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Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes

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Abstract

There has been a significant increase in obesity rates worldwide with the corresponding surge in diabetes. Diabetes causes various microvascular and macrovascular changes often culminating in major clinical complications, 1 of which, is stroke. Although gains have been made over the last 2 decades in reducing the burden of stroke, the recent rise in rates of diabetes threatens to reverse these advances. Of the several mechanistic stroke subtypes, individuals with diabetes are especially susceptible to the consequences of cerebral small vessel diseases. Hyperglycemia confers greater risk of stroke occurrence. This increased risk is often seen in individuals with diabetes and is associated with poorer clinical outcomes (including higher mortality), especially following ischemic stroke. Improving stroke outcomes in individuals with diabetes requires prompt and persistent implementation of evidence-based medical therapies as well as adoption of beneficial lifestyle practices.

Key Indexing Terms

Diabetes; Hyperglycemia; Stroke; Outcomes; Stroke prevention

INTRODUCTION

cardiovascular diseases (CVD), including stroke, are major healthcare issues in both developing and developed countries with deleterious effects at individual, family and societal levels. Between 2010 and 2030, the estimated total direct medical costs would escalate from $273–$818 billion in the United States alone.[1]

Major modifiable risk factors for stroke include hypertension, diabetes, smoking and dyslipidemia. Diabetes is a well-established risk factor for stroke. It can cause pathologic changes in blood vessels at various locations and can lead to stroke if cerebral vessels are directly affected. Additionally, mortality is higher and poststroke outcomes are poorer in patients with stroke with uncontrolled glucose levels. Whether tight control of hyperglycemia is associated with better outcomes in acute stroke phase needs to be further

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investigated in Phase III clinical trials. Controlling diabetes and other associated risk factors are effective ways to prevent initial strokes as well as stroke recurrence.

In this narrative article, we review the epidemiology linking diabetes and stroke; the pathophysiology of diabetes and stroke patterns and outcomes in individuals with diabetes. Additionally, we summarize the influence of hyperglycemia on poststroke outcomes and management of hyperglycemia during the acute phase of stroke. Finally, we review stroke prevention strategies for individuals with diabetes.

EPIDEMIOLOGY

An estimated 285 million individuals worldwide suffered diabetes during 2010, and the number is projected to increase to 439 million worldwide by 2030.[1] This global increase includes a 69% increase in adults with diabetes in developing countries and a corresponding 20% increase in developed countries. This dramatic increase in the prevalence of type II diabetes is likely attributable to the increase in the prevalence of obesity. The metabolic syndrome is believed to affect at least 1 in 5 adults, and carries a high risk of both type II diabetes and CVD. Diabetes can lead to various serious complications if not treated properly. These include retinopathy, chronic kidney disease, limb amputation, heart disease and stroke. Diabetes has 2 forms—type I (ie, insulin-dependent type) and type II (ie, insulin-insensitivity type). Type II diabetes is much more common, accounting for the majority (about 90%) of cases. Both the types of diabetes are associated with increased risks of CVD, but they exhibit different patterns. For example, individuals with type I diabetes are more likely to suffer coronary heart disease and peripheral arterial disease. On the contrary, individuals with type II diabetes are more likely to have obesity, peripheral arterial disease, large-artery atherosclerosis and stroke.[2]

In the United States, diabetes is the seventh leading cause of death and 65% of these deaths are attributable to CVD or stroke or to both.

