

TYPE 2 DIABETES AND ITS IMPLICATIONS IN CEREBROVASCULAR DISEASE

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Abstract

Type 2 diabetes represents an independent risk factor for vascular cerebral pathology, with a 2-3 times greater probability of stroke. The number of diabetic patients with stroke increased substantially from 6.2% to 11.3% during 1996-2006. Ischemic stroke, small or large vessels occlusion, is the main subtype of cerebrovascular disease, while a smaller percentage is attributed to cerebral hemorrhage. Hyperglycemia and hyperinsulinemia, excess free fatty acids, prothrombotic state cause endothelial dysfunction with blood flow disturbance and major cerebral vessels injury. Elevated blood sugar levels are also associated with a poor prognosis during post-stroke phase. From the total number of deaths caused by acute cerebrovascular events, 16% for men and 33% for women are due to diabetes.

key words: *type 2 diabetes, endothelial dysfunction, stroke, hyperglycemia*

Epidemiology

Cerebrovascular disease is an important cause of disability and mortality. According to World Health Organization 5 million deaths per year are caused by stroke, while a significant similar number of patients remains with major neurological deficits. Type 2 diabetes mellitus (T2DM) is known as an independent risk factor for stroke. The number of diabetic patients with stroke increased substantially from 6.2% to 11.3% in the period 1996-2006 [1]. The risk of stroke is 2-3 times higher among diabetic patients comparing

with those without diabetes. According to the Greater Cincinnati and Northern Kentucky Stroke Study relative risk for developing ischemic stroke is 2.1 in Caucasian population and 2.7 in African-American population, with a maximum incidence between 45-64 years for white population and between 35-54 years for African-American population [2]. A clinical trial conducted in Denmark showed a similar number of acute ischemic events among those with diabetes compared to those with myocardial infarction but without diabetes [3]. Risk of stroke is higher in younger diabetic patients, especially women, with a hazard ratio

of 4.7 in men and 8.2 in women between 35 and 54 years [4].

Type 2 Diabetes and Cerebrovascular Disease Pathology

T2DM predisposes patients to early and severe development of cerebrovascular disease, because of its metabolic and vascular changes: hyperglycemia, excess free fatty acids, insulin resistance, prothrombotic state and abnormal endothelial response.

Hyperglycemia

Hyperglycemia and diabetic angiopathy are closely related. Sustained exposure to high circulating levels of glucose leads to both microvascular and macrovascular complications. According to the United Kingdom Prospective Diabetes Study (UKPDS) an HbA1c of 9.5% is associated with a tenfold greater risk of microvascular complications and a double risk of macrovascular complications. Four main pathways are involved in the structural and functional alteration of the vascular wall caused by hyperglycemia and these are: the polyol and hexosamine pathways, production of advanced glycosylation end products (AGEs) and activation of protein kinase C (PKC).

The polyol pathway: Under normoglycemic conditions, conversion of glucose to sorbitol via the polyol pathway is a NADPH dependent reaction catalyzed by aldose reductase, that plays a minor role in glucose disposal (<5%). Hyperglycemia is associated with an increased production of sorbitol in the vascular cells causing damage through osmotic stress, decreased (Na⁺/K⁺) ATP-ase activity, increased cytosolic NADH/NAD⁺ and a decrease in cytosolic NADPH. Being a glutathione reductase

cofactor, NADPH depletion is associated with impaired reduced glutathione synthesis, hence leading to increased intracellular oxidative stress.

The hexosamine pathway: During hexosamine pathway fructose-6-phosphate, diverted from glycolysis, is converted to uridine diphosphate N-acetyl glucosamine (UDP-GlcNAc). Therefore UDP-GlcNAc leads to the increase production of plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor beta (TGF- β), resulting in vascular resistance and capillary occlusion [2, 5, 6, 7].

Activation of PKC: Hyperglycemia and hypoxia upregulate GLUT-1 expression on vascular cerebral wall. Consequently, increased glucose transport mediated by GLUT-1 leads to accelerated glycolysis with excess production of diacylglycerol and activation of PKC, primarily the β and δ -isoforms. Activation of PKC has numerous pathogenic effects: blood flow abnormalities due to increased endothelin1 (ET-1) and decreased endothelial nitric oxide synthase (eNOS) activity, vascular occlusion due to increased PAI-1 and TGF- β , pro-inflammatory gene expression caused by high levels of pro-inflammatory transcription nuclear factor kappa B (NF- κ B) and production of reactive oxygen species (ROS) due to activation of several NAD(P)H oxidases.

