Diabetes mellitus associated with stroke: a review literature.

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Abstract

Diabetes is the chronic illness with the fastest rates of global expansion. Because there is an increased incidence of obesity around the world with lifestyle modifications. In addition, nearly 50% of diabetes patients are completely unaware of their condition. The global diabetes prevalence in 2030 will increase to 10.2% of cases (578 million cases), and by 2045, it would reach 700 million cases. The purpose of this study is to address stroke, types, and causes, stroke patterns in diabetic individuals compared to non-diabetic people, post-stroke yperglycemic care, long-term management, and overly enthusiastic treatment leading to hypoglycemic brain.

Keywords: Diabetes, Stroke, Hyperglycemic (J Thai Stroke Soc. 2023;22(3): 25-32)

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Received 7 November 2022 Revised 21 April 2023 Accepted 25 April 2023

ความเกี่ยวข้องระหว่างโรคเบาหวานกับโรคหลอดเลือดสมอง: ทบทวนวรรณกรรมที่เกี่ยวข้อง

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บทคัดย่อ

โรคเบาหวานเป็นโรคเรื้อรังและลุกลาม เป็นปัญหาสาธารณสุขสำคัญปัญหาหนึ่งของโลก สาเหตุหลักสำคัญเกิดจากอัตราการเกิดโรคอ้วนที่เพิ่มขึ้นทั่วโลก เนื่องจากการเปลี่ยนแปลงวิถีชีวิตของมนุษย์ รวมถึงการไม่ตระหนักถึงอันตรายของเบาหวานในมากกว่าครึ่งหนึ่งของผู้ป่วยเบาหวาน ความชุกของโรคเบาหวานทั่วโลกเพิ่มขึ้นจาก 9.3% (463 ล้านคน) เป็น 10.2% (578 ล้านคน) ภายในปี 2573 และ 10.9% (700 ล้านคน) ภายในปี 2588 ในบทความนี้มุ่งหมายที่จะนำเสนอความสัมพันธ์ของโรคหลอดเลือดสมองกับพยาธิสรีรวิทยาของโรคเบาหวานที่นำไปสู่โรคหลอดเลือดสมอง รูปแบบโรคหลอดเลือดสมองในผู้ป่วยเบาหวานและผู้ป่วยที่ไม่เป็นเบาหวาน และการจัดการภาวะน้ำตาลในเลือดสูง

คำสำคัญ: โรคเบาหวาน, โรคหลอดเลือดสมอง, ภาวะน้ำตาลในเลือดสูง (J Thai Stroke Soc. 2023;22(3): 25–32)

Introduction

Stroke is a loss of blood supply to a part of the brain either due to rupture of a cerebral blood vessel (hemorrhagic stroke) or blockage of a cerebral blood vessel (ischemic stroke).

