Why Does Diabetes Mellitus Increase The Risk of Cardiovascular Disease?

Alwi Shahab

ABSTRACT

The main etiology for mortality and a great percentage of morbidity in patients with diabetes mellitus is atherosclerosis. The pathogenesis of cardiovascular disease (CVD) in diabetes is multifactorial and can be affected by metabolic and other factors. A hypothesis for the initial lesion of atherosclerosis is endothelial dysfunction, defined pragmatically as changes in the concentration of the chemical messengers produced by the endothelial cell and/or by blunting of the nitric oxide-dependent vasodilatory response to acetylcholine or hyperemia. Endothelial dysfunction has been documented in patients with diabetes and in individuals with insulin resistance or at high risk for developing type 2 diabetes. The way endothelial function altered in diabetic patients is not yet fully understood, but the loss of normal endothelial function could be involved in the pathogenesis of diabetic angiopathy, as endothelial dysfunction is associated with diabetic microangiopathy and macroangiopathy. Factors associated with endothelial dysfunction in diabetes include activation of protein kinase C, overexpression of growth factors and/or cytokines, and oxidative stress. Changes in endothelium function may lead to the coronary artery circulation being unable to cope with the increased metabolism of myocardial muscle independently of a reduced coronary artery diameter. Finally, recent reports indicate that an improved metabolic control in diabetic patients, whatever the treatment used, is associated with near normalization or restoration of normal endothelial function.

Key words: diabetes mellitus, cardiovascular disease.

INTRODUCTION

The major cause of morbidity and mortality in diabetic patient (either type 1 diabetes mellitus or type 2 diabetes mellitus) are cardiovascular disease. Microvascular complication is the cause of retinopathy, neuropathy, and nephropathy, while macro-angiopathy in diabetes manifests as early atherosclerosis, which may affect vital organs (the heart and the brain). There are multi-factors that may cause atherosclerosis in type 2 diabetes mellitus, which include complex interaction of various conditions such as hyperglycemia, hyperlipidemia, oxidative stress, early degenerative condition, hyperinsulinemia and/or hyperproinsulinemia and other changes of coagulation and fibrinolysis process. The recent hypothesis indicates that there are changes of endothelial cells function in the early atherosclerosis lesion. Endothelial dysfunction may occur either in type 2 or type 1 diabetes mellitus patient, especially if there is clinical manifestation of micro albuminuria. Endothelial dysfunction may also occur in patient with insulin resistance (obese patient) or patient with high risk of type 2 diabetes mellitus (impaired glucose tolerance) and gestational diabetes patient. In diabetes mellitus patient, the risk of congestive heart disease increases about 4 to 8 times. The increase risk is not only caused by ischemic heart disease. In recent years, it has been known that diabetes may influence heart muscles independently in addition to early atherosclerosis of coronary artery, which causes ischemic heart disease. We assume that it may be caused by some changes such as interstitial fibrosis process, collagen formation and hypertrophy of heart muscle cells. In cellular level, there are disruption of calcium release from cytoplasm, changes of troponin T structure and increase activity of Pyruvate Kinase. These changes cause distraction of heart muscles contraction and relaxation, as well as elevation of end-diastolic pressure that may cause restrictive cardiomyopathy. This literature review is intended to explain about pathophysiology of increase cardiovascular disease risk in diabetes mellitus patient. First, we will explain about the role of endothelial cell in maintaining vascular homeostasis.

