral imbalances including hyperphosphatemia, high levels of the phosphaturic hormone fibroblast growth factor 23 (FGF 23), and low levels of the active form of vitamin D. (1.25 vitamin D) and anti-aging vasculoprotective factor Klotho influence bioavailability NO and are critical for endothelial dysfunction in CKD. Large-scale multidimensional interventions are needed to counteract endothelial dysfunction in CKD, altering arterial disease and cardiovascular complications in this high-risk group.

**Keywords** Endothelial dysfunction, Nitric oxide, Cardiovascular risk, Chronic kidney disease (CKD), End-stage kidney disease (CKD)

## 1. Introduction

Over the past three decades, chronic kidney disease (CKD) has risen in the ranks of diseases responsible for the global mortality burden. In 2016, this disease ranked 13th in the list of causes of death, and in 2040 it is predicted to be the 5th cause of death [1]. With kidney disease affecting 850 million people, CKD is now considered a major global public health priority [2]. In addition to other risk factors, CKD itself is one of the strongest risk factors for death from cardiovascular disease, with 1.2 million deaths from cardiovascular disease secondary to CKD in 2013 [3]. The heavy burden of cardiovascular disease in this population is not explained by traditional risk factors [4]. CKD-specific cardiovascular risk factors including sodium retention and volume gain, low serum albumin, anemia [5], factors associated with metabolic bone disorders (MBD) in CKD [6] and accumulation of potentially toxic substances excreted by the kidneys [7] all contribute to the development of atherosclerosis, cardiomyopathy, and cardiovascular complications in these patients.

Atherosclerosis is a process that begins at the level of the endothelium [8], which is a dynamic, functionally complex organ involved in the regulation of a number of important biological mechanisms, including the maintenance of vascular tone and permeability, inflammatory responses, immunity and angiogenesis. Therefore, maintaining endothelial cell structure and function is fundamental to vascular health. Endothelial dysfunction (ED), which underlies atherosclerosis, is evident early in patients with CKD, and the prevalence of this change gradually increases as the disease progresses to end-stage renal disease (ESRD) [9]. Worsening ED at different stages of CKD is accompanied by an increasingly higher risk of death from cardiovascular disease in this condition. Indeed, the excess risk for this outcome is 40% (hazard ratio-HR = 1.4) in patients with glomerular filtration rate (GFR) from 45 to 59 ml/min/1.73 m<sup>2</sup> and 340% (HR = 3.4) in patients with ESKD (GFR < 15 ml/min/1.73 m<sup>2</sup>). Decreased bioavailability of nitric oxide (NO), a gaseous molecule with vasodilatory, anti-inflammatory, and antithrombotic properties [10], is a hallmark of ED in CKD. NO plays a fundamental role in ED and arterial remodeling through several mechanisms, including inhibition of platelet aggregation and monocyte adhesion to endothelial cells, inhibition of low-density lipoprotein (LDL) cholesterol oxidation, and suppression of smooth muscle cell hyperplasia

\* Corresponding author:

dilnoza\_tagaeva@mail.ru (Tagaeva D. R.)

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and hypertrophy.

The generation of NO from L-arginine is catalyzed by three NO synthase (NOS) isoenzymes. Although neuronal NOS (nNOS or NOS-1) is expressed in the nervous system and cytokine-inducible NOS (iNOS or NOS-2) is released by proinflammatory cytokines, the primary regulator of endothelial NO bioavailability is endothelial NO synthase (eNOS-2) or NOS-3. eNOS can be activated by both calcium-dependent and calcium-independent pathways. Several NO agonists, including acetylcholine (ACh), bradykinin (BK), adenosine triphosphate (ATP), adenosine diphosphate (ADP), endothelin-1, serotonin, histamine and thrombin, bind to their receptors or open ion channels at sites located on the endothelium of the cell. Membranes to increase the influx of calcium ions and stimulate its release from the endoplasmic reticulum, which serves as an intracellular calcium depot. eNOS is predominantly localized to flask-shaped invaginations of the plasma membrane, caveolae, which contain the protein caveolin-1. Increased intracellular calcium changes conformation calmodulin (CaM) through the formation of calcium-calmodulin complexes. Calcium-CaM-dependent dissociation of eNOS from caveolin-1 allows translocation eNOS into the cytosol, where all cofactors and substrates for activation of this enzyme are present in abundance [11].