Ischemic stroke is the most common type of stroke up to 80%. Fatty deposits, blood clots, and another atherosclerotic debris lodge into the brain's bloodstream blocking or narrowing the blood vessel thus leading to ischemic stroke. A hemorrhagic stroke happens when the blood vessel wall ruptures and bleeds into the brain. This is due to various causes including uncontrolled high blood pressure, aneurysmal rupture, trauma, overtreatment with anticoagulants, cerebral amyloid angiopathy which causes protein deposits in blood vessels, etc. Diabetes is one of the major risk factors for stroke. Diabetes is a condition where the blood glucose level is very high above the normal range of 126 mg/dL. There are two main types of diabetes mellitus in which in Type I DM the pancreas does not produce enough insulin and in Type II DM the body does not make good use of the insulin produced by the pancreas. Insulin is a hormone produced in the islets of Langerhans of the pancreas, which maintains the glucose level in the blood. Insulin is necessary for the cells of the body to uptake glucose and utilizes it for energy. In diabetes, glucose uptake of the cells is impaired. Thus, excess glucose leads to hyperglycemia. Hyperglycemia worsens stroke condition by increasing brain edema, increasing the infarct size thus leading to brain herniation and decreasing reperfusion1. Specifically persistent hyperglycemia at 6 and 24 hrs after the onset of stroke corresponds to a higher risk of mortality within 30 days (odds ratio = 24.0; confidence interval = 95% (2.8–199.3)) and can transfigure to hemorrhage (odds ratio = 13.3; confidence interval = 95% (2.7 – 66.1))[2]. Also, hyperglycemia leads to a lower apparent diffusion coefficient (ADC, r=–0.32, P <0.001)[2]. Thus, hyperglycemia (odds ratio= 0.239, P= 0.017) and lower ADC signal (odds ratio =0.239, P<0.0001) increase the chances of morbidity and mortality in stroke patients. Also, hyperglycemia is very common in post–stroke non–diabetic patients because the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system get activated in response to extensive brain injury[3]. Hyperglycemia at the time of admission affects the outcome in early reperfusion and after thrombolysis[4]. Patients with stress–induced hyperglycemia on the second day of admission had a severe stroke compared to diabetic patients[5]. Stress hyperglycemia ratio (SHR) is a new non–invasive way to screen for diabetes. This test measures the level of stress hormones in the saliva to identify patients with diabetes earlier in their disease process. It also identifies patients who are at risk of developing diabetes later in life. SHR screening is recommended for everyone between the age of 20 and 45 years[6]. Fasting hyperglycemia is an independent risk factor for determining stroke–associated pneumonia. When we combine fasting hyperglycemia with A2DS2 score (Age ≥ 75years, atrial fibrillation, dysphagia, male sex, and stroke severity) is better than A_2DS_2 score alone for assessing the risk of stroke–associated pneumonia[7]

Diabetes causes arterial stiffness and fatty deposits. This in turn triggers an atherosclerotic reaction resulting in blood clots (ischemia) in the brain's blood vessels. Diabetes increases the chances of stroke by 1.5 times. Blood vessels dilate with nitric oxide. But in diabetic patients, the smooth muscle wall of the blood vessels reacts less to nitric oxide (endothelial dysfunction). This makes the process of vasodilation difficult. Also, there is increased inactivation of nitric oxide in diabetic patients. Thus, there is a significant

narrowing of blood vessels which increases the risk of stroke many folds. Systemic Inflammation is amplified in diabetes. Increased levels of stress hormones in the body including Cortisol, Catecholamines, Growth Hormone, Glucagon, and Pro-inflammatory Cytokines including interleukin-1, interleukin-6, and tumor necrosis factor- α occur in the event of a stroke. All these factors increase the production of glucose in the body and decrease glucose uptake. This leads to hyperglycemia which causes fatty deposits in the blood vessel. This triggers the formation of atherosclerotic plaques leading to stroke.

Anaerobic glycolysis is a characteristic feature of ischemic stroke from Figure 2. Hyperglycemia ameliorates this process of anaerobic metabolism and causes lactic acid to accumulate leading to tissue (cortical) acidosis and mitochondrial dysfunction and thus slows down the recovery of high energy phosphates and the acidic pH back to normal pH. Also, Reactive Oxygen Species (ROS) especially superoxide is produced more by the damaged mitochondria by reducing O2 with the glucose-derived reducing equivalents. Also, through the Hexose monophosphate shunt pathway (NADPH oxidase pathway) increased ROS is produced[8, 9]. This oxidative stress damages the blood-brain barrier (BBB)[10-12] causing increased permeability and thus increasing the risk of brain edema and hemorrhagic transformation[13-15]. Also, neuronal ischemic death is accelerated by the release of cytochrome c into the cytoplasm due to caspase-3 cascade activation[16]