Increased formation of AGEs: Another important mechanism associated with hyperglycemia is the non-enzymatic reaction between glucose and NH₂-groups on tissue proteins, lipids and nucleic acids leading to the formation of AGEs. AGEs are responsible for causing vascular injury through 3 major mechanisms. The first one consists in damage to the intracellular proteins, causing modified

function of the basic fibroblast factor and of the proteins responsible for endocytosis. The second one is represented by impaired structure and function of extracellular matrix components. They form covalent cross-links with structural tissue proteins (collagen) increasing matrix production and decreasing matrix degradation, thus causing vascular stiffness. Finally, several receptors for AGE have been identified on vascular smooth muscle cell, one important class being receptors for AGEs (RAGE). Activation of RAGE upregulates NF- κ B level and promotes ROS production [2, 8, 9].

Excess free fatty acids

Accelerated lipolysis and diminished uptake by skeletal muscle lead to excess levels of free fatty acids (FFA). Furthermore, increased flux of FFA to the liver results in triglycerides synthesis stimulation, assembly and secretion of VLDL particles. Hypertriglyceridemia and low HDL cholesterol (due to cholesterol transport from HDL to VLDL) have been associated with atherosclerosis. It also seems that FFA formation activate ROS and PKC. Upregulation of PKC level and decrease phosphatidylinositol-3 kinase (PI3-K) pathway with secondary decrease in NO production may cause endothelial injury.

Insulin resistance

Another important mechanism that plays a central role in NO homeostasis is insulin resistance. Insulin acts via 2 pathways: PI3-K and mitogen-activated protein kinase (MAPK) pathway. Insulin signaling through the PI3-K is responsible for NO synthesis and has antiproliferative and anticoagulant effects, while its action through MAPK pathway has a

proatherogenic effect. In case of insulin resistance the first pathway is impaired while the second one remains intact, hence decreased endothelium-dependent vasodilatation and increased mitogenic effects being the main consequences [2, 10].

Prothrombotic state

Haemostasis abnormalities increase the risk of cerebral thrombosis. Impaired fibrinolysis, due to enhanced PAI-1 secretion, and platelet hyperactivity, caused by overexpression of glycoprotein IIb/IIIa and excess of thromboxane A₂, are consistent findings in diabetes mellitus. In addition, elevated levels of factor VII, VIII and thrombin-antithrombin complexes are found [2, 8, 11, 12, 13].

Endothelial dysfunction

Endothelial dysfunction is characterized by defective endothelium-dependent vasorelaxation due to altered NO homeostasis and increased production of ET-1 and other vasoconstrictor agents. NO is generated from L-arginine by endothelial eNOS. It is responsible for vasodilatation via guanylate cyclase pathway and inhibits plaque formation by blocking platelet-leukocyte interactions with vascular wall and by preventing smooth muscle cell migration and proliferation. Alteration of NO synthesis increases NF- κ B that is involved in activation of leukocyte cells adhesion molecules expression and production of cytokines. Secondary migration of monocytes and vascular smooth muscle cells into the intima and formation of macrophage foam cells initiate the process of atherosclerosis. As for ET-1, despite its vasoconstrictive role, it also has pro-inflammatory actions, mitogenic and proliferative effects [2, 5].

