CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1188219

Available online at: http://www.iajps.com Review Article

A REVIEW ARTICLE ON ENDOTHELIAL DYSFUNCTION IN PATIENT WITH TYPE 2 DIABETES MELLITUS

Sandhya Badoni *, Arun Kumar, Aarti Sati

*Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Dehradun, Uttarakhand, India

Abstract:

The endothelial cells involved in modulating vascular tone and structure. Endothelial cells produce a vast range of causes that also regulate cellular adhesion, smooth muscle proliferations and vessel wall inflammation. Endothelial function is important for homeostasis of the body and its dysfunction is associated with several pathophysiology conditions like diabetes, atherosclerosis. Sufferers with diabetes at all times exhibit an impairment of endothelium-dependent vasodilation. Therefore, working out and treating endothelial dysfunction is the principle focus within the prevention of vascular problems associated with all types of diabetes mellitus. This review will focus on the pathophysiology, assessment and therapeutics that exceptionally target endothelial dysfunction within the context of diabetic setting. Pathophysiology including nitric oxide, oxidative stress, angII, diabetes will be discussed. Pharmacological approaches that upregulate endothelium derives nitric oxide synthase and treatment that might prevent the development of diabetes associated vascular complications will be discussed.

Keywords: *endothelial dysfunction, nitric oxide, nitric oxide synthase ,vascular smooth muscle cells, endothelial-derived hyperpolarizing factors.*

Corresponding author:

Sandhya Badoni,

Division of Pharmaceutical Sciences,
Shri Guru Ram Rai Institute of Technology and Science,
Dehradun,
Uttarakhand, India

QR code

*Please cite this article in press as Sandhya Badoni et al, **A Review Article on Endothelial Dysfunction in Patient with Type 2 Diabetes Mellitus**, Indo Am. J. P. Sci, 2018; 05(02).*

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder which affects millions of inhabit worldwide. Numbers compiled by WHO reveal that approximately 150 million people comprise diabetes mellitus & this number may be double by the year of 2050. This may be direct to generously proportioned population, obesity, transform in dietetic practice etc [1][2][3].

Type 2 Diabetes Mellitus multiply the danger of cardiovascular disease. Hyperglycaemia is the key aspect which develops the endothelial dysfunction in diabetes mellitus. The mechanism underlying for this is however unpredictable. A number of studies suggested that NO-mediated vasodilation is abnormal in a patient suffering from type 2 diabetes mellitus [93].. Obese patients without type 2 Diabetes mellitus have been shown also to have an abnormal endothelial function (Steinberg et al 1996; Perticone et al 2001). Vascular endothelial provides a substantial barrier between the vessel wall and the lumen & also secrets several mediators like endothelin 1, thromboxane 2 (for vasoconstriction), nitric oxide (NO)/endothelial-derived hyperpolarizing factors (EDHF) for vasodilation. [5] Patients suffering from diabetes, can leads to an impairment of NO production and activity. Endothelium impairs due to diabetes mellitus, can cause endothelial dysfunction & which can be considered as the earliest tread of the cardiovascular disease (CVD)[4].Due to diabetes-induced endothelial dysfunction, it may cause various complications such as vascular ischemia, coronary artery disease (CAD), peripheral vascular disease (PVD) etc[1]. Up to 75% patient with diabetes dies due to dysfunction of endothelium.

1.1 Endothelial cell

Endothelial cell acts as a barrier which provides a physiological protection. Endothelial cell serves as pool between circulating blood and vascular smooth muscle cells (VSMC)[8][6][7] .The main function of the endothelium is coagulation, platelet adhesion,thrombosis,regulation of vascular tone, control volume & electrolyte content of intravascular and extravascular spaces [6][7].

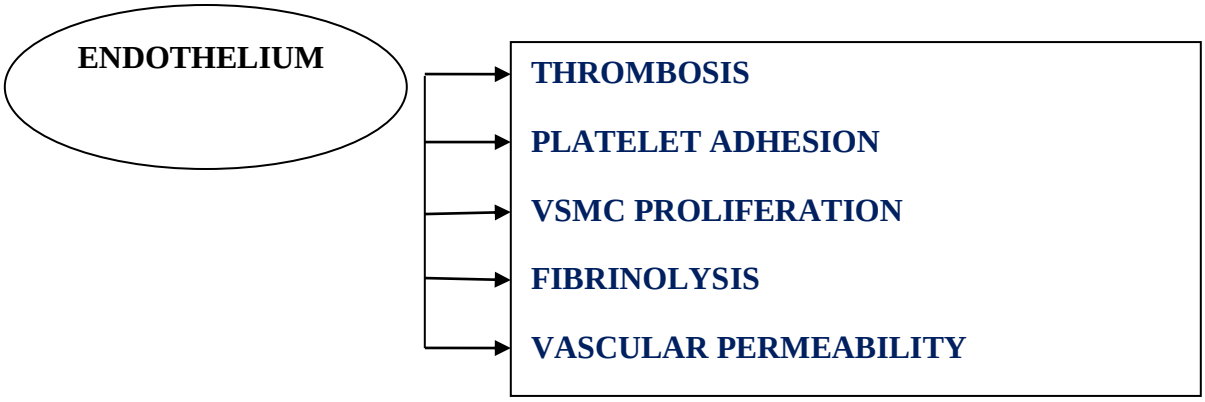


Fig 1: Functions performed by endothelium

Endothelium is enclosed by a glycocalyx that serves to the selectivity of its barrier function (van Haaren et al. 2003). Moreover, the endothelium assures the fluidity of blood by its contribution to hemostasis. Blood coagulation limit, the formation of a platelet thrombus and production of fibrinolysis regulators are prevented by living endothelial cells(van Hinsbergh 2001)[2].The endothelium, not individual responds to vasoactive agents but is also involved in the catabolism, metabolism, and synthesis of various vasoactive agents, particularly in the lung (Shaul 1999)[2].Endothelium-derived factors having a Vasodilating and antiproliferative property include endothelium-derived hyperpolarization factor (EDHF) , nitric oxide (NO) and prostacyclin (PGI2) . Ang II & ROS exerts vasoconstrictor effects [9].

Because endothelium is the central monitor of vascular homeostasis, it maintains the equilibrium between vasodilation and vasoconstriction.