Moreover, the association of this complex with heat shock protein 90 further induces eNOS activity. On the other hand, growth factors (vascular endothelial growth factor (VEGF)), hormones (insulin and adiponectin) and shear stress initiate phosphorylation eNOS, a post-translational modification that enhances eNOS activity independently of calcium [12]. Although eNOS is primarily synthesized as a monomeric compound, it is necessary to form dimers to bind its substrate and cofactors and achieve NO generation. The dimer consists of two subunits. The first subunit is an oxygenase domain with binding sites for zinc, iron protoporphyrin IX (heme Fe), tetrahydrobiopterin (BH4) and the substrate L-arginine. The second subunit is a reductase domain with cofactor binding sites flavin adenine (FAD), flavin mononucleotide (FMN), reduced nicotinamide adenine dinucleotide phosphate (NADPH) and CaM [13]. Molecular oxygen binds to eNOS in the oxidase domain, is reduced by NADPH and incorporated into L-arginine to form an intermediate, NG-hydroxy-L-arginine, which is ultimately converted to L-citrulline, NO and NADP<sup>+</sup>. The absence of BH4 results in a state called eNOS uncoupling, which involves the conformation eNOS from dimeric to monomeric form. In this form, eNOS releases superoxide anion, a highly reactive free radical, instead of NO. Under conditions of low intracellular calcium concentration, the store-operated calcium channel (SOC) is stimulated to uptake extracellular calcium, while shear stress activates the calcium-potassium channel, allowing calcium influx into endothelial cells. Once formed, NO diffuses across the smooth muscle cell membrane and enhances the expression of the enzyme soluble guanylyl cyclase (sGC), which catalyzes the reaction of guanosine triphosphate (GTP) with cyclic guanosine monophosphate (cGMP).

The effect of this reaction is the stimulation of protein kinase G (PKG), which activates calcium transport out of the cell and subsequently inhibits the activity of myosin light chain kinase (MLCK), causing relaxation of vascular smooth muscle cells [10]. However, cGMP-independent signaling such as S-nitrosylation of proteins; activation of endoplasmic reticulum calcium ATPase; and the formation of cyclic inosine monophosphate (cIMP) may also be involved.

ED can be defined as an imbalance between vasoconstrictor and vasodilator molecules generated by or acting on the endothelium. However, since the endothelium is a ubiquitous tissue, this disorder can be considered a systemic disease characterized by limited bioavailability of NO, which may result from either decreased synthesis or increased consumption. Due to its complex mechanism, the location of eNOS within the endothelial cell is critical to its function. Caveolae are lipid-containing endothelial plasma membrane microdomains where eNOS binds and is directly regulated by the protein caveolin. eNOS activity in caveolae can be regulated by a variety of extracellular factors that influence the eNOS-caveolin association. In particular, disorders of cholesterol and lipoprotein metabolism disrupt the normal localization and activity of eNOS. Oxidized LDL (Ox-LDL), but not native LDL, binds to the endothelial scavenger cell receptor cluster of differentiation 36 (CD36) to deplete cholesterol caveolae, thereby promoting the displacement of the eNOS-caveolin complex from caveolae into the cytoplasm, where eNOS activity is directly inhibited [14,15]. Moreover, in clinical studies, statin treatment causes a significant decrease in CD36 expression prior to changes in Ox-LDL [16]. In addition to this mechanism, Ox-LDL may also interfere with NO production through other cholesterol-independent mechanisms, including suppression of BH4 production, excessive production of superoxide anions, and disruption of ACh-induced and serotonin-induced eNOS activation. However, Ox-LDL does not affect phosphorylation eNOS [17]. In patients with CKD and hemodialysis (HD) patients, Ox-LDL levels are inversely associated with carotid artery distensibility and smoking in the general population [18]. Similarly, another population-based study found that the Ox-LDL/apoB100 ratio was inversely associated with vascular endothelial function [19], and Ox-LDL and severity of malnutrition were independent determinants of flow-mediated vasodilation in HD patients [20]. Moreover, intervention strategies that improve the lipidemic profile (including weight loss, healthy diet adaptations, physical activity, and administration of multiple antilipidemic agents) are associated with improvement in ED by suppressing Ox-LDL levels and oxidative stress (OS) [21-25].