Epidemiologic studies have shown that diabetes is a well-established independent but modifiable risk factor for stroke, both ischemic and hemorrhagic stroke (Table).[3–11] For example, findings from the Emerging Risk Factors Collaboration showed that the adjusted hazard ratios (HRs) with diabetes were 2.27 (1.95–2.65) for ischemic stroke, 1.56 (1.19–2.05) for hemorrhagic stroke and 1.84 (1.59–2.13) for unclassified stroke.[4]

Risk for stroke is actually higher in the young population with diabetes. According to data from the Greater Cincinnati/Northern Kentucky stroke study, diabetes increases ischemic stroke incidence in all age groups, but this risk is most striking before the age of 55 years in African Americans and before the age of 65 years in Whites.[6] Individuals with diabetes are more likely to suffer from hypertension, myocardial infarction (MI) and high cholesterol than individuals without diabetes. Even prediabetes (defined as impaired glucose tolerance or a combination of impaired fasting glucose plus impaired glucose tolerance) has been linked to a greater risk of stroke.[12]

PATHOPHYSIOLOGY

There are several possible mechanisms wherein diabetes leads to stroke. These include vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation and thickening of the capillary basal membrane. Abnormalities in early left ventricular diastolic filling are commonly seen in type II diabetes. The proposed mechanisms of congestive heart failure in type II diabetes include microvascular disease, metabolic derangements, interstitial fibrosis, hypertension and autonomic dysfunction (Figure 1). Vascular endothelial function is critical for maintaining structural and functional integrity of the vessel walls as well as the vasomotor control. Nitric oxide (NO) mediates vasodilation, and its decreased availability can cause endothelial dysfunction and trigger a cascade of atherosclerosis. For example, NO-mediated vasodilation is impaired in individuals with diabetes, possibly due to increased inactivation of NO or decreased reactivity of the smooth muscle to NO. Individuals with type II diabetes have stiffer arteries and decreased elasticity compared with subjects having normal glucose level. Type I diabetes is more often associated with an early structural impairment of the common carotid artery, commonly reflected as increased intima-medial thickness, and is considered as early sign of atherosclerosis. An increased inflammatory response is frequently seen in individuals with diabetes, inflammation plays an important role in the development of the atherosclerotic plaque. The C-reactive protein, cytokines and adiponectin are the main serum markers of inflammation. The C-reactive protein and the plasma levels of these cytokines including interleukin-1, interleukin-6 and tumor necrosis factor-α are independent predictors of cardiovascular risk. Adiponectin appears to be a modulator of lipid metabolism and systemic inflammation. A low level of adiponectin itself has also been associated with CVD.

STROKE PATTERNS IN DIABETES

Uncontrolled diabetes puts subjects at risk for both ischemic and hemorrhagic strokes. There are specific clinical patterns of ischemic stroke in individuals with diabetes. For example, individuals with diabetes are more likely to have limb weakness and dysarthria as signs of lacunar cerebral infarction when compared with those without diabetes. In the Lausanne Stroke Registry between 1983 and 2002, patients with diabetes had higher relative prevalence of subcortical infarction and lower relative prevalence of intracerebral hemorrhage (ICH).[10] In another study, significant differences were observed in patients with ischemic stroke along with diabetes in comparison with nondiabetics with higher frequency of lacunar infarct and hypertension.[13] In all, 2 cases of patients with diabetes with poorly controlled glucose presented with different type of strokes are illustrated in Figure 2.

HYPERGLYCEMIA AND ITS MANAGEMENT

Hyperglycemia is a common phenomenon presented in the early acute stroke phase. It may be related to nonfasting state and stress reaction with impaired glucose metabolism. Stroke triggers generalized stress reaction involving the activation of the hypothalamic-pituitary-adrenal axis, which subsequently leads to increased levels of serum glucocorticoids, activation of the sympathetic autonomic nervous system and increased catecholamine release. Increased levels of stress hormones raise rates of aerobic glycolysis, promote

glucose release from gluconeogenesis and glycogenolysis and inhibit insulin-mediated glycogenesis.