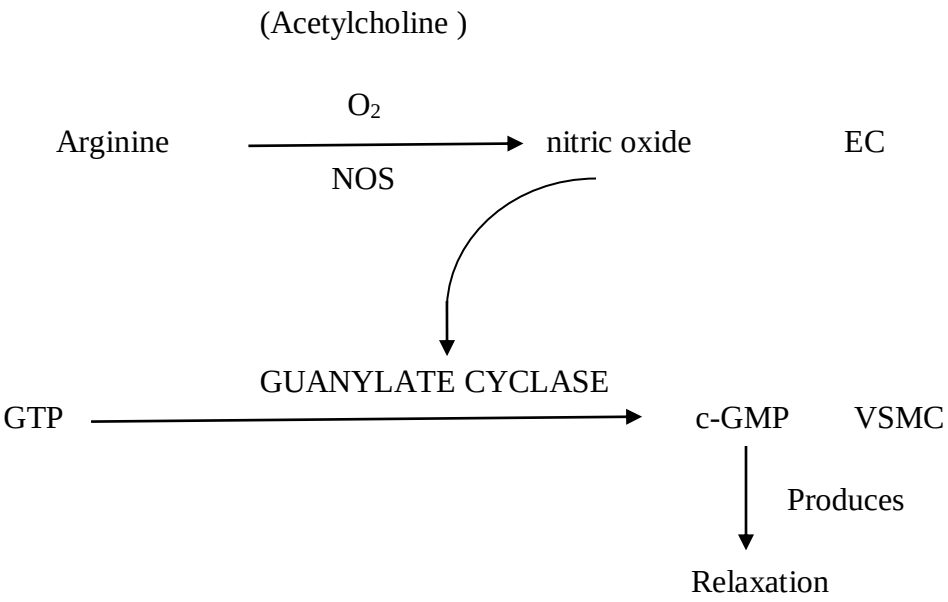


Fig.2: Endothelial cell as a regulator of the smooth muscle cells [8].

As shown in figure 2 the endothelial cell (EC) produces nitric oxide (NO), gas that diffuses into the vascular smooth muscle cells (VSMC) and activates the enzyme guanylate cyclase which produces recurring GMP. The latter induces muscle relaxation, which is physiologically translated into vasodilation. The direct originator of NO is the amino acid arginine and the basis enzyme in its creation is nitric oxide synthase (NOS) [8].Endothelial cells are as well reliable for the maintenance of blood fluidity and restoration of vessel partition integrity (when injured) to avoid bleeding [8].Endothelial cell-derived factors additionally are critical mediators of VSMC development and inflammation [6][10].

1.2 Nitric oxide

NO plays an essential role in vascular homeostasis. In endothelial cells, L-arginine converts in the presence of endothelial nitric oxide synthase (eNOS) to L-citrulline and furthermore synthesized nitric oxide. Circulating blood & receptor-operated substances such as acetylcholine; bradykinin derived a shear stress due to which NO released from endothelial cells [9][11][12].

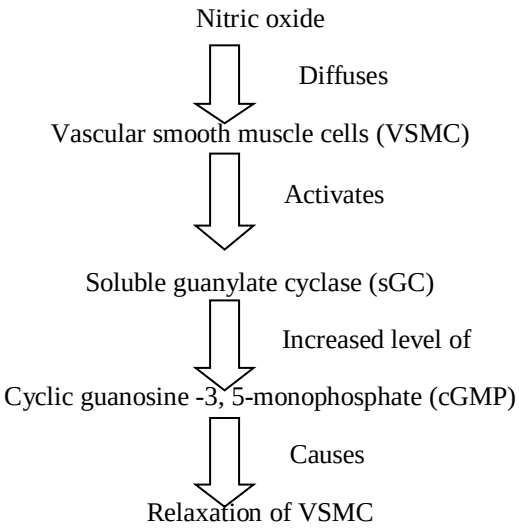


Fig 3. Nitric oxide function pathway [9]

Nitric oxide performs numerous functions such as vasodilation (maintains B.P.), decrease oxidation of LDL, reduces platelet aggregation, prevents leukocyte adhesion, decrease endothelin production [9][13][14].

Mechanism of action of NO*:* Nitric oxide is unconfined by the endothelial cells through assorted stimuli, such as 5-OH-tryptamine, acetylcholine, thrombin, arachidonic acid, changes in arterial pressure, etc., either as NO or bound to a -SH group-containing carrier molecule (e.g. L-cys) that stabilizes NO release[15][16][17]. In the smooth muscle cells, NO released and it activates the guanylate cyclase and mounting the intensity of intracellular messenger cGMP. This make happens relaxation of smooth muscle, inhibition of platelet aggregation [17][18].

NO is not as much stable than other endothelial vasodilators, such as prostacyclin. Mutually, endothelial agent's causes platelet aggregation & relaxation of vessels, but through different mechanism [16], that is the rise in cGMP flatten in platelet and central nervous system & increases in intracellular cGMP level respectively. In addition, NO free by neutrophills and other white cells enhance the platelet antiaggregant effect of PGI_2 [16]. NO be able to require to oxi-Hb & Fc-SH complexes of other proteins, thus modulating the movement of many hepatic enzyme [19][20] Studies on isolated hepatocytes showed that [21], phosphorilation of IP_3 (cGMP dependent protein kinase receptor) increases its sensitivity to P-inositol by the emit of free intracellular calcium ion. An additional hypothesis suggests that hyperpolarizing factor produces by endothelium may induce vasodilation. In the smooth muscles, it is demonstrated that NO induces hyperpolarization through the opening of K^+ channels [22][23].

1.3 Decreased level of NO

eNOS (endothelial nitric oxide synthase) is depending upon various factors for its multiple activity and functions.BH_4 (tetrahydrobiopterin) sustain the diamer structure & bioavailability of eNOS. Synthesis of BH_4 is completed by the enzyme called Guanosine-5-triphosphate cyclohydrolase 1 (GTPCH 1). GTPCH 1 is playing an important role to maintain BH_4 level & NO production [9]

A decreased activity of eNOS is mainly responsible for the decrease level of NO production. Oxidative stress causes eNOS uncoupling, in which activity of eNOS decreased and it will generate reactive oxygen species (ROS) as an alternative of nitric oxide. The mechanism through which eNOS uncoupled is – oxidation of BH4, depletion of enzyme L-arginine, and accumulation of endogenous methylarginine [9][25].

The activity of eNOS is also regulated by insulin inside the endothelial cells. By increasing BH4 synthesis, insulin can regulate the eNOS activity. Due to insulin resistance, insulin mediated endothelial vasodilation is impaired. Contrarily, because of the function of NO in peripheral tissues, eNOS plays an important role in the regulation of insulin sensitivity. Endogenous products of arginine metabolism (ADMA = asymmetric dimethyl-L-arginine) inhibited the eNOS [24]. After oxidative stress, there are changes in ADMA level & they cause a reduction in NO formation which causes endothelial dysfunction [9][24].

2. ENDOTHELIAL DYSFUNCTION AND DIABETES MELLITUS

Diabetes is besides measured as a vascular disease for the reason that it produces effects on macro and microcirculation of numerous vascular cells/beds [9]. As soon as endothelium loses its physiological properties such as affinity to promote vasodilation, fibrinolysis and anti-aggregation. In that case this is called endothelial dysfunction. Prolong exposure to hyperglycemia is the key culprit in the pathogenesis of diabetic complications, concerning augmented ROS and RNS production. Oxidative stress leads to an imbalance in the vascular homeostasis due to increased vasoconstriction and impaired vasorelaxtion that finally bring up diabetic endothelial dysfunction.

