Diabetes mellitus (DM), is a most common problem around the world & contributes to the development of different types of complications due to various pathological changes like change in thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation. Diabetes mellitus represents a strong independent risk factor for stroke. The current review is an attempt to summarize the possible mechanisms that has been associated with increased risk of stroke due to diabetes mellitus.

**Introduction**

Diabetes mellitus (DM) is a well known and most common metabolic disease characterized by chronic hyperglycemia resulting from the abnormalities in insulin action, insulin secretion or both.[1] Such complications arise due to regulatory systems derangements for storage and mobilization of metabolic fuels, including the catabolism and anabolism of carbohydrates, lipids and proteins.[2] Diabetes mellitus lead to abnormal carbohydrates, proteins, & fat metabolism due to deficient action of insulin.[1] Type I diabetes mellitus is insulin dependent [3] , whereas Type II is non insulin dependent or insulin resistant.[4] Gestational diabetes is the third form of DM that occurs when pregnant women develop a high blood glucose level.[5]

**Complications of Diabetes Mellitus**

Hyperglycemia due to diabetes is a key determinant of vascular complications and there is increasing evidence showing that acute and chronic both types of hyperglycemia has a deleterious effect. There are several mechanisms which are responsible for the developments of vascular complications due to hyperglycemia such as activation of the polyol and hexosamine pathways, activation of protein kinase C, increased oxidative stress, increased production of advanced glycation end-products, & increased synthesis of growth factors, cytokines and angiotensin II. These factors can, in turn, induce a diffuse endothelial dysfunction and contribute to the progressive development of micro and macrovascular complications.[6,7]

**Macrovascular complications**

Macrovascular complications of diabetes mainly consist an accelerated form of atherosclerosis that may affect coronary, carotid and peripheral arteries, thus increasing the risk of myocardial infarction, stroke & other macrovascular disease. Atherosclerotic macrovascular disease has always been considered a long term complication of type I and type II diabetes.[8] Furthermore studies have shown that the risk of myocardial infarction in diabetic patients is equivalent to the risk in nondiabetic patients which have the previous history of myocardial infarction.[9] Macrovascular complications include coronary artery disease (CAD), Peripheral vascular disease (PVD), and cerebrovascular events (CVA). Diabetes mellitus is the most common and independent risk factor for the development of atherosclerosis. On the other hand, atherosclerotic or macrovascular disease is responsible for more than 50% of all deaths in patients with Type 2 diabetes.[10] Atherosclerosis, which leads to narrowing of
arteries in the body is thought to result from chronic inflammation and injury in the walls of arteries in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from low density lipoprotein particles accumulate in the endothelium. The oxidation of these particles is promoted by Angiotensin II. Differentiation of monocytes into macrophages then takes place in arterial wall. Macrophages then accumulates oxidized lipids and form foam cells. After the foam cells are formed they stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce proliferation of smooth muscles in the arterial walls and accumulation of collagen. Net result of the process is the formation of a lipid-rich atherosclerotic lesion which contains a fibrous cap. Rupture of this lesion causes acute vascular infarction.[8, 11]

Microvascular complications
The primary mediator of microvascular complications in diabetes is hyperglycemia itself.[12] These complication occur as a result of damage of microvasculature of kidney, retina and neurons leads to complications like nephropathy, retinopathy and neuropathy respectively.[6] Diabetic retinopathy is a leading cause of blindness in diabetics. Diabetic nephropathy is another complication of the need for renal replacement therapy (dialysis or transplantation). Diabetic neuropathy and vascular diseases combine to make diabetes the major cause of nontraumatic lower extremity amputations.[13] Microvascular complications are also known as chronic complications. Chronic complication and macrovascular complication affect small and large blood vessels respectively.[14,15]

Tissue which are more sensitive to chronic complications are kidney, retina & vascular endothelium because glucose uptake in these tissues is independent of insulin activity. Thus the development of chronic diseases leads to the endothelial damage mediated by glucose, oxidative stress due to the production of superoxide, sorbitol and advance glycation end product production.[10] Different types of chronic complications are described in figure 1.