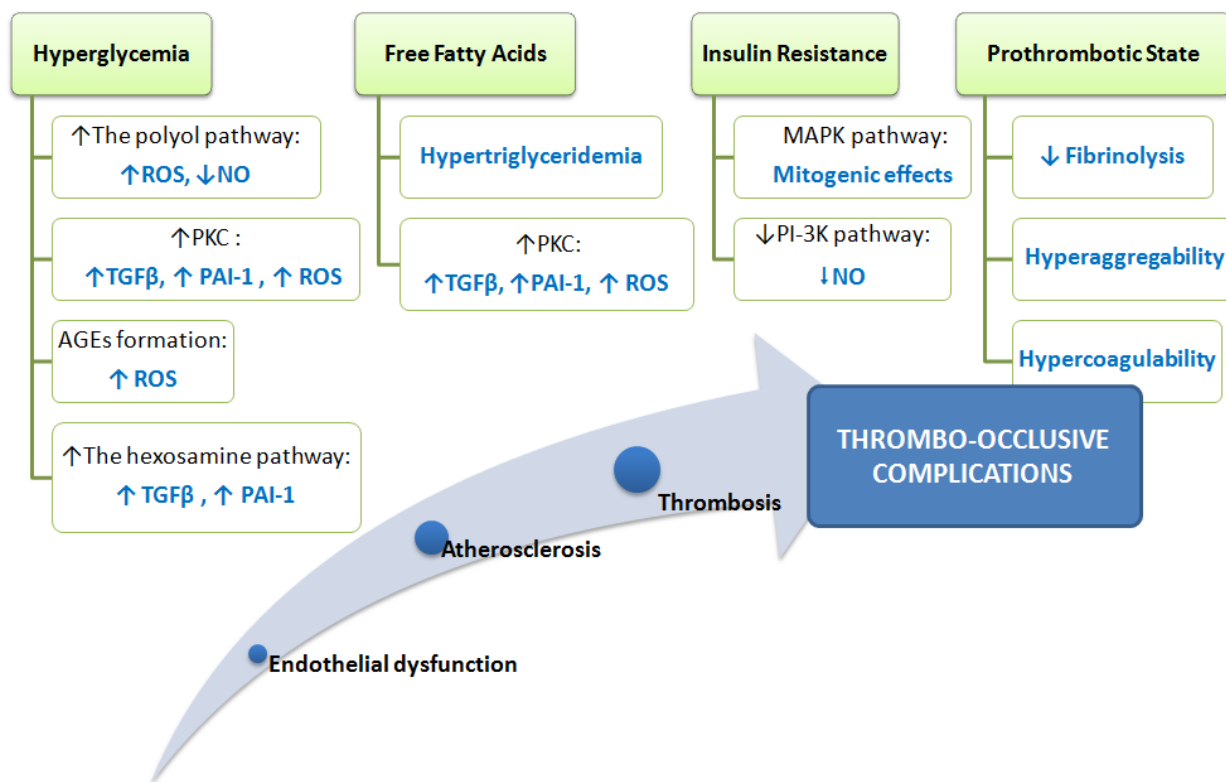


Figure 1. Risk Factors in Cerebrovascular Disease.

Hyperglycemia, excess free fatty acids and insulin resistance act via a common mechanism represented by increased production of ROS (particularly superoxide anion), which cause impaired endothelium-dependent, NO-mediated relaxation. Increased production of ET-1 and proliferation of vascular smooth muscle cells contribute equally to the abnormal endothelial function. Hypertriglyceridemia with consequently atherosclerosis together with platelet hyperactivity, decreased fibrinolysis and hypercoagulability are characteristics of the vascular environment in diabetic patients. Taken together, early and accelerated atherosclerosis, decreased endothelial function and increased thrombus formation highly predispose this type of patients to thrombo-occlusive events at the level of the cerebral circulation ([Figure 1](#)).

Subtypes of Cerebrovascular Disease in Type 2 Diabetes

Lacunar infarcts or occlusion of the penetrating arteries that provide blood to the brain deep structures are considered to be the main subtype of cerebrovascular disease in diabetic patients. About 28% to 43% of lacunar infarcts are due to diabetes. According to the The Atherosclerosis Risk in Communities study (ARIC), 26.3% of small vessels occlusion and 11.3% of large vessels occlusions are associated with diabetes presence [[14](#), [15](#)]. Frequent lacunar infarcts in women and nonlacunar infarcts in men are new findings from a 14 years follow-up study on a group of Japanese people [[16](#)].

Ischemic stroke, caused by occlusion of the large cerebral vessels, and *transient ischemic attacks* (TIA) are found in a smaller percentage compared to lacunar infarcts. It is important to take into consideration the link

between diabetes and cardiovascular disease, as it is known that coronary artery disease, myocardial infarction and subsequent development of atrial fibrillation are risk factors for cerebral embolism. CHADS2 is a widely used scale for assessing the risk of such vascular event in patients with atrial fibrillation. One point is given for each of the following: heart failure, hypertension, age greater than 75 years, diabetes and two points are given for history of TIA or stroke. To conclude, for a patient with atrial fibrillation and diabetes the risk of stroke increases from 1.9 to 2.8. Much less frequently diabetic patients present with TIA [2]. TIA are often associated with increased probability of stroke in the next two days (probability that can be appreciated by ABCD2 score which takes into account age, blood pressure, neurological symptoms, duration of the symptoms, presence of diabetes) [17, 18].

Hemorrhagic stroke is less frequent in diabetic patients, according to older studies (a possible explanation being the reduced fibrinoid necrosis typically found in hypertension) [15]. One study published in 2005 by Feldman assigned a relative risk for hemorrhagic stroke of 2.4 to diabetic patients [19]. Moreover the Caucasian men are at least 4.5 times more likely to suffer such a vascular event (Framingham Heart Study) [20].