The initial level of plasma glucose is highly correlated with poor poststroke outcomes. Acute hyperglycemia increases brain lactate production, reduces salvage of penumbral tissue and causes greater final infarct size. In the middle cerebral artery occlusion animal model, hyperglycemia increases the volume of mean lesion size in diffusion-weighted imaging by 118% and hemispheric cerebral blood volume is reduced by 37% in hyper-glycemic rats compared with normoglycemic rats.[14] Hyperglycemia further aggravates the stroke consequences through augmented reperfusion injury by increasing oxidative stress, stimulating systemic inflammation and increasing barrier permeability. Patients with acute ischemic stroke with both diabetes and hyperglycemia have an increase in aggregation and adhesion of platelets to the endothelium. A study conducted in Glasgow showed that higher plasma glucose predicted a poorer prognosis (relative HR = 1.87; 1.43–2.45) even after correcting for age, stroke severity and stroke subtype.[15]

Both acute hyperglycemia and hyperinsulinemia have been shown to increase plasminogen activator inhibitor type 1 and decrease free tissue plasminogen activator (tPA) activities by decreasing plasma fibrinolytic activity in animal model.[16] In tPA-treated patients, acute hyperglycemia delays reperfusion of the ischemic penumbra and decreases tPA-induced recanalization rates. Among patients with stroke who were treated with intravenous thrombolysis, hyperglycemia was associated with significantly lower rates of desirable clinical outcomes, higher rates of symptomatic ICH and reduced benefits from recanalization with thrombolytic therapy. In the National Institute of Neurological Disorders and Stroke rt-PA trial, the odds for symptomatic ICH increased to 75% when the admission glucose increased every 100 mg/dL.[17] Higher fasting glucose on the day following intravenous thrombolysis independently predicted 90-day clinical unfavorable outcome (ie, modified Rankin Scale, 3–6; odds ratio = 1.58; 95% CI: 1.05–2.34).[18] In another cohort analysis, patients with diabetes showed a higher risk of stroke-related death than patients without diabetes (HR = 1.15; 95% CI: 1.11–1.19; $P < 0.001$) in the United States.[19]

The influence of hyperglycemia to patients with ICH is similar to that of ischemic stroke. The effect of hyperglycemia on patients with ICH leading to poor outcomes may be related to exacerbation of hematoma expansion and perihematoma edema. In rat model, hyperglycemia can cause more profound brain edema and increased neuronal death around the hematoma.[20] Moreover, hyperglycemia following ICH activates the sympathetic nervous system and induces hormonal and metabolic alterations.

As hyperglycemia is associated with poor outcomes, proper management of poststroke hyperglycemia is critical for improving outcomes. The American Heart Association (AHA)/ American Stroke Association guidelines for the early management of patients with acute ischemic stroke recommends “to achieve serum glucose concentrations in the range of 140–180 mg/dL (7.8–10 mmol/L) during the first 24 hours after acute ischemic stroke in all hospitalized patients.”[21] The European Stroke Initiative guidelines also recommend “blood glucose of 180 mg/dL (10 mmol/L) or higher justifies immediate insulin titration.”[22] Typically, hyperglycemia in the acute stroke setting is treated with subcutaneous insulin

through a sliding scale. Normalization of blood glucose during the first 48 hours of hospitalization appears to confer survival benefits in patients suffering ischemic stroke. Results from the National Institute of Neurological Disorders and Stroke–funded Treatment of Hyperglycemia in Ischemic Stroke (THIS)[23] and the Glucose Regulation in Acute Stroke Patients (GRASP)[24] trials both demonstrated safety and feasibility of insulin infusion therapy for intensive glucose control in patients with acute ischemic stroke. However, a recently published systematic review of 11 randomized controlled trials involving over 1,500 participants with acute ischemic stroke did not suggest benefits of intensive glycemic control.[25] The participants in the included trials were randomly assigned to either the intensively monitored insulin therapy group or the usual care control group. There was no difference in the combined outcomes of death or dependency between the intervention and the control groups, and neither was a difference for the final neurologic deficit. The intervention group actually had a higher rate of symptomatic hypoglycemia.