Subcellular redistribution of eNOS induced by Ox-LDL can be improved by high-density lipoprotein (HDL) cholesterol through endothelial caveolae - scavenger receptor class B, type I (SR-BI)-induced kinase signaling. Moreover, HDL acts as an eNOS agonist by enhancing post-translational phosphorylation of the enzyme [26]. In clinical settings, HDL has been found to be an independent predictor of endothelial function [27,28]. In contrast, in patients with

coronary artery disease (CAD) and HDL depletion, a 25% increase in HDL levels induced by pharmacological treatment with niacin was associated with a significant improvement in ED [29]. Moreover, administration of apoA-1/phosphatidylcholine particles to hypercholesterolemic men and ATP-binding cassette transporter to HDL-depleted heterozygotes resulted in a significant increase in endothelial activity [30,31].

Several signal transduction molecules that regulate eNOS activity colocalize with eNOS within caveolae, including G protein-mediated and calcium-mediated protein kinase and lipid signaling molecules [32]. Among them, estradiol enhances eNOS activity through both genomic and nongenomic actions localized in caveolin estrogen receptor (ER)  $\alpha$ , even in the absence of CaM, calcium and other cofactors eNOS. ER antagonists, antibodies, and calcium chelation [33] inhibit the interaction between eNOS and ER $\alpha$  in caveolae. The mechanisms underlying the beneficial effects of estrogens are likely to be suppression of OS, which increases the bioavailability of NO and improves the response of smooth muscle cells to vasodilatory stimuli [34,35]. Compared with premenopausal women, ED is more severe in postmenopausal women with estrogen depletion and in men of the same age [36]. The protective effect of estrogens on arterial function may also be due to a decrease in vascular BH4, an important cofactor for eNOS activation, in postmenopausal women. BH4 supplementation improved arterial stiffness and increased endothelial -dependent vasodilation of the carotid and brachial arteries in postmenopausal women with estrogen deficiency, but had no effect in premenopausal women [37].

Flow-mediated vasodilation (FMD) is based on ultrasound imaging of the brachial artery in two conditions: baseline and after acute temporary arterial occlusion (cuff inflation) in the forearm. This test is based on the observation that there is a direct relationship between the magnitude of postocclusion arterial dilatation (a physiological response to ischemia dependent on the generation of NO by the vascular endothelium) [38]. Moreover, forearm FMD reflects endothelial function in the coronary arteries [39] and is considered a reliable indicator of NO bioavailability in various clinical conditions, including CKD, essential hypertension and CAD, and this biomarker has been studied and associated with the stage of CKD in patients with kidney disease [41]. Although it has been successfully used in clinical studies to test NO-dependent vasodilation, this method has conceptual limitations due to cyclooxygenase [42] and hydrogen peroxide [43], both of which affect FMD through NO-independent mechanisms. In addition, the generation of endothelium-induced vasoconstrictors or impaired sensitivity of vascular smooth muscle cells to the NO signal contribute to a decrease in vasodilation [11]. Therefore, in clinical studies aimed at assessing the bioavailability of NO, it is necessary to test inhibitors of eNOS and cyclooxygenases [11].

Laser Doppler flowmetry and imaging, a reliable indicator of skin microvasculature function, is based on the diffusion and refraction of a beam of laser light at a known frequency.

By shifting the direction of the laser beam away from the vessels, the change in wavelength of light (known as the Doppler effect) reflects the number and speed of red blood cells in the microvessels. In CKD, abnormal measurements obtained using this method not only detect ED, but also predict cardiovascular mortality [44,45]. Although simple and easy to perform, this method provides only an indirect measurement of skin perfusion rather than a direct assessment of blood flow. It should be noted that differences in anatomical structures may cause measurement variability, resulting in limited reproducibility of the method [46].