For example, the signs of lacunar infarction including dysarthria, difficulty in walking or moving the limbs, numbness, and confusion are more pronounced in diabetic patients than non-diabetic patients. Whereas signs of cortical infarct including loss of higher cognitive functions, astereognosis, and visual disturbances in the contralateral field are more pronounced in non-diabetic patients rather than diabetic patients. Thus, subcortical infarction is attributed to higher rates in diabetic patients, while intracranial hemorrhagic is relatively lesser associated with diabetic patients[17]. Both diabetic and non-diabetic patients had a greater association with ischemic stroke than hemorrhagic stroke. While stroke patients with diabetes comorbidity had a poorer outcome when compared to those stroke patients who are non-diabetic. Thus, in conclusion, diabetes is an independent risk factor for stroke. A stroke in diabetic patients differs in age, gender, association with other risk factors, and outcome when compared with a stroke in nondiabetic patients. Hypertension, high-density lipoprotein (HDL), and triglycerides (TG) levels were hugely associated with blood glucose levels in diabetes patients. stroke patients with diabetes had significantly increased levels of TG and lower mean HDL levels when compared to stroke patients without diabetes.

Post-stroke Management of Hyperglycemia:

There is the conventional method and intensive method of treating hyperglycemia in stroke. In the conventional method, in the first 48 hrs of the onset of stroke, the target is to bring down the blood glucose level to 140 to 189 mg/dl through intravenous insulin therapy. This is followed by subcutaneous insulin therapy with a target of maintaining the glucose level at 80-130 mg/dl for the next 3 months. Whereas in intensive iv insulin therapy, the target is to maintain the blood glucose level within the tight range of 81-108 mg/dl in the initial 48 hrs of stroke onset, this method of intensive therapy had higher mortality and a higher possibility of severe hypoglycemia where the blood glucose level falls less than 60

mg/dl. Maintaining a glycemic index < 110 mg/dl leads to a 4–9–fold higher risk of hypoglycemia[18]. Guidelines of the American Heart and American Stroke Association and the European Stroke Organisation recommend a glycemic index of 7.7–10 Mm (140–189mg/dl)[19, 20]. Intensive insulin therapy was associated with larger infarct growths in MRI scan (median, 27.9 cm^3 (95% CI: 14.6–40.7) VS 10.8 CM^3 (95% CI: 6.5–22.4); 60% OF INCREASE, P=0.04)[21]. Also, some meta–analyses indicated that intensive insulin therapy iv compared to no–treatment / subcutaneous insulin therapy did not enhance survival (RR= 0.99; 95% CI: 0.94–1.05) or the functional outcome (RR= 1.09; 95% CI: 0.87–1.37)[21]. Although several randomized clinical trials conducted including the Stroke Hyperglycemia Insulin Network Effort Trial and meta–analyses22, 23 show that intensive iv insulin administration was observed to have greater risk than benefit. Thus, in previously known diabetic patients, blood glucose levels should be regularly monitored on a periodic basis and steps must be taken to maintain normal blood glucose levels. This is done through multidisciplinary approaches such as lifestyle modification, abstinence from alcohol and smoking, a low–calorie diet, and regular exercise and through blood glucose–lowering drugs including sodium–glucose cotransporter 2 inhibitors ($SGLT2_{inhibitors}$), Dipeptidyl peptidase–4 inhibitors ($DPP4_{inhibitors}$) and glucagon–like peptide–1 receptor agonists ($GLP\text{–}1_{agonists}$).

Diabetic patients with stroke require tailored medical treatment depending on the severity of a stroke and other factors. GLP–1 receptor agonists, DPP–4 inhibitors, and to some extent SGLT–2 inhibitors are the medications best suited for neuroprotection and neuro repair in diabetic patients with stroke[1, 2]. Although the fact is unclear and this agent has its own unique set of risks and benefits, it is necessary to start treatment with neuroprotective agents at the earliest to prevent further damage. So, the physicians must be carefully considered before prescribing. Unfortunately, current treatment options are limited, and few promising drugs are in development for treating diabetic ischemic strokes. However, as more research becomes available, it will be possible to improve the identity which patients who will benefit from specific treatments.