Table 1: Difference between a healthy and dysfunctional endothelium

HEALTHY ENDOTHELIUM	DYSFUNCTIONAL ENDOTHELIUM
• Vasodilatory (↑ NO, PGI_2)	• impaired vasodilation (↓ NO, PGI_2)
• ↓ Oxidative stress, low uric acid	• ↑ Oxidative stress, uric acid
• ↑ Repair (EPCs), ↓ damage (CECs,MPs)	• ↓ Repair(EPCs), ↑ damage (CECs,MPs)
• ↓ Anti-coagulant	• ↑ Pro-coagulant

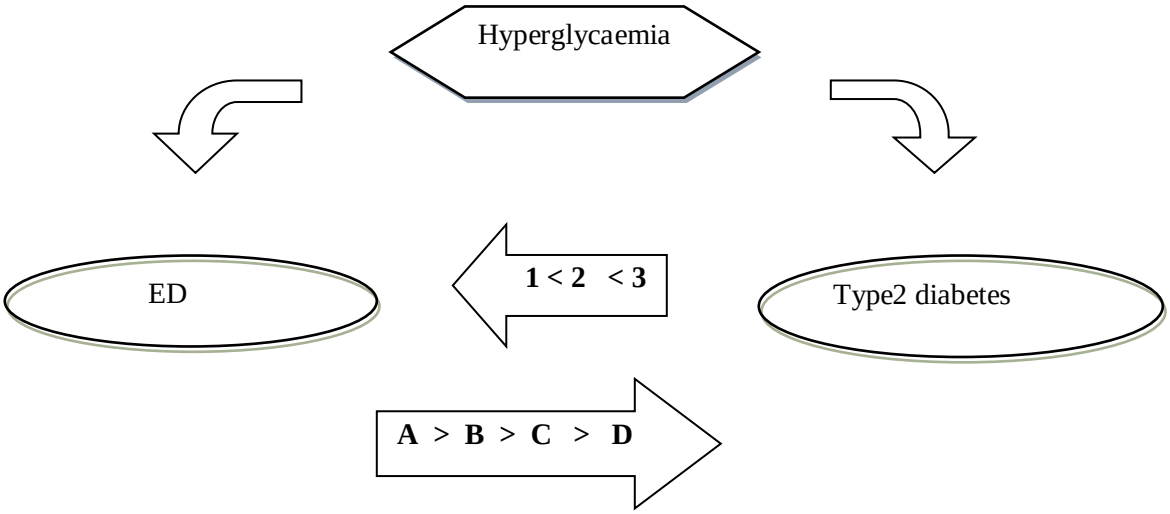
*NO- niric oxide *PGI_2-prostacyclin *EPCs-endothelial progenitor cells

*CECs-circulating endothelial cells *MPs-microparticles

Diabetics produce a 2- to 4-fold elevated hazard for cardiovascular events [26][29], and all but 80% of diabetes-associated deaths are caused by CVD [27][29]. The enhanced CVD possibility in diabetic patients is larger for women than men as women by and large enjoy a guard from CVD during their reproductive years, and this guard is missing in diabetics [28][29].

Hyperglycemia is a key take the risk of reason for the enlargement of cardiovascular disease and cardiovascular mortality [31][32].Diabetic complications are linked with oxidative stress and uncoupling of endothelial nitric oxide synthase (eNOS). Both parameters are measured notable pathological mechanisms in the development of vascular dysfunction in diabetic animals and patients [33][34]. A different key initiate for vascular damage under hyperglycemic conditions is based on noxious effect of glucose levels through the formation of advanced glycation end products (AGE) and activation of their exact receptors (RAGE) [30][35][36].

Main vascular defects in diabetes, in which hyperglycemia plays an essential role, include increased arterial stiffness and reduced NO production in resistance arteries and arterioles, reduced glomerular function and microalbuminuria in the kidney, and inappropriate neovascularization in the eye [2].



A: Impaired endothelium dependent vasodilation **B:** Decreased capillary recruitment

C: Impaired glucose uptake **D:** Hyperglycaemia

1: Endothelial dysfunction

2: Reactive oxygen intermediates

3: Hyperglycaemia

Fig 4: Endothelial dysfunction vs. type 2 diabetes

Mutual interaction of metabolic and vascular property add to the development of type 2 diabetes, which know how to be initiated by hyperglycemia, genetic factors, or other unidentified factors. One probable direct by which endothelial dysfunction results in type 2 diabetes is showed in A-B-C-D, in which impaired endothelial vasodilation results in a decrease of both capillary recruitment and glucose uptake, with a resulting increase in the levels of blood glucose. A probable path by which key in 2 diabetes consequences in endothelial dysfunction (showed in 1–2–3) is by the formation of reactive oxygen intermediates produced by the glycation pathway.(fig.3)

In patients with type 2 diabetes mellitus, the most important affect of mortality and morbidity is cardiovascular disease (CVD). Hypertension is give approximately two times as commonly in people with diabetes mellitus compared to persons without diabetes, and is accompanied by dyslipidaemia; hyperglycaemia, hypercoagulation and hyperinsulinemia[37]. The metabolic syndrome and type 2 diabetes are characterized by a number of

haemodynamic and metabolic abnormalities. Among these abnormalities, endothelial dysfunction plays a main character and is evident preceding to the beginning of Diabetes. Moreover, in the bigger CVD threat establish in persons with diabetes and hypertension dysfunction of the vascular endothelium drama an critical role. Compared to diabetes alone, the co-existence of hypertension and diabetes seems to correlate with decreased coronary flow responses [38]. Alterations in the vascular endothelium allied to diabetes that supply to endothelial dysfunction include elevated expression and plasma levels of vasoconstrictors such as angiotensin II and endothelin-1, better expression of grip molecules and linked enhanced adhesion of platelets and monocytes to vascular endothelium, plus impairment of NO release and reduce NO responsiveness.[39]

Endothelial dysfunction, which is a lot interconnected to impaired endothelium-dependent NO-mediated relaxation, occurs in mutually cellular and experimental models of diabetes[41][42] .Similarly, the widely held of clinical studies gain exposed an irregularity in endothelium needy vasodilation in patients with diabetes[43]. Thus, decreased levels of NO may underlie the atherogenic predilection of diabetes. Several of the metabolic conditions associated with diabetes, counting hyperglycemia, excess free fatty acid liberation, and insulin resistance intervene abnormalities in endothelial cell event by moving the synthesis or degradation of NO.[40][44] Type II diabetes is characterized by three key metabolic troubles (triggers): (1) hyperlipidemia, (2) basic hyperinsulinemia, and (3) hyperinsulinemia followed by pancreatic β-cell breakdown principal to hyperglycemia[45]. Every of these metabolic strife acts as "triggers" sooner or later causing endothelial dysfunction through the manipulate of different "mediator" molecules[46][47] In a clinical set it might be complicated to bear out how a great deal injury is caused in terms of endothelial dysfunction by each one of these metabolic changes. However, numerous defenses of signal meaning to the fact that "oxidative stress" caused by these metabolic changes plays a strategic character in ED [48][49][6].