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ENDothelial cell function

Endothelial cell lining cover the inner part of all blood vessels lumen and act as barrier between blood circulation and smooth muscle cells of blood vessel. In addition to their role as physical barrier between blood and the tissues, endothelial cells also facilitate various complex functions of smooth muscle cells in blood vessel and other cells in blood compartment. A range of study indicated that endothelial cells have very important role in homeostasis process, which occur through integration of various chemical mediators.9-11

This system has beneficial effect either against smooth muscle cells of blood vessels or the blood cells, which may cause various changes, such as:
1. Vasodilatation or vasoconstriction in order to regulate the needs of blood supply for all organs in human body.
2. Growth and or other phenotype characteristic changes of smooth muscle cells of the blood vessel
3. Pro-inflammation or anti-inflammation changes
4. Maintain blood viscosity and prevent bleeding

Nitric Oxide: a Key Mediator of Endothelial Cells

For several decades, it has been proven that nitric oxide has a role not only in controlling vasomotor tone but also in blood vessel and nerve homeostasis as well as immunologic process. Endogenous nitric oxide is produced through alteration of L-arginine amino acid into L-citrulline by NO-synthase (NOS) enzyme.12

Recently some isoforms of NOS have been purified and cloned as NOS-type I (which is isolated from the brain = neuronal NOS-type I) and NOS-type III (which is isolated from the endothelial cells = endothelial NOS- type III), which is also known as constitutive-NOS (cNOS). Both isoforms are regulated by Ca²⁺-calmodulin and NADPH, flavin adenine dinucleotide/mononucleotide (FAD/FMN) and tetrahydrobiopterin (HB4) as the co-factors. Neuronal-NOS type I has an important role in nerve-transmission process, blood vessel homeostasis control as well as in memory and learning process. In peripheral nervous system, NOS is related to nonadrenergic noncholinergic (NANC) nerve pathway.

Endothelial-NOS (eNOS type III) has important role in controlling blood vessel tone as a response against various stimulus, such as mechanical stimulus (shear stress), dependent receptor (acetylcholine) and independent receptor (calcium ionophore).

Nitric oxide produced by NOS type III in the endothelium will diffuse into smooth muscle cells of blood vessel which will activate guanylate cyclase enzyme. Together with GMP cyclic increase, there will be smooth muscle relaxation in the blood vessels. Hence, as a final result of nitric oxide increase, vasodilatation happened.

Endothelial cells produce nitric oxide (NO), which will diffuse into smooth muscle cells of blood vessel and activate guanylate cyclase enzyme, which produces cyclic GMP. Cyclic GMP will stimulate muscles relaxation, so that vasodilatation will occur. NOS type II also has a role in preventing abnormal platelet aggregation. NOS type II and IV (which are isolated from the macrophages) are independent against Ca²⁺ calmodulin and are also called as “inducible-NOS” because their activation might only occur when macrophages cause

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cycloxygenases (COX) and converting enzyme (ACE). Angiotensin II (ANG-II) production is regulated by the kidney, a key organ in the renin-angiotensin system (RAS). ACE is a proteolysis enzyme that converts angiotensin I, a peptide generated by the kidney during the renin-angiotensin system, into angiotensin II. Angiotensin II acts as a potent vasoconstrictor, increasing blood pressure and heart rate, and as a stimulant for growth and differentiation of smooth muscle cells of blood vessel. 

**Endothelial Cell as Hemostasis Regulator**

Endothelial cells secrete factors that regulate blood flow and prevent thrombosis. Endothelial cells express adhesion molecules that mediate the adherence of platelets and leukocytes to the endothelial surface, and they express coagulation factors such as von Willebrand factor (vWF) and tissue factor (TF). Endothelial cells also secrete endothelial nitric oxide synthase (eNOS), which produces nitric oxide (NO) that acts as a vasodilator and inhibitor of platelet aggregation. NO production is also regulated by local concentration of bradykinin. Bradykinin is a peptide that acts as a vasodilator and inhibitor of platelet aggregation.