It remains clinical equipoise on how best to treat hyperglycemia during acute ischemic stroke. An ongoing Stroke Hyperglycemia Insulin Network Effort (SHINE) is expected to be completed in 2016. This study is evaluating whether tight control of glucose with intravenous insulin can improve outcomes in patients with acute ischemic stroke.[26] Approximately 1,400 patients with hyperglycemia are expected to enroll and to receive either standard sliding scale subcutaneous insulin (blood glucose range: 80–179 mg/dL; 4.44–9.93 mmol/L) or continuous intravenous insulin (target blood glucose: 80–130 mg/dL; 4.44–7.21 mmol/L), starting within 12 hours of stroke symptom onset, and lasting for up to 72 hours. This definitive clinical trial would provide important evidence about the optimal management of hyperglycemia in acute stroke.

The targeted glucose level of hyperglycemia in ICH also remains to be clarified. The 2015 AHA/American Stroke Association guidelines for the management of spontaneous ICH recommended that “glucose should be monitored, and both hyperglycemia and hypoglycemia should be avoided.”[27] Although it is important to actively treat hyperglycemia, overtreatment and hypoglycemic events actually increase risk of mortality in patients and should be avoided. Severe or prolonged hypoglycemia can result in permanent brain damage, and is of greatest concern with insulin therapy. Low level (<60 mg/dL) of blood glucose should be to corrected urgently.[27]

STROKE PREVENTION

No major clinical trials have examined specific stroke prevention strategies in individuals with diabetes. Evidence is scarce in secondary stroke prevention. Most available data are based on studies focusing on primary stroke prevention.

For an average of 6.5 years of intensive diabetes therapy (INT) in type I diabetes of Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, former INT-reduced aggregate CVD risk by 42% (95% CI: 9–63%, $P = 0.016$) and that of the major CVD events (MI, stroke and CVD deaths) by 57% (25 versus 11 subjects, 95% CI: 12–79%, $P = 0.018$).[28] The INT (with the aim of achieving near-normal blood glucose and glycosylated hemoglobin concentrations) group in DCCT

consisted of 3 or more daily injections of insulin or treatment with an external insulin pump, with dose adjustments based on at least 4 self-monitored glucose measurements per day. Daily glucose goals were 70–120 mg/dL (3.9–6.7 mmol/L) before meals and peak levels of less than 180 mg/dL (10.0 mmol/L) after meals.[29]

Lifestyle changes including controlling weight, minimizing total fat intake, especially saturated fat intake, augmenting fiber intake and increasing physical activity, can reduce incidence of diabetes in high-risk individuals, however, intensive lifestyle interventions only aiming weight reduction does not lead to a corresponding reduction in CVD in overweight or obese individuals with type II diabetes. For example, in the "Look AHEAD" (Action for Health in Diabetes) trial,[30] there was no significant difference between the 2 groups in cardiovascular morbidity and mortality after a median follow-up of 9.6 years. Specifically, primary outcome (a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or hospitalization for angina) occurred in 418 individuals in the control group and in 403 individuals in the intervention group (1.92 and 1.83 events per 100 person-years, respectively; $P = 0.51$). Additionally, there is no difference in stroke occurrence (80 strokes in the control group versus 85 strokes in the intervention group, $P = 0.78$).

Although weight-loss itself does not seem to be effective in reducing cardiovascular events, intensified multifactorial intervention does show efficacy. In the Steno-2 study, subjects with type 2 diabetes and persistent microalbuminuria were randomized to either intensive (INT) therapy or conventional therapy. The INT group had defined targets including a glycosylated hemoglobin level of <6.5%, a fasting serum total cholesterol level of < 175 mg/dL, a fasting serum triglyceride level of < 150 mg/dL, a systolic blood pressure (SBP) of < 130 mm Hg and a diastolic blood pressure of < 80 mm Hg. The INT group had sustained beneficial effects with respect to cardiovascular events (HR = 0.41; 95% CI: 0.25–0.67; $P < 0.001$) as well as deaths from cardiovascular causes (HR = 0.43; 95% CI: 0.19–0.94; $P = 0.04$). During the averaged 13.3 years of follow-up, 6 individuals (6 strokes) in the INT group and 18 individuals (30 strokes) in the conventional group suffered strokes.[31]