Extracranial and intracranial carotid stenosis are found in up to 30% of strokes. According to North American Symptomatic Carotid Endarterectomy Trial (NASCET) patients with a severe carotid stenosis (70-90%) have a risk of cerebral ischemic events of 28% in the following 2 years [21]. Lesions are mostly located on the intracranial vessels, affecting the middle cerebral artery. Their severity is positively correlated with

lipid disorders [22]. An accurate marker for assessing the risk of stroke is the carotid artery intima-media thickening (IMT) assessed by Doppler ultrasound [23]. It is significantly increased among patients with diabetes and also among those with impaired glucose tolerance, reaching high values in those associating diabetes with ischemic brain pathology. Increased common carotid artery IMT is correlated with silent cerebral infarcts as a recent study on Japanese subjects showed [24]. The marker has predictive value for stroke occurrence and recurrence. For each standard deviation of 0.163 mm the relative risk increases with 1.57, while for every additional 0.1 mm in addition the risk of recurrent stroke increases by 18% [25].

Evolution and Prognosis of Cerebrovascular Disease in Patients with Type 2 Diabetes

Prognosis of cerebrovascular disease

Diabetes is an independent predictor of poor outcome [26]. Several clinical studies have highlighted the important impact of hyperglycemia during post-stroke phase. Elevated blood glucose concentration on admission was found in 39-89% of those with diabetes and in 8-63% of those without diabetes. It seems that hyperglycemia ≥ 155 mg/dL in patients with stroke, with or without diabetes, is associated with a threefold higher risk of short-term mortality and reduced chance of recovery [27, 28]. Compared to normoglycemic stroke patients, hyperglycemia may also lead to more severe neurological deficits [29].

There are three main mechanisms responsible for the presence of hyperglycemia during post-stroke phase: the activation of hypothalamo-hypophyseal-adrenal axis, the

inflammatory response and the carbohydrate metabolism disturbance. The first one leads to catecholamines and glucocorticoids release, with accelerated glycogenolysis and gluconeogenesis, hence leading to hyperglycemia [15]. It seems that lesions located in the insular cortex are accompanied by the highest blood glucose level. The explanation would be that damage to the insular cortex cause sympathoadrenal dysregulation, due to its connections with subcortical autonomic centers, resulting in sympathetic nervous system tone influence [30]. The second one is represented by high levels of IL6 and TNF α [31, 32, 33, 34] responsible for insulin resistance and increased blood glucose concentration. As for the third one, three months after the ischemic event nearly 30% of those with hyperglycemia on admission were found to have impaired glucose tolerance and 21-38% were diagnosed with T2DM.

After reaching the central nervous system, intracellular accumulation of glucose produces a series of biochemical changes responsible for the severe prognosis. Under hypoxic conditions glucose metabolism is associated with accumulation of lactic acid, causing vascular, neuronal, glial cells lesions and infarct expansion. At the same time hyperglycemia is associated with increased thrombosis susceptibility and reduced fibrinolytic activity compromising revascularization of the infarcted area and lowering the efficacy of thrombolysis [35]. Clinical studies have shown reduced impact of thrombolysis in patients with middle cerebral artery occlusion [36].

Evolution of cerebrovascular disease

The early risk of stroke or TIA recurrence within 30 days is approximately two times higher (4.9% vs 2.7%) in diabetic patients, while within three years it reaches 19.8% for those with diabetes compared to 12.3% for those without diabetes. Vertebrobasilar infarcts are much more frequent (3-4 times more common in pons and diencephalon). Lesions larger than 5 mm were more common among those over 65 years.

Mortality after stroke in diabetic patients reaches 16% in men and 33% in women. Five-year survival is 20%. Risk factors like hypertension, atrial fibrillation, heart failure and myocardial infarction may be responsible for severe evolution. Hemorrhage after thrombolysis and limited effects of aspirin reduce the survival rate of these patients [15].

Conclusions

T2DM causes a significant increase in the risk of cerebral ischemia, morbidity, mortality and recurrence of a similar event. Microvascular and macrovascular complications have a central role in developing endothelial dysfunction and cerebrovascular disease. Blood glucose should be maintained at near-normal levels, as it seems that hyperglycemia is closely related to prognosis of patients with stroke. A proper antihypertensive, antiplatelet, anticoagulant, lipid-lowering therapy should be started if necessary, with a close follow-up of this group of patients.

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