Non Vascular Complications
Non Vascular complications include the complications of skin and mucous membrane like chronic pyogenic infections, fungal infections and other skin infections for which diabetic patients are more prone.[16]
Epidemiology of stroke in diabetes

Stroke occurs when blood supply to the brain is interrupted therefore the proper functioning of brain is disturbed. Blood supply is interrupted either due to ischemia or hemorrhage. Stroke affect approx 780000 people each year in united state and causes death of 1 from every 18 peoples. Men are affected greater than women and people older than 55 years have higher risk than younger ones.[17] Most of the surveys on stroke in diabetes based on the population were conducted from different parts of India. These population based surveys showed the annual incidence rate was 105/100,000 in Kolkata and 262/100,000 in a rural community of Bengal. The prevalence rate of stroke in diabetic patients was between 250-350/100,000 during the last decade. Hypertension is considered as the most common risk factor for mortality from stroke in diabetics. 1.2% of total deaths in India is due to stroke.[18] According to WHO , 86% of deaths due to stroke worldwide occurred in developing countries. South Asia is the highest contributor to stroke mortality in the world, accounting for more than 40% of global stroke deaths. In this region, stroke mortality rates might be as high as those for coronary artery disease.[19]

Key risk factors for stroke in diabetic patients

Hypertension

More than 80% of patients with diabetes mellitus develop hypertension, and 20% of patients with hypertension develop diabetes. This combination of risk factors will account for a large proportion of cardiovascular morbidity and mortality.[20,21] The co-existence of these disorders appears to accelerate microvascular and macrovascular complications and greatly increases the cardiovascular risk, risk of stroke and renal diseases. Arterial hypertension is clearly related to nephropathy type I diabetics. In patients with type II diabetes insulin resistance play an important role in the pathogenesis of hypertension. Along with the interactive effects of diabetic nephropathy and macrovascular disease with hypertension, some other factors contribute to the genesis and maintenance
of an elevated blood pressure in both insulin dependent diabetes mellitus (IDDM) and noninsulin dependent diabetes mellitus (NIDDM).[15,22]

Diabetes and hypertension both are associated with insulin resistance which is the major feature of type II diabetes.[23] Insulin activate the phosphatidylinositol-3-kinase (PI3K) pathway. This pathway then promotes nitric oxide (NO) production in the endothelium and glucose uptake in insulin-sensitive tissues. Angiotensin II (Ang-II) inhibits PI3K pathway activation mediated by insulin, thereby impairing endothelial Nitric oxide production and Glut-4 (glucose transporter-4) translocation in insulin-sensitive tissues, which results in vascular and systemic insulin resistance, respectively. On the other hand, insulin-mediated activation of the mitogenactivated protein kinase (MAPK) pathway is respectively. On the other hand, insulin-mediated activation of the mitogenactivated protein kinase (MAPK) pathway is enhanced by Ang-II, which leads to vasoconstriction and pathologic vascular cellular growth. Therefore, the interaction of Ang-II with insulin signaling is fully operative in insulin-sensitive tissues as well as cardiovascular tissues, thereby linking insulin resistance and cardiovascular diseases.[24] Inappropriate activation of rennin angiotensin aldosterone system (RAAS), oxidative stress and inflammation all are the primary mediator of hypertension in diabetes.[25] The rennin–angiotensin system (RAAS) is considered as an endocrine system & the Angiotensin II (Ang-II) is the active metabolite of RAAS which is produced by enzymatic cleavage from the angiotensinogen substrate. Rennin which is a highly specific protease, converts the angiotensinogen into the decapeptide Ang-I in to the blood stream. Ang-I in turn is converted to Ang II by the angiotensin-converting enzyme (ACE)[26]. Angiotensin II acts via specific receptors. Activation of AT1 receptor results in vasoconstriction, sodium retention, aldosterone secretion, fibrosis, cellular proliferation.[27]. RAAS, in particular Ang-II, is closely related to atherosclerosis, which is an another most important factor in pathophysiology of stroke. Ang-II promotes generation of oxidative stress in the vasculatures, which appears to be a key mediator of endothelial dysfunction, endothelial cell apoptosis and peroxidation of lipoproteins. Ang-II also induces cellular adhesion molecules, and pro-inflammatory cytokines, all of which participate in the induction of an inflammatory response in the vessel wall. In addition, Ang-II mediates responses in vascular smooth muscle cells that lead to proliferation, migration and a phenotypic modulation, which results in production of growth factors and extracellular matrix. All these effects contribute to neointima formation and development of atherosclerotic lesions. Ang-II may also be involved in acute complications of atherosclerosis by promoting plaque rupture and a hyperthrombotic state.[28,28,29,30]