**Endothelial Cell as Growth Mediator of Smooth Muscle Cells of Blood Vessel and Inflammation Process**

Endothelial cells secrete growth factors that stimulate the proliferation and differentiation of smooth muscle cells of blood vessel. These growth factors include fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF-1), and platelet-derived growth factor (PDGF). These growth factors act as main messengers against growth signals such as insulin-like growth factor 1 (IGF-1), PDGF, basic fibroblast growth factor (bFGF), etc. However, various evidences indicate that growth stimulation of smooth
muscle cells in blood vessel is mediated by local production of PGF and ANG-II. NO and prostacyclin (PGI2) are the main antagonist of ANG-II effect on growth stimulation of smooth muscle cells in blood vessel.\textsuperscript{19} Endothelial cell is also included in various molecule productions which are important in inflammation process, i.e. LAM, intracellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM). These molecules are known as “adhesion molecule” and their function is to activate cells participating in inflammation reaction. Recent study indicates that there is increase blood level of inflammation marker (acute phase proteins) in atherosclerosis process.\textsuperscript{20}

PATHOPHYSIOLOGY OF INCREASED CARDIOVASCULAR DISEASE RISK IN DIABETES MELLITUS PATIENT

The pathophysiology of increased cardiovascular disease risk in diabetes mellitus patient has not been known accurately. However, from the study result we found that:

1. The incidence of atherosclerosis is higher in diabetic patient compared to non-diabetic population.
2. Diabetic patient has a high risk of having thrombosis, decreased fibrinolysis and increased inflammation response.
3. In diabetic patient, there is protein glycosylation that will affect the integrity of blood vessel wall.

Haffner et al\textsuperscript{21} demonstrate that atherosclerosis in diabetic patient is started before clinical onset of diabetes occurs. Epidemiology study also demonstrates that increased risk of heart failure in diabetic patient compared to non-diabetic population actually because of a poor blood glucose control in long-term period. Besides, there are several factors that also exaggerate the risk of heart failure and stroke in diabetic patient such as hypertension, insulin resistance, hyperinsulinemia, hyperamilinemia, dyslipidemia and coagulation system disorder and hyperhomosisteinemia.

All of these risk factors sometimes may occur in one individual and they are a group of symptoms, which is known as insulin resistance syndrome or metabolic syndrome.

Endothelial dysfunction, which initiates atherosclerosis lesion in diabetes mellitus patient, may occur because of:

**Hyperglycemia**

Chronic hyperglycemia causes endothelial dysfunction through various mechanisms, such as:\textsuperscript{22-26}

1. Chronic hyperglycemia causes non-enzymatic glycosylation of proteins and macro-molecules such as DNA, which will cause changes of antigenic characteristic in protein and DNA. This condition will cause changes of intravascular pressure and disturb the cerebrovascular reactivity because of NO and prostaglandin imbalance.
2. Hyperglycemia increase intracellular PKC activation that will cause distraction of NADPH pool, which will inhibit NO production.
3. Hyperglycemia will increase diacylglycerol (DAG) synthesis through glycolysis pathway. Increased DAG level will enhance the PKC activity. Either DAG or PKC has important role to modulate the vasoconstriction.
4. Endothelial cells are very sensitive against the effect of oxidative stress. Hyperglycemia will likely cause a tendency of oxidative stress and increase the amount of oxidized lipoprotein, especially small dense LDL-cholesterol (oxidized LDL), which is more atherogenic. The increase of free-fatty acid level and hyperglycemia condition may enhance phospholipids and protein oxidation.
5. Hyperglycemia will be accompanied by prothrombosis tendency and platelet aggregation. These conditions are related to several factors such as decreased NO production and decreased fibrinolytic activity because of increased PAI-1 level. Moreover, in type 2 diabetes mellitus there is increased coagulation activity because of various factors such as the formation of advanced glycocylation end products (AGEs) and decreased heparin sulfate synthesis.
6. Although there is no direct correlation between coagulation activation and endothelial dysfunction, recurrent coagulation activation may cause over-stimulation of endothelial cells that may produce endothelial dysfunction.

**Insulin Resistance and Hyperinsulinemia**

A few years ago, Jialal et al\textsuperscript{27} found an insulin receptors i.e. IGF-I and IGF-II of the small and large blood vessel cells with the same binding characteristic of other cells. They indicate that receptor IGF-I and IGF-II of endothelial cells have been proven to have physiological role of vascular complication in diabetes.