GLP–1 receptor agonists (or glucagon–like peptide–1 agonists) are potent diabetes medications. GLP–1 receptor agonists act on a specific receptor in the brain known by stimulating the release of insulin after eating. They will be triggering neurons to release dopamine and serotonin. In addition, these neurotransmitters are essential for regulating mood and thought. A lack of these neurotransmitters has been linked to low mood and decreased motivation to exercise and eat healthily in diabetics. GLP–1 receptor agonists can improve mood and encourage diabetic patients to make positive lifestyle changes by increasing dopamine and serotonin levels.

DPP–4 inhibitors are oral drugs to control blood glucose levels and lower the risk of cardiovascular disease for type II diabetes. They function by blocking GLP–1 and other incretin–containing gut hormones from being broken down before being absorbed into the bloodstream. Due to the lack of incretins, Type II diabetics have excessive blood glucose production, which raises blood glucose levels. These medications raise blood levels of incretins and aid in the regulation of glucose levels by inhibiting DPP–4. The potential of DPP–4 inhibitors for both diabetes and stroke treatments is currently being explored to determine their efficacy in this population1. DPP–4 inhibitors can help persons with diabetes and stroke by reducing

brain inflammation and enhancing blood flow[3]. SGLT-2 inhibitors are used to treat type II diabetes and help reduce glucose levels in the body. Their mechanisms are acting at the kidneys by blocking the reabsorption of glucose, forcing them to excrete the excess glucose in the urine. Ultimately, these drugs are currently being explored to determine their efficacy for kidney disease in people with type 1 diabetes and the risk of stroke in patients with diabetes[33].

Hypoglycemic Brain Injury due to Overenthusiastic Treatment:

Mechanisms that cause molecular cell injury are activated by hypoglycemia. Hypoglycemia triggers the autonomic nervous system and releases catecholamines which increase the production of glucose by the liver and increase the glycogen breakdown. But this is associated with a pathologic increase in systolic BP, tachycardia, increased myocardial contractility, and decreased central venous pressure[24] thus this increased pressure due to hypoglycemia increases the risk of hemorrhage.

In acute hypoglycemia[25] observed that serum fibrinogen and coagulation factor VIII increased. Thus, this resulted in the procoagulant state leading to ischemic clots. Also, various inflammatory markers including interleukin-6, tumor necrosis factor-alpha, C-reactive protein, endothelin-1 and P-selectin[26, 27] are released causing vasoconstriction that leads to secondary ischemia and formation of new thrombi.

Severe hypoglycemia leads to decreased phosphocreatine, ATP, and adenosine monophosphate[28]. These are the brain energy metabolites. Hypoglycemia worsens this bioenergetic deficit that occurs in the ischemic brain[29, 30]. Also, the mitochondrial reactive oxygen species (ROS) is increased due to a hypoglycemic state. This decreases the mitochondrial membrane potential[32]. Thus, these are some of the ways through which a hypoglycemic state worsens the stroke patients' condition.

Conclusion:

The best possible strategy would be to strengthen the neuroprotective pathway in a stroke patient with DM. GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors would be the medications of choice for neuroprotection in these cases. It is valuable to evaluate the pharmacodynamics and pharmacokinetics of these medications when treating stroke in hyperglycaemic situations. For reasons of safety, one must take into account their ensuing adverse effects.

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Figure 1. *The pathophysiology of how diabetes leads to stroke*

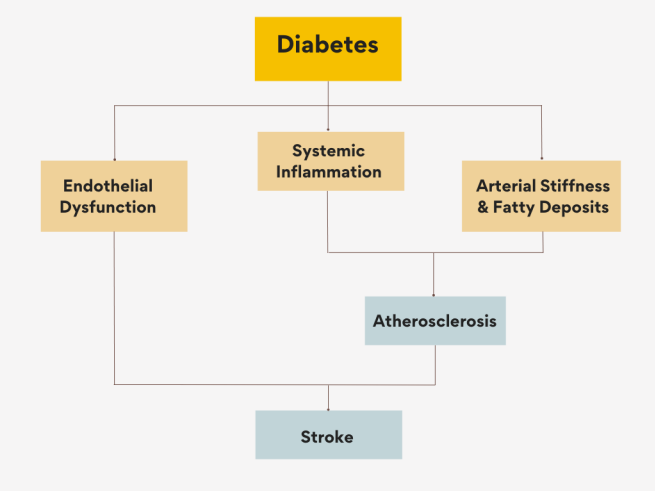

Figure 2. *Metabolic mechanisms of hyperglycemia effects in acute ischemic stroke in an animal model (modified from Ref. 31)*