**Lipid levels**

Free fatty acids (FFA) are stored as triglycerides in adipose tissues and serve as an energy source during fasting conditions. Insulin is a potent anti-lipolytic hormone and restrains the release of FFA (lipolysis) from the adipocyte by inhibiting the enzyme lipase. The impact of insulin resistance on the adipocyte is important. The fat cells in type 2 diabetics and patients with the metabolic syndrome are resistant to the inhibitory effect of insulin on lipolysis. This leads to a release of large amounts of Free Fatty Acids into the blood serum. Increase free fatty acid produces lipid abnormalities; the most common is increased triglycerides and decreased HDL. The increased triglycerides lead to an increased production of small dense lipoproteins & these dense particles contribute to endothelial dysfunction and inflammation.[35]

**Life style**

Various lifestyle factors have been associated with increasing the risk of brain stroke. These include lack of exercise, alcohol intake, diet, obesity, smoking, drug abuse, and stress. Obesity has been associated with higher levels of blood pressure, blood glucose, serum lipids (atherogenic), which are independent risk factors for stroke. [36] High daily dietary intake of fat is associated with obesity and may act as an independent risk factor or may affect other risk factors of stroke such as hypertension, diabetes, hyperlipidemia, and cardiac diseases. Homocysteine is another important dietary component associated with the risk of brain stroke, while other dietary stroke risk factors are thought to be mediated through the daily intake of several vitamins and antioxidants. Most of epidemiological data suggest that heavy alcohol intake increases the alcoholic’s risk of suffering a hemorrhagic or ischemic stroke. During a hemorrhagic stroke, the blood flow to a brain area is impaired due to a ruptured blood vessel that results in bleeding in the brain. If the blood flow is interrupted because a blood vessel is blocked by a
blood clot, the condition is called an ischemic stroke. Alcohol conceivably can contribute to both conditions by interfering with the normal coagulation system and by reducing fibrinolysis, respectively.[37] The effect of long working hours is closely related to lack of sleep. Lack of sleep is generally thought to increase the reactivity of the circulatory and sympathetic nervous systems. High angina pectoris and myocardial infarction morbidity among persons getting less than 7 hours sleep a day and 2.07 times higher mortality from ischemic stroke and cerebrovascular disease among those getting less than 4 hours sleep a day than 8 hours have been reported in some studies.[38] Despite the obstacles to the modification of lifestyle factors, health professionals should be encouraged to continue to identify such factors and help improve our ability to prevent stroke.[39]

**Hyperglycemia as a risk factor for stroke**

Stroke is a long term complication of diabetes.[40] Diabetes and stroke both are the conditions which share various common threats. A patient with Diabetes has higher risk of stroke as compared to non Diabetics. Diabetes and stroke both affects the blood vessels and both are associated with other risk factors such as hypertension and dyslipidemia. High blood pressure increases the risk of stroke.[41] Hyperglycaemia is described as a toxic metabolic milieu, that results in increased morbidity and mortality. Different types of molecular signaling mechanism activated by hyperglycaemia are Protein kinase C activation, Increased polyl pathway flux, Increased hexosamine pathway flux and Increased Advanced glycation end products (AGEs) formation.[40,42] have demonstrated that elevation of extracellular glucose level leads to the increased activity of protein kinase C (PKC) and the mechanism of the activation is due to an enhanced denovo synthesis of diacylglycerol (DAG). The elevated diacylglycerol denovo synthesis is due to increased formation of precursors derived from glucose metabolism.[43] Protein kinase C has been associated with vascular alteration such as increase in contractility, permeability, cell growth and apoptosis, angiogenesis, adhesion of leucocytes and activation of cytokine, caused by different PKC isoforms.[44] Hyperglycaemia increases polyl pathway flux, forming sorbitol and NADH. NADH and glucose stimulate the formation of Diacylglycerol which in turn activates protein kinase C. Advance glycation end products (AGEs) which are produced by glycation of proteins also stimulate PKC or cause reactive oxygen species (ROS) activation directly. Production of ROS is the final common pathway for atherosclerosis. PKC is also activated by fatty acids and angiotensin II.[45]

Possible mechanism of hyperglycemia-mediated increased stroke occurrence and exacerbated stroke outcome are as follows-

**Acidosis**

Several studies has reported that excessive lactic acid in tissues has shown to aggregate structural damage of neurons in the brain.[46] Intracellular acidosis is a critical factor in ischemic cell damage. Hyperglycemia accentuate cell damage by further enhancing anaerobic glycolysis and lactic acidosis.[47] Acidosis is considered to be a major contributor to cerebral damage during ischemia which is an anaerobic condition. During ischemia glucose is the only energy substrate in the brain. In this condition glycolysis produces significant amount of ATP and lactate. Accumulation of lactic