Insulin deficiency and chronic hyperglycemia may increase the total level of protein kinase C (PKC) and diacylglycerol (DAG). Insulin has a direct effect on blood vessel tissues. In the study of obese Zucker rat’s blood vessel tissue, there is a resistance against PI3-kinase signal.\textsuperscript{28} This finding shows that insulin resistance will cause direct disturbance of blood vessel function. King
et al\textsuperscript{29} in their study of utilizing physiologic insulin level, found that this hormone may increase the activity and concentration of eNOS mRNA, by 2 times fold after 2-8 hours of endothelial cell incubation. They conclude that insulin has not only acute vasodilatation effect but also blood vessel tone modulation.

Insulin toxicity (hyperinsulinemia/hyperprinsulinemia) may be associated with insulin resistance/metabolic syndrome and early state of type 2 diabetes mellitus. Insulin increase the number of AT-1 receptor and activate the Renin Angiotensin Aldosterone System (RAAS). Recently, there is identification of AT-1 receptor extent in beta cells and in the capillary endothelial cells of langerhans islands in pancreas. Therefore, hyperinsulinemia is correlated to Ang-II and it will cause increased oxidative stress of langerhans islands in pancreas because of increased insulin, proinsulin and amylin level.\textsuperscript{15,16,30}

**Hyperamylinemia**

Amylin or Islet Amyloid Polypeptide (IAPP) is polypeptides that have 37 amino acid molecules. It is synthesized and secreted by beta pancreas cells together with insulin. Hence, hyperamylinemia state will be accompanied by hyperamylinemia and vice versa if there is decreased insulin level then it will be hypoamylinemia state. Hyperinsulinemia and hyperamylinemia may be associated with insulin resistance/metabolic syndrome and type 2 diabetes mellitus. Amyloidosis (accumulation of amylin deposit) in islet is assumed to be correlated with duration and severity of insulin resistance and type 2 diabetes mellitus. In contrast, accumulation of amylin deposit in beta pancreas cells will decrease its function of insulin secretion. Sakuraba et al recently found that in type 2 diabetes mellitus, the increase of oxidative stress is correlated to increased IAPP formation in beta pancreas cells. In this condition, there is decreased expression of SOD along with IAPP formation and decreased mass of beta cells. This finding demonstrates a correlation between oxidative stress and IAPP formation, decreased mass and cell density of beta pancreas cells. Amylin may also stimulate lipolysis and one of several factors that cause insulin resistance. Recently, amylin binding site is also found in renal cortex where amylin may activate RAAS, causing increased level of renin and Aldosterone. Janson et al found some Amyloid particles (intermediate sized toxic amyloid particles = ISTAPs), which have cytotoxic effect against beta pancreas cells that may cause apoptosis by destroying the cell membrane.\textsuperscript{31,32}

**Inflammation**

In recent years, it has been proven that inflammation not only causes complications of acute cardiovascular disease, but also as the main cause of progressive and development of atherosclerosis. Various inflammation markers had been found in atherosclerosis lesion, i.e. cytokines and growth factors, which are released by macrophages and T cells. Cytokines will increase platelet activating factor synthesis, stimulate lipolysis, express the adhesion molecules and up-regulates the synthesis and expression of pro-coagulant in endothelial cells. Therefore, cytokines have important role not only in the early process of atherosclerosis development, but also in progressiveness. Cytokines are much more released in diabetic patient, because of increased various process that activate the macrophages (and cytokines release), such as oxidation and glycoxidation of protein and lipid.

