Diabetes, Endothelium and Atherosclerosis

AK Chauhan

Director, Chauhan Sanjeevani Hospital, Bareilly.

38

A B S T R A C T

Atherosclerosis is a major cause of disability and death in DM. It substantially increase the risk of developing coronary, cerebral and peripheral arterial vascular disease. Pathophysilogy of this involves endothelium, vascular smooth muscle and platelet factor. The metabolic abnormality of DM-Hyperglycemia increased free fatty acid insulin resistance each provoke molecular mechanism that contributes to vascular dysfunction including decreased bioavailability of NO ↑ oxidative stress, disturbance of intracellular signaling activation of AGE receptor with excessive production of AGE. Platelet function of abnormal with several prothrombotic factors. This contributes to cellular events that ultimately produce atherosclerosis and adverse cardio vascular events that occur in Diabetic patients.

Diabetes mellitus, affecting about 100 million persons worldwide i.e. 90 to 95% of them are (Non-Insulin Dependent Diabetes). The incidence and prevelance is markedly increasing in the entire globe, but much more in Indian subcontinent due to changing life style and eventually developing the obesity.

People with BMI > 30 kg./m^2 is 5 times more prone for the risk of diabetes than normal BMI (25 kg/m^2) In every kg. of in weight gain the risk of diabetes increase approximately 9% approx. four out of time five diabetics will die of vascular disease (CVD), essentially the same risk for the non diabetics with established CAD, Hence the evidence suggests that patient with DM-2 suffer from accelerated atherosclerosis.

PATHOPHYSIOLOGY OF DIABETIC VASCULAR DISEASE

Endothelelial cells and vascular smooth muscle cells are responsible to maintain a normal haemostasis. In healthy endothelial cells because of their strategic position between the circulating blood and the vessel wall, regulate structure and vascular functions normally they secrete active substances, which are released to maintain vascular homeostasis ensuring adequate blood flow and nutrient delivery, while preventing thrombosis and leukocyte diapedesis. Among the important molecules synthesized by endothelial cells are nitric oxide (EDRF) prostacycline and endothelial derived constricting factors (EDCF) endothelin-I and thromboxane A-2. They balance the effect of vascular tone and structure and a smooth non-thromboitic - luminal surface (Fig. 1).

NO is produced by endothelial no synthase through oxidation of L-Arginine. It causes vasodilatation by activating guanlylul cuclase on vascular smooth muscles cells it saves the blood vessels from endogenous injury i.e. atheroseclerosis by mediating molecular signals that prevent platelet + luckocyte interaction in the vascular wall and inhibit vascular smooth muscle cell proliferation and migration.

Conversely the loss of NO increased proinflammatory transcription factor (NFKB) resulting in expression of Leukocyte adhesion molecule and production of chemokines and cytokines. These actions promote monocyte and vascular smooth cell migration into the intima and formation of macrophage foam cell-which breaks down and forms the inner layer of plaque with

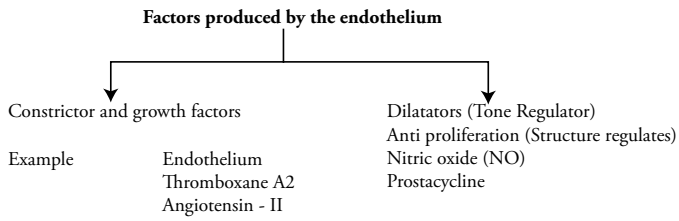

Fig. 1 : Factors produced by the endothelium

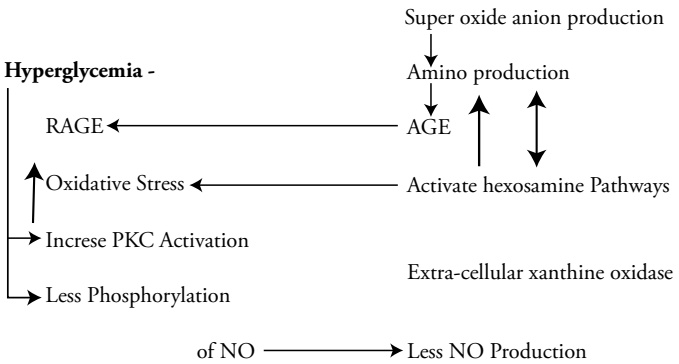

Fig. 2 :

metloprotinease production and oxidisal LDL + other lipid-rich material with plaque, (initial morphology of arteriosclerosis).

The bioavailability of NO reflects the balance between its production NOS and its degradation particularly by oxygen derived free radicals. Many of the de arrangement known to occur in diabetes including hyperglycemia increase free fatty acids liberation, insulin resistance obesity, mediate abnormality either in production or degradation of NO.

Hyperglycemic and NO Intracellular Glucose

induces a series of cellular events that increase the production of reactive oxygen species. That in activates NO to form per oxynitrite-

Hyperglycemia → Oxygen derived free radicals (super oxide anions increases activator of PKC.

Mitochondrial production of super oxide anions increase intracellular production of advanced glycation end products (AGE), they in turn affect protein function and by activation of receptor for AGE, they further increase super oxide anion production (Fig. 2).

FREE FATTY ACID LIBERATION & EF

Circulating free fatty acids are elevated in diabetes because of that excess liberation from adipose tissues and diminished uptake by skeletal muscles.

FFA ↑ Oxygen derived free radicals.
↑ PKC Activation ↓ Insulin receptor signalling
↑ Dyslipedemia (VLDL production non-HDL apolip-B ↓ HDL The mechanism is oxidative stress

INSULIN RESISTANCE AND NO

Insulin stimulates NO production from endothelial cells by ↑ the activity of NO'S

Abnormal endothelial dependent vasodilation in IR is due to alteration in intracellular signaling ↓ NO production

IR → FFA → Abnormalities
Adipocytokines IL6
Leptin
TNFa
Resistin
PAI Inhibitor
Adiponectin

ENDOTHELIAL PRODUCTION OF VASOCONSTRICTORS

Beside decreased NO there is also the increase synthesis of prostanoids and endothelium.

Endothelium promotes inflammation & causes vascular smooth muscle cells contraction and growth.

Endothelin concentration ↑ after insulin in healthy as well as T2DM persons.

DIABETES AND VASCULAR SMOOTH MUSCLE FUNCTION

In Type2 DM vasodilation response to exogenous NO Donar is diminished and vasoconstruction response to endothelium ↑ is disregulated.

Type 2 DM ↑ PKC activator
↑ NFKB Production
↑ Free Redicals

and vascular smooth muscle cell migrates into nascent atherseclerotic lession, where they replicate and produce extracellular matrix steps into mature lession formation. Smooth muscle cells apoptosis. and cytokines ↓ smooth muscles cells synthesis and reduce its content in plaque which makes it unstable plaque.

DIABETES, THROMBOSIS, COAGULATION

Platelet functions is abnormal in DM expression of both Glycoprotein Gp IIB/IIIA receptors are increased augmenting both platelet VIII and fibril platelet interaction.

Intracellular glucose in platelet produces free superoxide anions and ↑ PKC activity ↓ platelet derived NO activity. This platelet aggregation and activation and release of mediators are increased.

In diabetics plasma coagulation factor VII, thrombic and lession basel coagulants (tissue factors) are increased.

Endogenous anticoagulant - thrombomodulin and protein is reduced and also the PAI-I, a fibroinolysis inhibitor is increased, thus a propensity for platelet activation & aggregation coupled with a tendency for coagulation and thrombosis.