Venous occlusion plethysmography was the first method used to assess peripheral endothelial function [47], but is now rarely used because it is impractical and time-consuming. This technique involves inflating a cuff around the wrist and upper arm to block venous drainage. Vascular reactivity is assessed by measuring changes in forearm volume in response to reactive hyperemia or infusion of vasoactive compounds [47].

Markers of OS, inflammation, endothelial -leukocyte cell adhesion molecules, NO levels, eNOS inhibitors (such as ADMA) and new endothelial- specific markers are considered markers of ED. Because there is a well-established bidirectional relationship between ED and inflammation, levels of circulating inflammatory biomarkers correspond to the severity of ED. This category includes circulating C-reactive protein (CRP), interleukins (IL), tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), MCP-1, and CD40 ligand. Perhaps the most endothelial -specific biomarkers of endothelial damage are cell adhesion molecules, vascular adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), endothelial selectin, and compounds involved in the coagulation pathway, such as plasma fibrinogen, and von Willebrand factor (VWF). However, most compounds listed as biomarkers of ED, including EF, are nonspecific to the vascular endothelium and therefore may not reflect ED in the coronary system [48].

Renal synthesis of the NO precursor L-arginine is reduced in patients with CKD. Moreover, the transport of L-arginine into endothelial cells and the shunting of this amino acid into other pathways, such as arginase, contribute to a decrease in the availability of this NO precursor. In patients with hypertension, mechanical hemolysis occurs, leading to an increase in free hemoglobin. Because this oxygen carrier molecule is also a recognized NO scavenger, free hemoglobin may contribute to decreased NO bioavailability in HD patients.

## 2. Conclusions

The endothelium is the most important protective system against atherosclerosis. In CKD, damage to the vascular endothelium occurs early, develops as the disease progresses, and significantly contributes to cardiovascular complications in these patients. ED in patients with CKD reflects multifactorial endothelial damage combined with impaired endothelial repair and regeneration. Pathways underlying these processes include various uremic toxins such as

endogenous eNOS inhibitors, proinflammatory cytokines and OS, AGE, phosphate and FGF23, as well as subnormal levels of vascular endothelial protective factors such as Klotho and vitamin D.

To effectively counteract or prevent ED and associated atherosclerotic complications in CKD, a large-scale multidimensional intervention is required, including suppression of OS and inflammation, correction of disturbances in mineral homeostasis, and removal of toxins.