![Fig.3 Role of PKC in diabetic complications](image)
acid in brain is called lactic acidosis which generates excess hydrogen ions and thereby results in a severe lowering of intracellular pH which is responsible for the excess damage of brain neurons.[48] Pretreatment with 2-deoxyglucose reduces the risk of mortality by acidosis because 2-DG is the competitive inhibitor of glycolysis exacerbated ischemic brain damage.[49]

**Oxidative stress**

Mitochondria is involved in the development of this tissue injury due to modifications of their major role in supplying ATP and to changes in their properties that can contribute to the development of apoptotic and necrotic cell death.[50] Mitochondrial dysfunction and the accumulation of Ca++ is considered a major source of free radicals generation after ischemia-reperfusion. As a result of this mitochondrial dysfunction two events seem to play an important role in the death of neurons: the increase in the production of free radicals,[51,52], and the induction of the apoptosis.[53,54] However, free radicals interact with proteins, lipids, carbohydrates, and nucleic acids and may irreversibly destroy or alter the function of the target molecule. Consequently, free radicals have been increasingly identified as major contributors to damage in biological organisms. Enzymatic components mainly comprise superoxide dismutases (SOD), catalases, glutathione, glutathione reductase/glutathione peroxidases (GR/GPX), and peroxiredoxins are responsible for the reduction of free radicals. When an imbalance occur either by increasing free radicals or decreased antioxidant defense , the accumulation of free radicals is known as the state of oxidative stress. ROS are small oxygen-derived molecules, including the superoxide anion radical (O2⁻), hydroxyl radical (OH.), and certain non-radicals that are either oxidizing agents or easily converted into radicals, such as hydrogen peroxide (H₂O₂) and the oxygen singlet (¹O₂). The primary source of free radical generation in cells during cerebral ischemia is due to a decrease in mitochondrial redox potential causing ROS production from the Endothelial cell , mainly at the level of cytochrome III. After ischemia, an excess of cytosolic free Ca++ due to excitotoxicity may overload the mitochondrial proton circuit, which leads to failure in oxidation together with increased ROS production[51,55]. Overproduction of ROS by mitochondria causes the impairment of the ETC, which leads to decreased ATP production, increased formation of free radicals, altered calcium homeostasis and mitochondrial dysfunction.56 Transient middle cerebral artery occlusion (MCAO) in rats induces ROS production and mitochondrial dysfunction, including the inactivity of ETC enzymes.[57]

**Inflammation**

Inflammatory activation plays a vital role in the pathophysiological mechanisms of stroke, exerting deleterious effects on the progression of tissue damage and may lead to the vascular damage in diabetes.[58] Inflammation in the vascular wall may drive atherosclerosis, leading to stroke and vascular dementia.[59] Acute activation of the phagocyte NADPH oxidase (PHOX) found in microglia is the principal mechanism of inflammation. PHOX (Phagocytic NADPH oxidase) is a key regulator of inflammation. However, activation of PHOX alone causes little or no death, but when combined with iNOS (Inducible Nitric oxide synthase) expression results in apoptosis via peroxynitrite production. Phagocytic cells such as neutrophils, macrophages, and microglia have a specific NOX (NADPH oxidase) known as PHOX (phagocytic oxidase), consisting of subunits gp91, p22, p47, p67, p40. In the healthy, noninflamed brain. However, PHOX is not active unless acutely stimulated by, TNF-α, IL-1β, chemokines, β-amyloid, lipopolysaccharide (LPS), ATP, or phagocytosis. When activated, it rapidly produces high levels of superoxide extracellularly, which may either dismutate to hydrogen peroxide (catalyzed by extracellular superoxide dismutase) or react with nitric oxide to produce peroxynitrite . These oxidants contribute to the killing of pathogens by phagocytes, but may also damage neurons.[60] One another mechanism of inflammation is the activation of nuclear factor κB. Glucose intake results increase in nuclear factor κB (NF-κB) binding and a decrease in inhibitor kappa B (I kB) expression. NF-κB is a nuclear transcription factor that normally stays in the cytoplasm in association with I kB. In response to an inflammatory stimulus, there is an increase in I kB kinase-α and I kB kinase-β, which phosphorylate I kB and result in its ubiquitination and proteosomal degradation. Degradation of I kB leads to release of NF-κB and in its translocation from the cytoplasm to the nucleus, where it stimulates the transcription of proinflammatory cytokines. Activation of NF-κB leads to increased production cytokines and chemokines such as tumor necrosis factor- and monocyte chemoattractant protein (MCP-1). These inflammatory mediators attracts leukocytes to the ischemic area.[30]