Cytokines release, which is activated by AGEs, will be accompanied by over-production of various growth factors such as:

- PDGF (Platelet Derived Growth Factor)
- IGF-1 (Insulin Like Growth Factor-1)
- GMCSF (Granulocyte/Monocyte Colony Stimulating Factor)
- TGF-\(\alpha\) (Transforming Growth Factor-\(\alpha\))

All of these factors mainly affect the function of blood vessel cells. In addition, there is also an increase of immune complex formation, which contains modified lipoprotein. A high level of immune complex containing modified LDL will increase the risk of macro vascular complication in diabetic patient, either type 1 or type 2 diabetes mellitus. The immune complex not only stimulates a large number of cytokine releases but also stimulates the expression and release of metalloproteinase-1 without stimulating the inhibitor synthesis. The macrophage activation by such immune complex will stimulates tumor necrosis factor (TNF) release, which causes up-regulation of C-reactive protein synthesis. Recently, an adequate level of C reactive protein is found in patient with insulin resistance. Increased immune complex level in diabetes mellitus patient not only causes atherosclerosis and its progressiveness but also has a role in rupture process of atherosclerosis plaque and consequent cardiovascular complication. There is an increased of macrophage content in atherosclerosis lesion of diabetic patient, which is caused by increased macrophage recruitment into blood vessel’s wall because of increased cytokine level. Increased oxidized LDL level in diabetic patient will increase T cell activation that will enhance interferon-\(\gamma\) release.
Interferon-γ release will cause homeostasis disturbance of blood vessel cells. Activation of T cells will also inhibit smooth muscle cells, proliferation of blood vessel and collagen biosynthesis that will cause vulnerable plaque, so that it will cause acute cardiovascular complication. Up to now, there are still a lot of contra-versions about why on pathologic anatomy examination, the plaque of type 1 diabetes mellitus has more fibrous and calcified characteristics, while in type 2 diabetes mellitus, it has more cellular characteristic and contain more lipid. In a serial examination of coronary artery of type 2 diabetes mellitus patient after a sudden death, there are necrosis area, calcification and an extensive plaque rupture. While on type 1 diabetes mellitus, there is an increase content of connective tissues with a few of foam cells among the plaque, which facilitate a relatively more stable atherosclerosis lesion.33

Thrombosis/Fibrinolysis

Diabetes will be accompanied by pro-thrombotic condition, i.e. changes of thrombosis and fibrinolysis process. Such alteration is caused by insulin resistance, which mainly occurs in type 2 diabetes mellitus patient. However, it may also be found in type 1 diabetes mellitus patient. Increased fibrinogen level and activity of factor VII and PAI-1, either in plasma or in atherosclerotic plaque, will cause decreased urokinase and increased platelet aggregation. It is considered that the cause of increased fibrinogen is enhanced activity of factor VII, which is correlated to post prandial hyperlipidemia state. Over-expression of PAI-1 is considered because of direct effect of insulin and pro-insulin. Recent study indicates that decreased PAI-1 level after thiazolidinediones therapy for type 2 diabetes mellitus has supported the hypothesis of insulin resistance role in development of PAI-1 over-expression process. Increased PAI-1 level either in plasma or in atherosclerosis plaque not only inhibits migration of smooth muscle cells of blood vessel, but also decreases urokinase expression in blood vessel wall, as well as the atherosclerosis plaque.

Dyslipidemia

Dyslipidemia which will cause oxidative stress usually occurs in insulin resistance/metabolic syndrome and type 2 diabetes mellitus. This condition occurs because of metabolism disorder of lipoprotein, which is usually known as “lipid triad”, including:
1. Increase VLDL or triglyceride level
2. Decrease HDL cholesterol level
3. The formation of small dense LDL, which is more atherogenic.

Increase VLDL, triglyceride and small dense LDL cholesterol level and decrease HDL cholesterol level, which has anti-atherogenic, anti-oxidant and anti-inflammation effects will reduce the natural anti-oxidant storage.