## REFERENCES

- [1] Foreman K.J., Marquez N., Dolgert A., Fukutaki K., Fullman N., McGaughey M., Pletcher M.A., Smith A.E., Tang K., Yuan C.-W., et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: Reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet (Lond. Engl.)* 2018; 392: 2052–2090. doi: 10.1016/S0140-6736(18)31694-5. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [2] Jager K.J., Kovesdy C., Langham R., Rosenberg M., Jha V., Zoccali C. A single number for advocacy and communication -Worldwide more than 850 million individuals have kidney diseases. *Nephrol. Dial. Transplant.* 2019; 34: 1803–1805. doi: 10.1093/ndt/gfz174. [PubMed] [CrossRef] [Google Scholar]
- [3] Thomas B., Matsushita K., Abate K.H., Al-Aly Z., Årnö J., Asayama K., Atkins R., Badawi A., Ballew S.H., Banerjee A., et al. Global Cardiovascular and Renal Outcomes of Reduced GFR. *J. Am. Soc. Nephrol.* 2017; 28: 2167–2179. doi: 10.1681/ASN.2016050562. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [4] Weiner D.E., Tighiouart H., Elsayed E.F., Griffith J.L., Salem D.N., Levey A.S., Sarnak M.J. The Framingham Predictive Instrument in Chronic Kidney Disease. *J. Am. Coll. Cardiol.* 2007; 50: 217–224. doi: 10.1016/j.jacc.2007.03.037. [PubMed] [CrossRef] [Google Scholar]
- [5] Zoccali C. Traditional and emerging cardiovascular and renal risk factors: An epidemiologic perspective. *Kidney Int.* 2006; 70: 26–33. doi: 10.1038/sj.ki.5000417. [PubMed] [CrossRef] [Google Scholar]
- [6] Zoccali C., Vanholder R., Massy Z.A., Ortiz A., Sarafidis P., Dekker F.W., Fliser D., Fouque D., Heine G.H., Jager K.J., et al. The systemic nature of CKD. *Nat. Rev. Nephrol.* 2017; 13: 344–358. doi: 10.1038/nrneph.2017.52. [PubMed] [CrossRef] [Google Scholar]
- [7] Vanholder R., Pletinck A., Schepers E., Glorieux G. Biochemical and clinical impact of organic uremic retention solutes: A comprehensive update. *Toxins*. 2018; 10: 33. doi: 10.3390/toxins10010033. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [8] Gimbrone M.A., García-Cardena G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ. Res.* 2016; 118: 620–636. doi: 10.1161/CIRCRESAHA.115.306301. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [9] Yilmaz M.I.M.I., Saglam M., Caglar K., Cakir E., Sonmez A., Ozgurtas T., Aydin A., Eyileten T., Ozcan O., Acikel C., et al. The determinants of endothelial dysfunction in CKD: Oxidative stress and asymmetric dimethylarginine. *Am. J. Kidney Dis.* 2006; 47: 42–50. doi: 10.1053/j.ajkd.2005.09.029. [PubMed] [CrossRef] [Google Scholar]
- [10] Vanhoutte P.M., Zhao Y., Xu A., Leung S.W.S. Thirty Years of Saying NO: Sources, Fate, Actions, and Misfortunes of the Endothelium-Derived Vasodilator Mediator. *Circ. Res.* 2016; 119: 375–396. doi: 10.1161/CIRCRESAHA.116.306531. [PubMed] [CrossRef] [Google Scholar]
- [11] Vanhoutte P.M., Shimokawa H., Feletou M., Tang E.H.C. Endothelial dysfunction and vascular disease—A 30th anniversary update. *Acta Physiol.* 2017; 219: 22–96. doi: 10.1111/apha.12646. [PubMed] [CrossRef] [Google Scholar]
- [12] Heiss E., Dirsch V. Regulation of eNOS Enzyme Activity by Posttranslational Modification. *Curr. Pharm. Des.* 2014; 20: 3503–3513. doi: 10.2174/13816128113196660745. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [13] Peng H.M., Morishima Y., Pratt W.B., Osawa Y. Modulation of heme/substrate binding cleft of neuronal nitric-Oxide synthase (nNOS) regulates binding of Hsp90 and Hsp70 proteins and nNOS ubiquitination. *J. Biol. Chem.* 2012; 287: 1556–1565. doi: 10.1074/jbc.M111.323295. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [14] Blair A., Shaul P.W., Yuhanna I.S., Conrad P.A., Smart E.J. Oxidized low density lipoprotein displaces endothelial nitric-Oxide synthase (eNOS) from plasmalemmal caveolae and impairs eNOS activation. *J. Biol. Chem.* 1999; 274: 32512–32519. doi: 10.1074/jbc.274.45.32512. [PubMed] [CrossRef] [Google Scholar]
- [15] Gharavi N.M., Baker N.A., Moulliselleaux K.P., Yeung W., Honda H.M., Hsieh X., Yeh M., Smart E.J., Berliner J.A. Role of endothelial nitric oxide synthase in the regulation of SREBP activation by oxidized phospholipids. *Circ. Res.* 2006; 98: 768–776. doi: 10.1161/01.RES.0000215343.89308.93. [PubMed] [CrossRef] [Google Scholar]
- [16] Puccetti L., Sawamura T., Pasqui A.L., Pastorelli H., Auteri A., Bruni F. Atorvastatin reduces platelet-oxidized-LDL receptor expression in hypercholesterolaemic patients. *Eur. J. Clin. Invest.* 2005; 35: 47–51. doi: 10.1111/j.1365-2362.2005.01446.x. [PubMed] [CrossRef] [Google Scholar]
- [17] Kinlay S., Libby P., Ganz P. Endothelial function and coronary artery disease. *Curr. Opin. Lipidol.* 2001; 12: 383–389. doi: 10.1097/00041433-200108000-00003. [PubMed] [CrossRef] [Google Scholar]
- [18] Nawrot T.S., Staessen J.A., Holvoet P., Struijker-Boudier H.A., Schiffrers P., Van Bortel L.M., Fagard R.H., Gardner J.P., Kimura M., Aviv A. Telomere length and its associations with oxidized-LDL, carotid artery distensibility and smoking. *Front. Biosci. Elit.* 2010; 2: 1164–1168. [PubMed] [Google Scholar]
- [19] van der Zwan L.P., Teerlink T., Dekker J.M., Henry R.M.A., Stehouwer C.D.A., Jakobs C., Heine R.J., Scheffer P.G. Circulating oxidized LDL: Determinants and association with brachial flow-Mediated dilation. *J. Lipid Res.* 2009; 50: 342–349. doi: 10.1194/jlr.P800030-JLR200. [PubMed] [CrossRef] [Google Scholar]
- [20] Demir M., Kucuk A., Sezer M.T., Altuntas A., Kaya S. Malnutrition-inflammation score and endothelial dysfunction in hemodialysis patients. *J. Ren. Nutr.* 2010; 20: 377–383. doi: 10.1053/j.jrn.2010.03.002. [PubMed] [CrossRef]