**Endothelial dysfunction**

The endothelium is the biological active inner layer of the blood vessels, which serves as an important locus of control of vascular and thus organ functions. The endothelium actively regulates vascular tone and permeability, the balance between coagulation and fibrinolysis, the composition of the subendothelial matrix, the adhesion and extravasation of leucocytes, and inflammatory activity in the vessel wall.[61] Among important molecules synthesized by endothelial cells is nitric oxide, which is an important endothelium-derived mediator, because of its vasodilator, anti-platelet, anti-proliferative, permeability-decreasing and anti-inflammatory properties.[62] Endothelial dysfunction is thought to play an important role not only in the initiation of atherosclerosis, but also in its progression of it. Risk factors such as hypercholesterolemia, dyslipidaemia, smoking and diabetes initiate atherosclerosis through endothelial activation and therefore endothelial dysfunction. Endothelial dysfunction in diabetes originates from three main sources. Hyperglycaemia and its immediate biochemical sequelae directly alter endothelial function or influence endothelial cell functioning indirectly by the synthesis of growth factors, cytokines and...
vasoactive agents in other cells. Finally, the components of the metabolic syndrome can impair normal endothelial function.[63]

Endothelial dysfunction is believed to be the earliest functional abnormality in the blood vessels that is seen in diabetes and serves as a very important surrogate marker for future atherosclerosis in them. Accelerated atherosclerosis is also the major cause of morbidity in diabetes and is the underlying cause of macroangiopathy that includes coronary artery disease, stroke and peripheral vascular disease. Insulin receptors have been demonstrated in vascular endothelium and recent evidence suggests that insulin has a vasodilatory role. Insulin resistance results in activation of PKC in vascular issues that leads to endothelial dysfunction and vascular damage. The pathogenesis of endothelial dysfunction in type 2 diabetes is complex and involves many mechanisms. Visceral obesity, insulin resistance, hypertension, post prandial hyperlipidemia particularly post prandial hypertriglyceridaemia, fasting and post prandial hyperglycemia result in an increased oxidative stress. Vascular endothelium is very susceptible to oxidative stress damage and this enhanced oxidative stress seen in diabetic individuals in turn causes endothelial dysfunction. In early stages, insulin resistance and free fatty acids act directly on e-NOS activity and mitochondrial function. This leads to oxidative stress and increase generation of superoxide radicals. Oxidative stress activates several pathways – PKC, glycation of cellular DNA and other macromolecules, polyol, hexosamine and nuclear factor KappaB pathways - all of which contribute to worsening of endothelial dysfunction in diabetes. Hyperglycemic patients are relatively deficient in insulin. This leads to both reduced peripheral uptake of glucose (increasing the amount of glucose available to diffuse into brain) and increased circulating free fatty acids. Free fatty acids may impair endothelium-dependent vasodilation[64].

**Conclusion**

Diabetes mellitus is not only a highly important risk factor for stroke at all ages, but especially in old age with risk ratios showing more than a 5-fold. Studies suggest that diabetes (both type I & type II) worsens the outcomes and increase the risk of ischemia. Mechanism of stroke in diabetes is complex and all the possible mechanisms are interactive, interdependent and modulate each other. Reactive oxygen species (ROS) play a central role in all the possible mechanism related to brain damage. It is known that during the development of diabetes a number of biochemical and mechanical factors converge on the endothelium, resulting in endothelial dysfunction and vascular inflammation. This provides a basis for the vascular disease seen in diabetes. Endothelial dysfunction is a common mechanism which leads to oxidative stress. Different life style factors are responsible for stroke including stress. Type of work, including work hours, environment of work place, and work-related psychological stressors based on the characteristics of work have been shown to be associated with the occurrence of stroke and coronary heart disease and the course of the disease after the onset. Modification in life style such as weight loss, physical exercise and smoking cessation may reduce the complication due to diabetes mellitus.

By considering all above facts and mechanisms we can summarize that diabetes may increase stroke outcomes through modulating various mechanisms like free radical generation, acidosis, hyperglycemia, hyperlipidemia, inflammation etc. all the factors have an impact on drug metabolism and toxicity in diabetic stroke.

We also conclude that adoption of healthy life style has proven to be beneficial in preventing cardio vascular disease in patients with previous history of diabetes.

**Conflict of interest statement**

We declare that we have no conflict of interest.

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