Frequently, individuals with diabetes have coexistent hypertension that is another modifiable risk factor for stroke. Controlling the blood pressure (BP) has been proven to be effective in preventing stroke both in individuals with diabetes and individuals without diabetes, but whether tighter BP control can convey more cardiovascular benefits to individuals with diabetes remain controversial. National High Blood Pressure Education Program recommended "patients with diabetes and chronic kidney disease, BP goal should be < 130/80 mm Hg."[32] The 2014 evidence-based guideline for the management of high BP in adults did not conclude the benefit of lower BP goal and recommended "BP goal of < 140/90 mm Hg regardless of diabetes status."[33] In The United Kingdom Prospective Diabetes Study, it showed risk reduction in the group assigned to tight control (144/82 mm Hg) as compared to that assigned to less tight control (154/87 mm Hg) was 44% in strokes ($P = 0.001$).[34] The ACCORD study also showed that in subjects with type II diabetes, targeting SBP < 120 mm Hg reduced the risk of any strokes (HR = 0.59; 95% CI: 0.39–0.89) and nonfatal strokes (HR = 0.63; 95% CI: 0.41–0.96) compared with subjects whose SBP target was < 140 mm Hg.[35]

In terms of lipid control in individuals with diabetes, the American College of Cardiology/AHA guidelines for the prevention of stroke in patients with stroke or transient ischemic attack[36] outlined “statin benefit groups” for drug treatment to reduce risk for atherosclerotic CVD. This included 1 group with “diabetics aged 40–75 years with low-density lipoprotein cholesterol of 70–189 mg/dL and without clinical atherosclerotic CVD.”

Clopidogrel may be more effective than aspirin in stroke prevention in individuals with diabetes along with atherosclerosis. In an ad-hoc analysis of CAPRIL trial,[37] the annual event rate (vascular death, MI, stroke or rehospitalization for ischemia or bleeding) for clopidogrel group versus aspirin is 11.8% versus 12.7%, 15.8% versus 17.7% and 17.7% versus 21.5% for individuals without diabetes, for all individuals with diabetes and for individuals with diabetes who were treated with insulin, respectively. Additionally, the risk of bleeding is lower in the clopidogrel group (1.5% versus 2.8%, $P = 0.031$). Such benefit was not observed in individuals without diabetes. This finding needs to be confirmed in a dedicated clinical trial.

Several glucose-lowering agents may have advantages in stroke prevention. For example, patients with diabetes along with acute ischemic stroke who had been taking and continued taking sulfonylurea were less likely to have symptomatic hemorrhagic transformation.[38] Thiazolidinedione drugs (rosiglitazone and pioglitazone) can reduce insulin resistance, have favorable effects on blood vessels, reduce blood vessel inflammation and potentially prevent atherosclerosis. In a subgroup analysis from PROACTIVE (PROspective pioglitAzone Clinical Trial in macroVascular Events) study,[39] pioglitazone can prevent more fatal or nonfatal strokes in high-risk patients with type II diabetes. This benefit was only observed in the subgroup of patients with prior strokes. The recently published Insulin Resistance Intervention after Stroke Trial (IRIS) showed patients without diabetes who had insulin resistance along with a recent ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo (9.0% versus 11.8% with 95% CI of 0.62–0.93; p=0.007). Interestingly, Pioglitazone was associated with lower risk of diabetes but with higher risk of weight gain.[40]

CONCLUSIONS

Diabetes is an important modifiable risk factor for stroke, especially ischemic strokes. Hyperglycemia during the acute stroke phase is associated with poor outcomes in both ischemic and hemorrhagic strokes. It needs to be actively corrected but optimal management remains unknown. Aggressive glucose control through lifestyle change or medications and modification of other associated risk factors (such as BP and dyslipidemia) are critical steps toward effective stroke prevention.