3. PATHOPHYSIOLOGY OF ENDOTHELIAL DYSFUNCTION

The pathophysiology of endothelial dysfunction involves various mechanisms.

A. NITRIC OXIDE(NO) AND OXIDATIVE STRESS

NO is vasodilating substance released by endothelium, which acts as a vasodilator, inhibits growth and inflammation & has an anti-aggregant effect on platelets [50]. Low level of NO has been reported in the case of impaired endothelial function. It may conclusion from reduced activity of endothelial NO synthase and to decreased bioavailability of NO [50]. ROS are recognized to suppress NO with formation of peroxynitrite [51], which is a cytotoxic oxidant, and through nitration of proteins will change protein go and therefore endothelial function. Peroxynitrite is an essential third party of oxidation of LDL, emphasizing its proatherogenic function. Moreover, peroxynitrite leads to degradation of the eNOS cofactor tetrahydrobiopterin (BH4) [52], primary to "uncoupling" of eNOS.

Oxidant excess increases BH2 level by the reduction in BH4 level. Oxidant overkill will as well consequence in diminution of BH4 with step up in BH2. While this occurs, formation of the functioning dimer of eNOS with oxygenase activity and production of NO is decreased (uncoupling of eNOS) [50]. Oxidative stress is connected to the proinflammatory state of the vessel wall. Inflammation decreases NO bioavailability. The major basis for oxidative stress in the vasculature is NAD(P)H oxidase [53][54]. Other sources consist of xanthine oxidase, the mitochondria and uncoupled NOS [55][50].

In animal models of diabetes, increased oxidative stress furthermore led to endothelial dysfunction.ROS involved in the mediation of endothelial injury which may cause programmed cell death or apoptosis & to a procedure of apoptosis characterized by detachment of endothelial cells called anoikis [50].

B. ANGEOTENSIN II (Ang II)

Ang II has been mixed up in the pathophysiology of hypertension and persistent renal failure. Ang II infusion induces endothelial dysfunction in rats, increases ROS by stimulating NAD (P) H oxidase, and promotes vascular inflammation [56]. In hypertensive humans, interruption of the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers restores endothelial function in contrast to a parallel extent of BP lowering with a β-blocker, which has no get consequence on endothelium-dependent vasodilation[50][57].

C.INVOLVEMENT OF ADVANCED GLYCATION END PRODUCT (AGEs)

In patients with diabetes, cardiovascular complications are the essential purpose of morbidity & mortality and account for up to 65% of diabetic fatalities. It has been mentioned that 33% of diabetic sufferers on insulin

care may have died from CVD via the age of 50 years. It is inspiration that a AGE have a central function within the pathophysiological strategies that lead to the progress of such cardiovascular complications discovered in diabetes. AGE are derived from proteins, lipid & nucleic acid which may be glycated or oxidized non-enzymatically in a process referred to as Maillard reaction.[58]

AGE levels in plasma proteins are extended in patients with diabetes. The high blood glucose levels want the occurrence of spontaneous reaction (glycation) between glucose and proteins, resulting in the formation & immoderate deposition of AGE. Among the mechanism through which AGE may contribute to the development & progression of vascular issues of diabetes, is the interplay of these compounds with receptor on the surface of more than a few cell types, such as RAGEs(Receptors for Advanced Glycation End Products)[60].The AGE-RAGE interactions in the endothelial cells prompts the transcription of nuclear factor-kappaB (NK-κB),with the induction of proinflammatory cytokines, such as tumor necrosis factor(TNF),intrlukin-1(IL-1), interlukin-6(IL-6), monocytes chemotactic protein 1(MCP-1) enhances the expression of vascular cell adhesion molecule-1(VCAM-1).[59][60]

Furthermore, interaction in monocytes induces their activation to macrophages & promotes monocytes chemotaxis. In some studies, it is demonstrate that AGE may promote atherogenesis by oxidizing LDL. Certainly, AGE form crosslink's with LDL, which end up more atherogenic, not more succeptible to absorption & subsequent clearance. In addition, LDL modified with the AGE is more easily captured by means of receptor placed on macrophages, generating foam cells (cells with fat droplets & cholesterol).[60]

As compared to non-diabetic patients, type 2 diabetes patients with peripheral artery disease, exhibited larger levels of serum AGEs. Hyperglycemia leads to advanced glycation end products (AGE), which were exposed to quench NO and impair endothelial function, as evidenced by inhibition of advanced glycosylation with amino guanidine .Acute hyperglycemia itself can reduce NO and ease endothelium-dependent vasodilation in humans in vivo [61][50].

4. ASSESSMENT OF ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is able to be measured by exploratory vasodilator responses to endothelium dependent substances such as acetylcholine, bradykinin and serotonin in likeness with responses to endothelium- independent molecules such as NO donor in the deficiency and presence of NOS inhibitor and COX inhibitor in vivo[64] and in isolated vessels[62][63]

The clinical method to measure endothelial dysfunction includes:

I.Invasive methods by means of quantitative angiography and intracoronary Doppler line within coronary distribution

Invasive Assessment-For the assessment of endothelial function, vasodilation in responses to specific endothelium-dependent and –independent can be measured [66]

- ❖Coronary endothelial function-evaluated by intracoronary infusion of endothelium-dependent vasodilation.
- ❖Doppler wire- measure of conductance & resistance vessel endothelial function[67]

Dilation of epicardial vessels & microcirculation is a normal response. Endothelium-independent function is assessed by measuring dose reaction to greater than ever concentrations of vasodilators that donate NO directly (eg.nitroglycerin, nitroprussid)[68]

II. Non-invasive methods, including venous occlusion plethysmography to measure forearm blood flow, flow-mediated dilatation in brachial artery, and peripheral arterial tonometry measuring pulsatile measurements changes in the distal figure. [62][65].

a. Venous occlusion plethysmography -This method is used to study forearm blood flow and for preserving arterial blood inflow (approximately 40mmHg) an inflated cuff around the arm is used to arresting venous outflow & it is enough to occlude venous outflow[68]

The ratio and extent of swelling reflect forearm vascular resistance, whereas the volume, restrained by means of voltage dependent strain gauge, increase in absolute percentage to forearm blood flow. This method allows management of vascular resistance by administering endothelial agonist (eg.acetlycholine) and direct smooth muscle relaxant (eg.nitrate) without general effects [68]. This method is well tolerated and very well reproducible[69]

b. Flow-mediated dilation (FMD)-By using high resolution ultrasound, change in brachial diameter measuring, by the help of FMD technique. A blood pressure cuff is inflated below the antecubital fossa to suprasystolic pressure. After the releasing of cuff, reactive hyperemia is quantified [68]. Arterial diameter is recorded by using electrocardio graphic gating. Percent change in diameter from baseline

expressed the FMD. FMD correlates with coronary endothelial function. FMD is lowered by aging, body mass index, blood pressure & smoking and FMD improved by exercise, training and medical therapy (eg.statins) [70]. This technique is operator dependent [68].

c. Peripheral arterial tonometry (PAT)-It is noninvasive technique. It consists of probes which contain inflatable latex air cuffs & it is connected by pneumatic tubes to an inflating device [71].
Pulsatile quantity changes in the distal figure induce pressure alterations in the cuff and are sensed by transducer. Decrease in arterial column changes due to the decreases in the arterial blood volume & it is reflected as a decreased PAT signal & vice versa. By reactive hyperemia PAT index, endothelial function is measured. The ratio of reactive hyperemic response to basal flow is calculated by computer algorithm, listed to the contralateral control arm.PAT hyperemic flow in rely upon NO & the ratio correlates with coronary endothelial perform [71][68]. FMD and myocardial perfusion imaging reports [68].