[Google Scholar]

- [21] Walker A.E., Kaplon R.E., Lucking S.M.S., Russell-Nowlan M.J., Eckel R.H., Seals D.R. Fenofibrate improves vascular endothelial function by reducing oxidative stress while increasing endothelial nitric oxide synthase in healthy normolipidemic older adults. *Hypertension*. 2012; 60: 1517–1523. doi: 10.1161/HYPERTENSIONAHA.112.203661. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [22] Yubero-Serrano E.M., Delgado-Casado N., Delgado-Lista J., Perez-Martinez P., Tasset-Cuevas I., Santos-Gonzalez M., Caballero J., Garcia-Rios A., Marin C., Gutierrez-Mariscal F.M., et al. Postprandial antioxidant effect of the Mediterranean diet supplemented with coenzyme Q 10 in elderly men and women. *Age (Omaha)* 2011; 33: 579–590. doi: 10.1007/s11357-010-9199-8. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [23] Merino J., Ferré R., Girona J., Aguas D., Cabré A., Plana N., Vinuesa A., Ibarretxe D., Basora J., Buixadera C., et al. Even low physical activity levels improve vascular function in overweight and obese postmenopausal women. *Menopause*. 2013; 20: 1036–1042. doi: 10.1097/GME.0b013e31828501c9. [PubMed] [CrossRef] [Google Scholar]
- [24] Kaplon R.E., Gano L.B., Seals D.R. Vascular endothelial function and oxidative stress are related to dietary niacin intake among healthy middle-Aged and older adults. *J. Appl. Physiol*. 2014; 116: 156–163. doi: 10.1152/jappphysiol.00969.2013. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [25] Orem A., Yucesan F.B., Orem C., Akcan B., Kural B.V., Alasalvar C., Shahidi F. Hazelnut-Enriched diet improves cardiovascular risk biomarkers beyond a lipid-Lowering effect in hypercholesterolemic subjects. *J. Clin. Lipidol*. 2013; 7: 123–131. doi: 10.1016/j.jacl.2012.10.005. [PubMed] [CrossRef] [Google Scholar]
- [26] Mineo C., Deguchi H., Griffin J.H., Shaul P.W. Endothelial and antithrombotic actions of HDL. *Circ. Res*. 2006; 98: 1352–1364. doi: 10.1161/01.RES.0000225982.01988.93. [PubMed] [CrossRef] [Google Scholar]
- [27] Li X.P., Zhao S.P., Zhang X.Y., Liu L., Gao M., Zhou Q.C. Protective effect of high density lipoprotein on endothelium-Dependent vasodilatation. *Int. J. Cardiol*. 2000; 73: 231–236. doi: 10.1016/S0167-5273(00)00221-7. [PubMed] [CrossRef] [Google Scholar]
- [28] Kuvlin J.T., Patel A.R., Sidhu M., Rand W.M., Sliney K.A., Pandian N.G., Karas R.H. Relation between high-Density lipoprotein cholesterol and peripheral vasomotor function. *Am. J. Cardiol*. 2003; 92: 275–279. doi: 10.1016/S0002-9149(03)00623-4. [PubMed] [CrossRef] [Google Scholar]
- [29] Kuvlin J.T., Rämetsä M.E., Patel A.R., Pandian N.G., Mendelsohn M.E., Karas R.H. A novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol: Enhanced vasorelaxation and increased endothelial nitric oxide synthase expression. *Am. Heart J*. 2002; 144: 165–172. doi: 10.1067/mhj.2002.123145. [PubMed] [CrossRef] [Google Scholar]
- [30] Bisoendial R.J., Hovingh G.K., Levels J.H.M., Lerch P.G., Andresen I., Hayden M.R., Kastelein J.J.P., Stroes E.S.G. Restoration of endothelial function by increasing high-Density lipoprotein in subjects with isolated low high-Density lipoprotein. *Circulation*. 2003; 107: 2944–2948. doi: 10.1161/01.CIR.0000070934.69310.1A. [PubMed] [CrossRef] [Google Scholar]