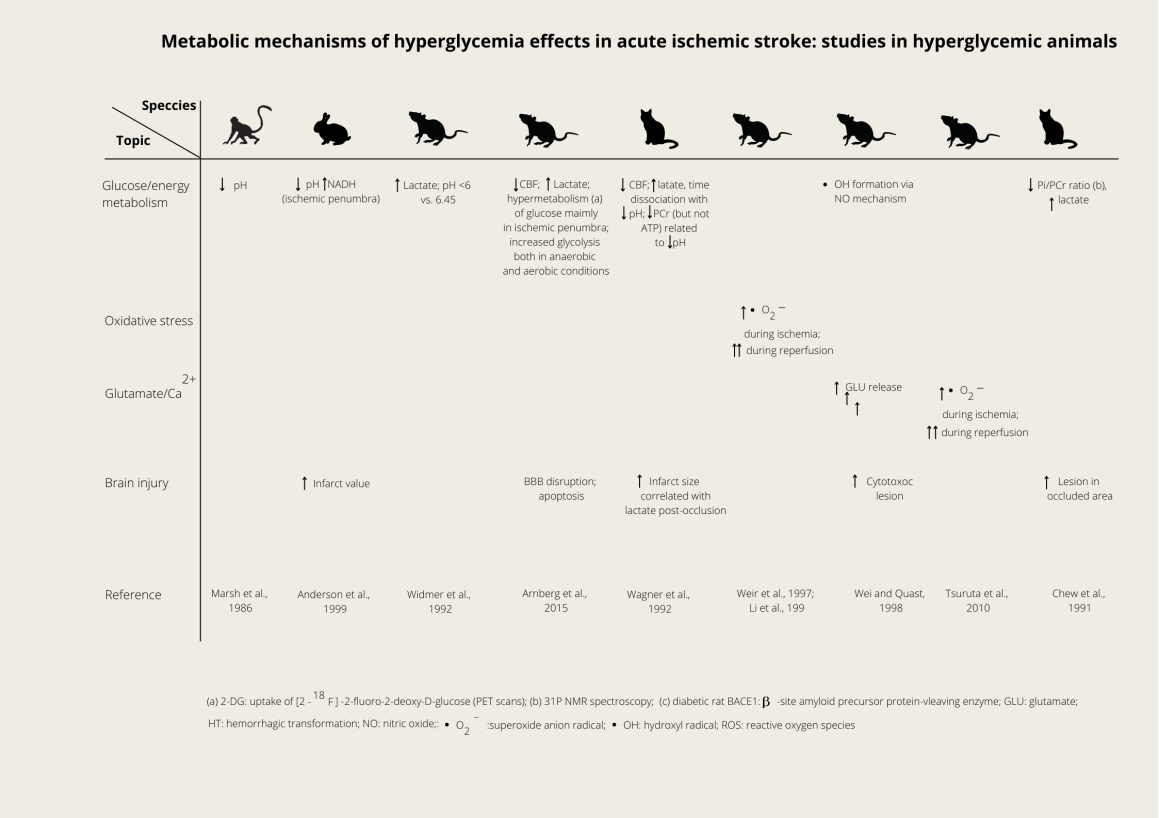

Table 1. *Stroke patterns in diabetic versus non-diabetic patients*

Stroke	Diabetic Patients (% of cases)	Non-Diabetic Patients (% of cases)
Ischemic Stroke	85	62.5
Hemorrhagic Stroke	15	37.5
Cortical Infarcts	50	52.5
Lacunar Infarcts	32.5	10