5. TREATMENT OF ENDOTHELIAL DYSFUNCTION

Experimental and medical experiences have proven that numerous presently used or investigational drugs can make stronger endothelial operate, despite the fact that they have exceptional structure and mechanism of actions [62].

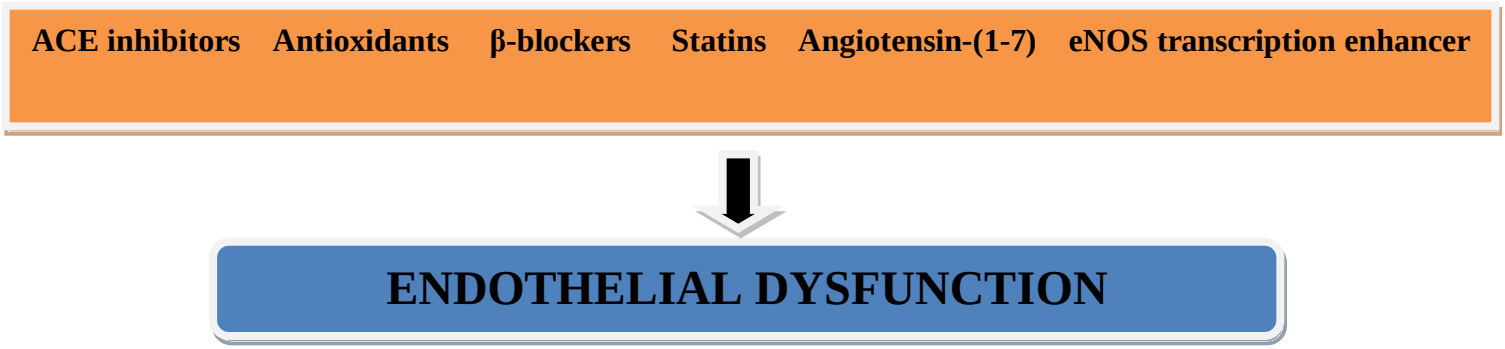


Fig 5: therapeutic strategies for treating the endothelial dysfunction

The nonpharmacological techniques like lifestyle forms modification and lower oxidative stress enhance insulin sensitivity and proper dyslipidaemia and hence enhance endothelial function [72]

A number of pharmacological interventions have been proven to make stronger endothelial dysfunction. On account that dyslipidaemia is most often associated with endothelial dysfunction. The endothelial protecting results may be mediated by statins, antioxidants and anti-inflammatory and their capability to revive vascular NO bioavailability [7].

1.ACE inhibitors and AT1 blockers

ACE inhibitors and AT1 blockers are greatly used to the treatment of hypertension, arthrosclerosis, diabetes and a few autoimmune diseases. It is well based that ACE inhibitors can improve endothelial perform in animals with coronary heart failure and in patients with coronary artery disorder [73]. This effect is said to each discount in angiotensin II and increase in bradykinin accumulation.
The effect of ACE inhibitor on eNOS expression is mediated via bradykinin B2 receptors, which will also be blocked by means of B2 receptors blockers [74]. ACE inhibitors and AT1 blockers also inhibit ROS creation and COX-2derives vasoconstrictors, which contribute to endothelial protecting effects of these medicines [62][75].

2. Antioxidant agents

A few components having very special molecular structure and properties, such as vitamin C and E, N-acetylcysteine and genistein exert antioxidant results through exceptional mechanisms [62].
Vitamin C can give a boost to endothelium-dependent response in circumstances similar to power smoking, diabetes mellitus, hypercholesterolemia and hypertension. Vit.C protects the endothelium by means of scavenging superoxide, which on flip prevents NO scavenging, lipid peroxidation, platelet and neutrophills

activation, and adhesion molecule upregulation [76][62].

In smoking and hypercholesterolemia, vit E exerts an endothelia-protective effects but is effects in diabetes mellitus controversial [77].vit E act as a lipid soluble antioxidant, scavenging hydroperoxyl radicals in lipid milieu [78]. N-acetylcysteine is used in the therapy of cough. However, experimental reviews have tested that N-acetylcysteine is a strong antioxidant. It acts on the creation of glutathione, which protects the cardiovascular process from damaging effects of TNF-α that induces glutathione depletion and ROS production through NADPH oxidase and ceramide [79]. The effect of N-acetylcysteine on endothelial dysfunction is related to inhibition of NADPH oxidase expression, leukocyte adhesion and inflammatory cytokine secretion [60].

3. Beta blockers

Some β blockers, specifically the β-1 selective β blockers exert endothelial protecting effects. Nebivolol, a β-1 antagonist with β-2,3 agonist property, improves endothelium dependent vasodilator responses in patients with major hypertension and in people who smoke [81]. Carvedilol, a non- selective β1 and β2 antagonist with α-antagonist property, also improves endothelium-based responses in sufferers with principal hypertension however this seems to be regarding its antioxidant ability[82]. The combination of Carvedilol with ACE inhibitors produces extra invaluable influence on endothelial function than each and every drug alone in hypertensive patients with obesity [83]. For this reason, this kind of β-blockers and its mixture are compatible for the treatment of endothelial dysfunction associated with hypertension, atherosclerosis and most of the time diabetes [62].

4.Statins

Statins, inhibitors of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase are a category of medications utilized to reduce hypercholesterolemia, specifically LDL cholesterol. In 1994, pravastatin used to be shown to make stronger endothelium dependent response of coronary and peripheral arteries in patients with hypercholesterolemia, which was confirmed later by other experiences [84]. The important result of statins on endothelial operate entails more than one mechanisms. Statins making improvements to endothelial dysfunction is partly due to their reducing LDL cholesterol outcomes, even as native LDL and OxLDL cut back eNOS expression and develop levels of caveolin-185[]. Statins also exert direct antioxidant effects on LDL to lower electronegative type of LDL. Statins increase NO bioavailability by way of activating eNOS through the PI3K/Akt signaling pathway, agonist-prompted eNOS-hsp90 interaction [85], and BH4-mediated eNOS coupling. This latter used to be validated in sufferers with atherosclerosis and in rat mannequin of insulin resistance of diabetes [86]. These reports confirmed that atorvastatin multiplied vascular BH4 content material and NO bioavailability and diminished O2 - production through upregulating GTP cyclohydrolase I gene expression and recreation [62].