- [31] Spieker L.E., Sudano I., Hürliemann D., Lerch P.G., Lang M.G., Binggeli C., Corti R., Ruschitzka F., Lüscher T.F., Noll G. High-Density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation*. 2002; 105: 1399–1402. doi: 10.1161/01.CIR.0000013424.28206.8F. [PubMed] [CrossRef] [Google Scholar]
- [32] Shaul P.W., Anderson R.G.W. Role of plasmalemmal caveolae in signal transduction. *Am. J. Physiol. - Lung Cell. Mol. Physiol*. 1998; 275: L843–L851. doi: 10.1152/ajplung.1998.275.5.L843. [PubMed] [CrossRef] [Google Scholar]
- [33] Chambliss K.L., Yuhanna I.S., Mineo C., Liu P., German Z., Sherman T.S., Mendelsohn M.E., Anderson R.G., Shaul P.W. Estrogen receptor alpha and endothelial nitric oxide synthase are organized into a functional signaling module in caveolae. *Circ. Res*. 2000; 87: e44–e52. doi: 10.1161/01.RES.87.11.e44. [PubMed] [CrossRef] [Google Scholar]
- [34] Costa T.J., Ceravolo G.S., Dos Santos R.A., De Oliveira M.A., Araújo P.X., Giaquinto L.R., Tostes R.C., Akamine E.H., Fortes Z.B., Dantas A.P., et al. Association of testosterone with estrogen abolishes the beneficial effects of estrogen treatment by increasing ROS generation in aorta endothelial cells. *Am. J. Physiol. Heart Circ. Physiol*. 2015; 308: 723–732. doi: 10.1152/ajpheart.00681.2014. [PubMed] [CrossRef] [Google Scholar]
- [35] Zuloaga K.L., Davis C.M., Zhang W., Alkayed N.J. Role of aromatase in sex-specific cerebrovascular endothelial function in mice. *Am. J. Physiol. Heart Circ. Physiol*. 2014; 306: H929–H937. doi: 10.1152/ajpheart.00698.2013. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [36] Harris R.A., Tedjasaputra V., Zhao J., Richardson R.S. Premenopausal women exhibit an inherent protection of endothelial function following a high-fat meal. *Reprod. Sci*. 2012; 19: 221–228. doi: 10.1177/1933719111418125. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [37] Moreau K.L., Meditz A., Deane K.D., Kohrt W.M. Tetrahydrobiopterin improves endothelial function and decreases arterial stiffness in estrogen-Deficient postmenopausal women. *Am. J. Physiol. Heart Circ. Physiol*. 2012; 302: H1211–H1218. doi: 10.1152/ajpheart.01065.2011. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [38] Corretti M.C., Anderson T.J., Benjamin E.J., Muntagha S., Celermajer D., Charbonneau F., Creager M.A., Deanfield J., Drexler H., Gerhard-herman M., et al. Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery A Report of the International Brachial Artery Reactivity Task Force. *J. Am. Coll. Cardiol*. 2002; 39: 257–265. doi: 10.1016/S0735-1097(01)01746-6. [PubMed] [CrossRef] [Google Scholar]
- [39] Brocq M.L., Leslie S.J., Milliken P., Megson I.L. Endothelial dysfunction: From molecular mechanisms to measurement, clinical implications, and therapeutic opportunities. *Antioxid. Redox Signal*. 2008; 10: 1631–1673. doi: 10.1089/ars.2007.2013. [PubMed] [CrossRef] [Google Scholar]
- [40] Anderson T.J., Gerhard M.D., Meredith I.T., Charbonneau F., Delagrè D., Creager M.A., Selwyn A.P., Ganz P. Systemic nature of endothelial dysfunction in atherosclerosis. *Am. J. Cardiol*. 1995; 75: 71B–74B. doi: 10.1016/0002-9149(95)80017-M. [PubMed] [CrossRef] [Google Scholar]
- [41] Flammer A.J., Anderson T., Celermajer D.S., Creager M.A., Deanfield J., Ganz P., Hamburg N.M., Lüscher T.F., Shechter