Lipoprotein acts as lipid distributor to all of human body, where LDL especially important in apolipoprotein transport (Apo) B 100; VLDL has an important role of triglyceride transport, which contain Apo E, while HDL has a role to redistribute the cholesterol which contains natural anti-inflammation and anti-oxidant, which is ApoA. Protein molecules of such lipoprotein will be modified by oxidation, glycosylation, and glycoxidation process with a final result of increased oxidative stress and radical oxygen species formation. In addition, the modified lipoprotein will cause resistance of tunica intima and initiates atherogenesis development.37

Hypertension

Hypertension is one of several factors in insulin resistance/metabolic syndrome and it is frequently found along with type 2 diabetes mellitus. In type 1 diabetes mellitus patient, hypertension may occur if there is sign of renal dysfunction, characterized by microalbuminuria. Hypertension will exaggerate endothelial dysfunction and increase the risk of cardiovascular disease. Hypertension is also accompanied by increased oxidative stress and activity of radical oxygen species that consequently will mediate vascular disorder by Ang II activation and decrease activity of super oxide dismutase. In contrast, glucotoxicity will cause increased RAAS activity that it will increase the risk of hypertension. Recent study found an increase amylin level (hyperamilinemia) in individual with familial hypertension and insulin resistance.14-16,38

Hyperhomocysteinemia

In either type 1 or type 2 diabetes mellitus patient, there is a gene polymorphism of methylene tetrahydrofolate reductase enzyme that may cause hyperhomocysteinemia. The gene polymorphism especially occurs in patient with deficient folic acid nutrition. Severe hyperhomocysteinemia is corrected by folic acid supplementation. Homocysteine will be increased, especially if renal dysfunction occurs. Increased Homocysteine level usually occurs along with decrease of glomerulus filtration rate. Hyperhomocysteinemia will cause inactivation of nitric oxide through inhibition against glutathione peroxidase (GPx) expression.39
MANAGEMENT OF ENDOTHELIAL DYSFUNCTION IN DIABETES MELLITUS

Strict Blood Glucose Control
The study result of DCCT (Diabetes Control and Complications Trial) for 7 years on 1440 type 1 diabetes mellitus indicates that intensive insulin therapy may decrease the incident of microalbuminuria by 39% and microalbuminuria by 54%.40

Insulin Sensitizers
As mentioned before, insulin resistance will occur along with endothelial dysfunction. Therefore some researchers try to demonstrate whether drugs increasing insulin sensitivity are also able to repair the endothelial dysfunction.

Pasceri et al41 found that troglitazone (PPAR γ activator and also an insulin sensitizer) in vivo, inhibits the expression of VCAM-1 and ICAM-1 on activated endothelial cells. This drug also decreases the amount/content of monocyte/macrophage in atherosclerotic plaque significantly. In other studies, the drug also reduces the expression of VCAM-1, ICAM-1 and E-selectin, which are induced by oxidized LDL and TNF. In another study, Tack et al42 found that troglitazone may improve insulin sensitivity, but it has no effect on vascular response which is endothelium dependent. Those studies indicate the short-term benefit of insulin sensitizer against endothelial function of type 2 diabetes mellitus patient of insulin resistance. However, to date, there is no long-term study which may conclude that insulin sensitizer has benefits in preventing or slowing progressive atherosclerosis in type 2 diabetes mellitus patient or insulin resistance.

ACE Inhibitors
TREND (Trial on Reversing Endothelial Dysfunction) research is intended to prove a theory that ACE inhibitor and quinapril may improve endothelial dysfunction in coronary heart disease patient, with normal tension and without heart failure, cardiomyopathy or dyslipidemia. After 6 month-therapy, the group treated with quinapril indicates a significant improvement of vasodilatation response against certain concentration of acetylcholine compared to the placebo group. The researcher assumed that the benefit of ACE inhibitor occurs because of improved ANG-II effect against contraction and superoxide production as well as increased NO production of endothelial cells as a response against decreased Bradykinin metabolism.43