5. Angiotensin-(1-7)

In endothelial cells, angiotensin-(1-7) activates eNOS by the Mas/PI3K/Akt passageway and inhibits angiotensin II-induced NAD(P)H oxidase activation[87]. Returning behavior with angiotensin-(1-7) improves renal dysfunction coupled with apolipoprotein E-deficiency [88] and diet induced obesity in mice, which is probable mediated by greater than ever NO release and eNOS expression[89]. NAD(P)H oxidase in hypertensive or diabetic rats. Angiotensin-(1-7) restores NO/cGMP fabrication and migration, decreases NADPH oxidase activity, and enhances survival and proliferation of endothelial progenitor cells inaccessible from the blood of diabetic patients in a Mas/PI3K/Akt-dependent manner [62].

6. eNOS transcription enhancer

Apparently, special concentrating on eNOS transcription with a chemical compound,AVE3085, raises eNOS expression however reduces oxidative stress and platelet activation, which is associated with extended endothelial-dependent reduction and cardiac function in animals with specific experimental diseases[90]. This compound moreover prevents the inhibitory looks of ADMA on endothelium-dependent vasodilation in human inside thoracic artery rings and in pig coronary artery rings[91][92]. Thus, this compound showed a prospective for the cure of endothelial dysfunction even though its results in human medical circumstances stay to be verified [62]

7. CONCLUSIONS:

Endothelial function is predominant for the homeostasis of the body & its dysfunction is associated with few pathophysiological stipulations including atherosclerosis, hypertension and diabetes. Working out and treating endothelial dysfunction is a important obstacle within the prevention of vascular issues associated with all types of diabetes mellitus. Endothelial dysfunction regularly occurs as complication but there after contributes to the progress and progression of organ injury. Naturally more than one mechanism such as inflammation, increased ROS & RNS and so on are involved in endothelial dysfunction. However, a diminished NO bioavailability seems to play a imperative position on account that in many pathologies, there is a overproduction of NO, a reduction in NO bioavailability happens ultimately based on one of a kind danger explanations. Medicinal drugs with endothelium protective property may just yield more therapeutic effect. Due to the change in risk

factors, mechanism of action, healing of endothelial dysfunction with medications needs to be implemented according to specific mechanism underlying endothelial dysfunction of the sickness. Concurrent discount of hyperglycemia, oxidative stress, infection and insulin resistance is also essential to ameliorate the hostile results that growth to diabetic vasculopathy in patients with cardiovascular risk factors.

REFERENCES:

1.Ding H., Triggle C.R., Endothelial cell dysfunction and the vascular complications associated with type 2 diabetes: assessing the health of the endothelium, *Vascular Health and Risk Management* 2005; 55-71.

2. Bakker W., Eringa E.C., et.al. Endothelial dysfunction and diabetes: roles of hyperglycemia, impaired insulin signaling and obesity, (2009); 335:165–189.

3.Lumsden N.G.,Andrews K.L.,Bobadilla M., Endothelial dysfunction in patients with type 2 diabetes post acute coronary syndrome, *Diabetes & Vascular Disease Research* 2013;10(4): 368–374.

4.Anderson T.J., NO ,atherosclerosis and the clinical relevance of endothelial dysfunction,2003;8(1) 71-86.

5.Avogaro A., Albiero M.*et al*.2011; Endothelial Dysfunction in Diabetes The role of reparatory mechanisms; *Diabetic care*,2011; 34:285-290.

6.Basha B., Samuel S.M.,et.al., Endothelial Dysfunction in Diabetes Mellitus: Possible Involvement of Endoplasmic Reticulum Stress, *Hindawi Publishing Corporation Experimental Diabetes Research*, 2012; 1-14.

7.Dr. Namrata Chhabra, Endothelial dysfunction – A predictor of atherosclerosis, *Internet Journal of Medical Update*, 2009; Vol. 4:33-41.

8.Escandon J.C., Cipolla M., Diabetes and Endothelial Dysfunction: A Clinical Perspective , *Endocrine Reviews*,2001; 22(1): 36–52.

9.Cristina M. Sena, Ana M. Pereira, *et al*.**,** Endothelial dysfunction — A major mediator of diabetic vascular disease; *Biochimica et Biophysica Acta* 2013;1832; 2216-2231.

10.D. B. Cowan and B. L. Langille, Cellular and molecular biology of vascular remodeling,*Current Opinion in Lipidology*, 1996; 7: 94–100.

11.P. Vallance, N. Chan, Endothelial function and nitric oxide: clinical relevance, Heart, 2001; 85:342–350..

12.C. Boulanger, T.F. Luscher, Release of endothelin from the porcine aorta: inhibition by endothelium-derived nitric oxide, J. Clin. Invest. 85 (1990) 587–590.

13.S.B. Wheatcroft, I.L.Williams, A.M. Shah,M.T. Kearney, Pathophysiological implications of insulin resistance on vascular endothelial function, *Diabet.Med.*2003;20: 255–268.

14.Avogaro A., Fadini G.P., Endothelial dysfunction in type 2 diabetes mellitus, *Nutrition, Metabolism & Cardiovascular Diseases* ,2006; 16: S39-S45.

15.Kilbourn R, Nitric oxide: Moving towards the clinic,*Molec.Med.Today*,1996; 324-325.

16.Martin J, Rodriguez-Martinez AM ,*NO*, oxygen derived free radicals and vascular endothelium, *J.Auton Pharmacol.*, 1995;15: 279 – 307.

17. Moncada S, Palmer Higgs AE ,NO physiology, pathophysiology and pharmacology, *Pharmachol.Rev*, 1991; vol 43:109 – 42.

18. Moncada S, Higgs A , Mechanisms of disease; The L-Arg-NO-Pathway', *New Engl. J. Med.* 1993; 329: 2002–12.

19. Barry AL ,The role of NO in hepatic metabolism, *Nutrition*, 1998; vol.14: p.376-390.

20. Beckman JS, Koppenol WH ,Nitric oxide, superoxide and peroxynitrite: the good, the bad and the ugly, 1996; vol.271: C1424-37.

21. Harbrecht BG, Billiar T - The role of NO in Kupffer Cell hepatocytes interaction, (1995), p.79.

22. Harbrecht BG, Glutathione regulated NO-synthase in cultured hepatocytes, Ann.Surg. 1997; .225:, 76-87.

23. Jerca1 L., Jerca O., et.al. Mechanism of action and biochemical effects of nitric oxide (NO•) *the journal of preventive medicine*,2002;10 (2): 35-45.

24. Vallance P., Importance of asymmetrical dimethyl arginine in cardiovascular risk, Lancet. 358 (2001); 2096–2097.

25. Antoniades C., Shirodaria C., Leeson P., Antonopoulos A.,et.al.,Association of plasma asymmetrical dimethylarginine (ADMA) with elevated vascular superoxide production and endothelial nitric oxide synthase uncoupling: implications for endothelial function in human atherosclerosis, *Eur. Heart J.2009;* 30: 1142–1150.