- M., Taddei S., et al. The assessment of endothelial function: From research into clinical practice. *Circulation*. 2012; 126: 753–767. doi: 10.1161/CIRCULATIONAHA.112.093245. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [42] Nohria A., Kinlay S., Buck J.S., Redline W., Copeland-Halperin R., Kim S., Beckman J.A. The effect of salsalate therapy on endothelial function in a broad range of subjects. *J. Am. Heart Assoc.* 2014; 3: e000609. doi: 10.1161/JAHA.113.000609. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [43] Kang L.S., Chen B., Reyes R.A., Leblanc A.J., Teng B., Mustafa S.J., Muller-Delp J.M. Aging and estrogen alter endothelial reactivity to reactive oxygen species in coronary arterioles. *Am. J. Physiol. Heart Circ. Physiol.* 2011; 300: H2105–H2115. doi: 10.1152/ajpheart.00349.2010. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [44] Kruger A., Stewart J., Sahityani R., O’Riordan E., Thompson C., Adler S., Garrick R., Vallance P., Goligorsky M.S. Laser Doppler flowmetry detection of endothelial dysfunction in end-Stage renal disease patients: Correlation with cardiovascular risk. *Kidney Int.* 2006; 70: 157–164. doi: 10.1038/sj.ki.5001511. [PubMed] [CrossRef] [Google Scholar]
- [45] Stewart J., Kohen A., Brouder D., Rahim F., Adler S., Garrick R., Goligorsky M.S. Noninvasive interrogation of microvasculature for signs of endothelial dysfunction in patients with chronic renal failure. *Am. J. Physiol. Heart Circ. Physiol.* 2004; 287: H2687–H2696. doi: 10.1152/ajpheart.00287.2004. [PubMed] [CrossRef] [Google Scholar]
- [46] Strisciuglio T., De Luca S., Capuano E., Luciano R., Niglio T., Trimarco B., Galasso G. Endothelial dysfunction: Its clinical value and methods of assessment. *Curr. Atheroscler. Rep.* 2014; 16: 417. doi: 10.1007/s11883-014-0417-1. [PubMed] [CrossRef] [Google Scholar]
- [47] Wilkinson I.B., Webb D.J. Venous occlusion plethysmography in cardiovascular research: Methodology and clinical applications. *Br. J. Clin. Pharmacol.* 2001; 52: 631–646. doi: 10.1046/j.0306-5251.2001.01495.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [48] Blann A.D. A reliable marker of vascular function: Does it exist? *Trends Cardiovasc. Med.* 2015; 25: 588–591. doi: 10.1016/j.tcm.2015.03.005. [PubMed] [CrossRef] [Google Scholar]