QUIET (Quinapril Ischemic Event Trial) research studied 1750 patients with normal left ventricle function who had angiography and angioplasty, who randomly were given quinapril or placebo of 20 mg/day and monitored for 3 years. From this research, no conclusion is gained about the role of ACE inhibitor as anti-atherosclerosis because all of patients participated in this research has had atherosclerosis.44 The recent study, i.e. HOPE (Heart Outcomes Prevention Evaluation), studied about the role of ramipril in patient with high risk of cardiovascular complication but without left ventricle dysfunction or heart failure. A number of 9297 patients (over than 55 years of age) with blood vessel disease of diabetes mellitus together with one cardiovascular risk factor were given ramipril (10 mg per day) or placebo for approximately 5 years period. The final result includes myocardium infarct, stroke or death because of cardiovascular complication. This study result indicates that ramipril significantly decreases mortality rate in the cardiovascular cause of death and morbidity of myocardium infarct as well as stroke in high-risk patient. This study demonstrates that ACE inhibitor ramipril usage may prevent progressiveness of silent atherosclerosis.45

Hypolipidemia Drugs
As mentioned before, among other factors, hyperlipidemia and increased oxidized LDL level are the risk factor of endothelial dysfunction development in diabetes patient. Statin has been used extensively for hypercholesterolemia therapy in type 2 diabetes mellitus patient, but there is no evidence that indicates the effect of this drug for endothelial function in type 2 diabetes mellitus patient. In a mini-study (consists of 21 type 2 diabetes mellitus patient + hypercholesterolemia) treated with simvastatin (10 mg/day) for 24 weeks indicates no significant improvement of endothelial function. Evan et al studied the short-term (3 months) effect of fibrate therapy on endothelial function and oxidative stress in type 2 diabetes mellitus patient. They found that fibrate therapy improved endothelial function of type 2 diabetes mellitus patient together with improved triglyceride serum level.47

Supplementation of Arginine and Anti-oxidant
L-arginine is a substrate of NOS formation. Hence, it is assumed that L-arginine supplementation may activate NOS and increase NO production as well as improve vasodilatation. This hypothesis has been studied in various condition associated with endothelial dysfunction such as chronic heart failure, cyclosporine-induced endothelial damage and type 2 diabetes mellitus. But not all of those studies are able to demonstrate that L-arginine supplementation affect the NO production and enhance vasodilatation. Until now, it is not clear yet about how increased L-arginine plasma
levels able to increase NOS activation. Some opinion said that vitamin E and vitamin C as well as other anti-oxidant therapy are able to improve the function of diabetes mellitus patient’s blood vessel. Reaven et al. in their study found that vitamin E supplementation by 1600 IU/day for 10 weeks may decrease the sensitivity against LDL oxidation. Pinkney et al. have studied the hypothesis about correlation between endothelial function and LDL oxidation by giving 500 IU/day vitamin E on 46 type 1 diabetes mellitus patients for 3 months period. They found that vitamin E supplementation on type 1 diabetes mellitus patient may improve the endothelial function without any changes on LDL oxidation. This result indicates that improved endothelial function is not mediated by decrease LDL oxidation.

**Hormone Replacement Therapy**

Hormone replacement therapy by using estrogen is considered to be able to improve endothelial function. However, until now, there is no specific study that has been conducted to recognize the estrogen effect on endothelial function in post-menopause diabetic woman.

**CONCLUSION**

Endothelial dysfunction may occur either in type 1 or type 2 diabetes mellitus patient or individual with insulin resistance.

Endothelial dysfunction is the initial condition of atherosclerosis lesion, which in diabetic patient, it may occur earlier.

A strict blood glucose control has been proven to be able to slow down the progressiveness of endothelial dysfunction in diabetes.

At least there are 2 studies with a great scale (TREND and HOPE study) offering optimism about therapy of endothelial dysfunction with ACE inhibitor which may slow down the progressiveness of atherosclerosis.

The role of insulin sensitizer and or anti-oxidant therapy and hypolipidemia drugs still call for further study. There is no evidence data of hormone replacement therapy effect by using estrogen against improved endothelial function in post menopause diabetic woman.

**REFERENCES**