26. Ding H. and Triggle C. R., Endothelial cell dysfunction and the vascular complications associated with type 2 diabetes: assessing the health of the endothelium, *Vascular Health and Risk Management*, 2005; vol. 1: 55–71.

27. Winer N. and Sowers J. R., Epidemiology of diabetes, *Journal of Clinical Pharmacology*, 2004;vol. 44:, 397–405.

28. Pajunen P., Taskinen M. R., Nieminen M. S., et.al.Angiographic severity and extent of coronary artery disease in patients with type 1 diabetes mellitus,*American Journal of Cardiology*, 2000;vol. 86:1080–1085,.

29. Funk S.D., Yurdagul A., Hyperglycemia and Endothelial Dysfunction in Atherosclerosis: Lessons from Type 1 Diabetes, *International Journal of Vascular Medicine***,**2012;1-19.

30. Stevena S., Oelzea M., Hanfa A., Kröller-Schöna S. et al.,The SGLT2 inhibitor Empagliflozin improves the

primary diabetic complications in ZDF rats. 2017; 370-385,http://dx.doi.org/10.1016/j.redox.2017.06.009.
31. Nathan D.M., Cleary P.A., Backlund J.Y., et.al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, *N. Engl. J. Med*,. 2005;353: 2643–2653.
32. Zinman B., Wanner C., Lachin J.M.,et.al. . Investigators, empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, *N. Engl. J. Med*. 2015; 373: 2117–2128.
33. Heitzer T., Krohn K., Albers S., Meinertz T.et.al., Tetrahydrobiopterin improves endothelium- dependent vasodilation by increasing nitric oxide activity in patients with Type II diabetes mellitus, *Diabetologia 2000;43* : 1435–1438.
34. Cassuto J., Dou H., Czikora I., Szabo A.,et.al , Peroxynitrite disrupts endothelial caveolae leading to eNOS uncoupling and diminished flow-mediated dilation in coronary arterioles of diabetic patients, *Diabetes*,2014; 63:1381–1393.
35. Forbes J.M., Cooper M.E., Thallas V., Burns W.C.,et.al , Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy, *Diabetes*,2002;51: 3274–3282.
36. Y. Yamamoto, S. Yamagishi, H. Yonekura, T. Doi, et.al , Roles of the age-RAGE system in vascular injury in diabetes, Ann. *N. Y Acad. Sci. 902* (2000) 163–170.
37. JR Sowers. Hypertension in Type II Diabetes: Update on Therapy. *J Clin Hypertens (Greenwich)* 1999;41-47.
38. JO Prior, MJ Quinones,et al. Coronary circulatory dysfunction in insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus. *Circulation* 2005;2291-98.
39. Hartge M.M., Unger T., Kintscher U.,The endothelium and vascular inflammation in diabetes, *diabetes and vascular disease research*,2015;,84-88.
40. Kolluru G.K., Bir S.C., Kevil C.G., Endothelial Dysfunction and Diabetes: Effects on Angiogenesis, Vascular Remodeling, and Wound, *Healing, International Journal of Vascular Medicine*, 2012;,1-30.
41. Bohlen H. G. and Lash J. M., Topical hyperglycemia rapidly suppresses EDRF-mediated vasodilation of normal rat arterioles, *American Journal of Physiology*, 1993;vol. 265: 219–225.
42. Tesfamariam B., Brown M. L., Deykin D., and Cohen R. A., Elevated glucose promotes generation of endothelium-derived vasoconstrictor prostanoids in rabbit aorta, *Journal of Clinical Investigation*, 1990; vol. 85: 929–932.
43. Johnstone M. T., Creager S. J., Scales K. M.,et al., "Impaired endothelium-dependent vasodilation in patients with insulin- dependent diabetes mellitus, 1993;vol. 88: 2510–2516.
44. King G. L., The role of hyperglycaemia and hyperinsulinaemia in causing vascular dysfunction in diabetes, *Annals of Medicine*, 1996:vol. 28: 427–432.
45. Poornima I. G., Parikh P., and Shannon R. P., Diabetic cardiomyopathy: the search for a unifying hypothesis,*Circulation Research*, 2006;vol. 98: 596–605.
46. Arcaro G., Cretti A., Balzano S. et al., Insulin causes endothelial dysfunction in humans: sites and mechanisms,*Circulation*, 2002;vol. 105: 576–582.
47. Lee I. K., Kim H. S., and Bae J. H., Endothelial dysfunction: its relationship with acute hyperglycaemia and hyperlipidemia,*International Journal of Clinical Practice, Supplement*, 2002; 59–64.
48. Calles-Escandon J. and Cipolla M., Diabetes and endothelial dysfunction: a clinical perspective, *Endocrine Reviews*, 2001;vol. 22: 36–52.
49. Katsuki. A., Sumida Y., Urakawa H. et al., Increased oxidative stress is associated with serum levels of triglyceride, insulin resistance, and hyperinsulinemia in Japanese metabolically obese, normal-weight men,*Diabetes Care*, 2004;vol. 27:, 631–632.
50. Endemann D. H. and Schiffrin E., Endothelial Dysfunction, *Journal of the American Society of Nephrology*, 2004;1983–1992.
51. Koppenol WH, Moreno JJ, Pryor WA, ry al.,Peroxynitrite, a cloaked oxidant formed by nitric oxide and superoxide. *Chem Res Toxicol* 1992; 834–842.
52. Milstien S, Katusic Z, Oxidation of tetrahydrobiopterin by peroxynitrite: Implications for vascular endothelial function. *Biochem Biophys Res Commun* 1999;681–684.
53. Hamilton CA, Brosnan MJ, Al-Benna S, Berg G, Dominiczak AF,NAD(P)H oxidase inhibition improves endothelial function in rat and human blood vessels. *Hypertension* ,2002;40: 755–762 .
54. Touyz RM, Chen X, Tabet F, Yao G, He G,et al., Expression of a functionally active gp91phoxcontaining neutrophil-type NAD(P)H oxidase in smooth muscle cells from human resistance arteries: Regulation by angiotensin II. *Circ Res* ,2002;90: 1205–1213.
55. Du X, Matsumura T, Edelstein D, Rossetti L,et al., Inhibition of GAPDH activity by poly- (ADP-ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. *J Clin Invest* ,2003;112: 1049–1057.
56. Schiffrin EL, Touyz RM, Multiple actions of angiotensin II in hypertension: Benefits of AT1 receptor blockade,*J Am Coll Cardiol* ,2003;42: 911–913.

57. Schiffrin EL, Park JB, Pu Q, Effect of crossing over hypertensive patients from a beta-blocker to an angiotensin receptor antagonist on resistance artery structure an on endothelial function,*J Hypertens*,2002;20: 71–78.
58. Hegab Z., Gibbons S. et al., Role of advanced glycation end products in cardiovascular Disease. *World J Cardiol* ,2012; April 26; 4(4): 90-102.
59. Zhang L, Zalewski A, Liu Y, Mazurek T,et al., Diabetes-induced oxidative stress and low-grade inflammation in porcine coronary arteries. *Circulation*,2003; 108: 472–478.
60. Deborah Markowicz Bastos, Érica Monaro et al., Maillard Reaction Products in Processed Food: Pros and Cons.281-300.
61. Williams SB, Goldfine AB, Timimi FK, Ting HH, et al.,Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo, *Circulation*,1998;97: 1695–1701.
62. Su J.B., Vascular endothelial dysfunction and pharmacological Treatment, *World J Cardiol*,2015; 719-741.
63. Su JB, Barbe F, Houel R, Guyene TT, Crozatier B, Hittinger L., Preserved vasodilator effect of bradykinin in dogs with heart failure. *Circulation* ,1998; 98: 2911-2918.
64. Kaiser L, Spickard RC, Olivier NB. Heart failure depresses endothelium-dependent responses in canine femoral artery. *Am JPhysiol* ,1989; 256: H962-H967 .
65. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. *J Am Coll Cardiol* ,2012; 60: 1455-1469.
66. Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA, Surrogate markers for cardiovascular disease: functional markers. 2004;109:IV31– 46.
67.Hasdai D, Lerman A, The assessment of endothelial function in the cardiac catheterization laboratory in patients with risk factors for atherosclerotic coronary artery disease.1999);24:544 –7.
68.Marti C.N., Gheorghiade M., Endothelial Dysfunction, Arterial Stiffness, and Heart Failure, *Journal of the American College of Cardiology*,2011;1455 1469.
69. Silva BM, Neves FJ, Rocha NG, et al.,Intra- and inter-tester reproducibility of venous occlusion plethysmography: comparison between a manual and a semiautomatic method of blood flow analysis,2009;30: 1267–79.
70. Woo KS, Chook P, Yu CW, et al. Effects of diet and exercise on obesity-related vascular dysfunction in children. Circulation ,2004;109:1981– 6.
71. Kuvin JT, Patel AR, Sliney KA, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J*,2003;146:168 –74.
72. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up patients with mild coronary artery disease and endothelial dysfunction. *Circulation*.,2000;101 (9): 948-54.
73. Varin R, Mulder P, Tamion F, Richard V,et al., Improvement of endothelial function by chronic angiotensin-converting enzyme inhibition in heart failure: role of nitric oxide, prostanoids, oxidant stress, and bradykinin. *Circulation* ,2000; 351-356.
74. Fujii M, Wada A, Tsutamoto T, Ohnishi M, Isono T, Kinoshita M. Bradykinin improves left ventricular diastolic function under long-term angiotensin-converting enzyme inhibition in heart failure. *Hypertension* ,2002; 952-957.
75. Mukai Y, Shimokawa H, Higashi M, Morikawa K,et al,Inhibition of renin-angiotensin system ameliorates endothelial dysfunction associated with aging in rats. *Arterioscler Thromb Vasc Biol*,2002; 1445-1450.
76. Heitzer T, Just H, Münzel T. Antioxidant vitamin C improves endothelial dysfunction in chronic smokers. *Circulation* ,1996;6-9.
77. E supplementation improves endothelial function in type I diabetes mellitus: a randomized, placebo-controlled study. *J Am Coll Cardiol* ,2000; 94-102.
78. Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. *Free Radic Biol Med* ,2011; 1000-1013.
79. Corda S, Laplace C, Vicaut E, Duranteau J. Rapid reactive oxygen species production by mitochondria in endothelial cells exposed to tumor necrosis factor-alpha is mediated by ceramide. *Am J Respir Cell Mol Biol* ,2001;762-768.
80. Scioli MG, Bielli A, Agostinelli S,et al.,Antioxidant treatment prevents serum deprivation- and TNF-α-induced endothelial dysfunction through the inhibition of NADPH oxidase 4 and the restoration of β-oxidation. *J Vasc Res* ,2014;327-337.
81. Vyssoulis GP, Marinakis AG, Aznaouridis KA,et al.,The impact of thirdgeneration beta-blocker antihypertensive treatment on endothelial function and the prothrombotic state: effects of smoking. *Am J Hypertens* ,2004; 582-589.
82. Zepeda RJ, Castillo R, Rodrigo R, Prieto JC,et al., Effect of carvedilol and nebivolol on oxidative stress-related parameters and endothelial function in patients with essential hypertension. *Basic Clin Pharmacol Toxicol* (2012)309-316.
83. Kelly AS, Gonzalez-Campoy JM, Rudser KD,et al.,Carvedilol-lisinopril combination therapy and endothelial function in obese individuals with hypertension. *J Clin Hypertens* (Greenwich), 2012; 85-91.
84. Treasure CB, Klein JL, Weintraub WS, Talley JD,et al., Beneficial effects of cholesterol-lowering

therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* ,1995; 481-487.
85. Feron O, Dessy C, Desager JP, Balligand JL,Hydroxy-methylglutaryl- coenzyme A reductase inhibition promotes endothelial nitric oxide synthase activation through a decrease in caveolin abundance. *Circulation*,2001; 113-118.
86. Okamura T, Tawa M, Geddawy A, Shimosato T,et al.,Effects of atorvastatin, amlodipine, and their combination on vascular dysfunction in insulin-resistant rats. *J Pharmacol Sci*,2014;76-85.
87. Sampaio WO, Souza dos Santos RA, Faria-Silva R,et al.,Angiotensin-(1-7) through receptor Mas mediates endothelial nitric oxide synthase activation via Akt-dependent pathways. *Hypertension*,2007; 185-192.
88. Stegbauer J, Potthoff SA, Quack I, Mergia E, Clasen T,et al., Chronic treatment with angiotensin-(1-7) improves renal endothelial dysfunction in apolipoproteinE-deficient mice. *Br J Pharmacol*,2011; 974-983.
89. Costa MA, Lopez Verrilli MA, Gomez KA,et al.,Angiotensin-(1-7) upregulates cardiac nitric oxide synthase in spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* .2010; H1205-H1211.
90. Westermann D, Riad A, Richter U, Jäger S, Savvatis K,et al.,Enhancement of the endothelial NO synthase attenuates experimental diastolic heart failure. *Basic Res Cardiol* ,2009; 499-509.
91. Xuan C, Chang FJ, Liu XC, Bai XY,et al.,. Endothelial nitric oxide synthase enhancer for protection of endothelial function from asymmetric dimethylarginine-induced injury in human internal thoracic artery. *J Thorac Cardiovasc Surg*,2012; 697-703.
92. Xue HM, Yu CM, Underwood MJ,et al.,AVE3085 protects coronary endothelium from the impairment of asymmetric dimethylarginine by activation and recoupling of eNOS. *Cardiovasc Drugs Ther*,2012; 383-392.
93. Williams S.B., jorge B.S., cusco A. et al., Impaired Nitric Oxide-Mediated Vasodilation in Patients With Non-Insulin-Dependent Diabetes Mellitus,1996;567-574.