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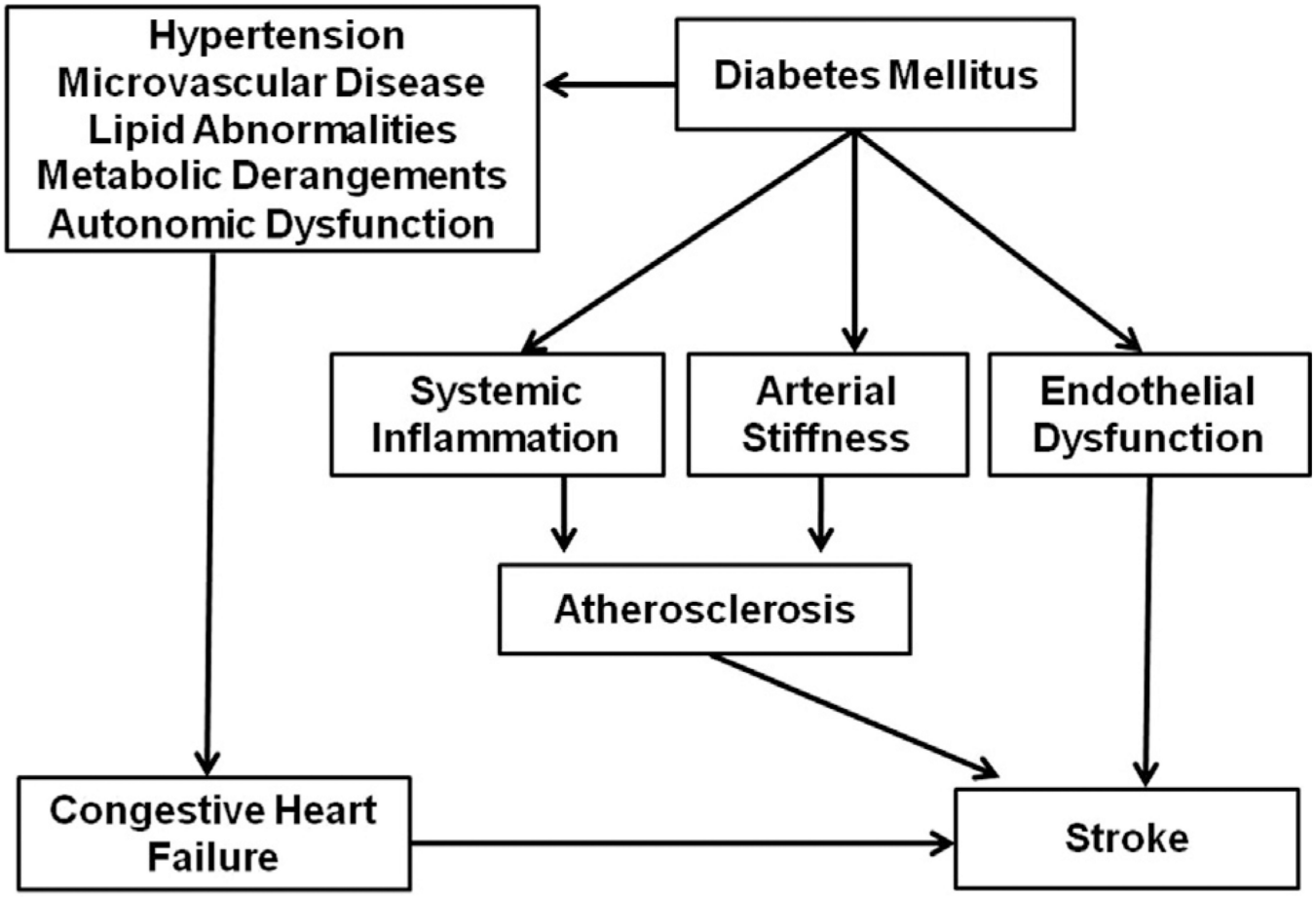

FIGURE 1.
Possible mechanisms of stroke in individuals with diabetes.

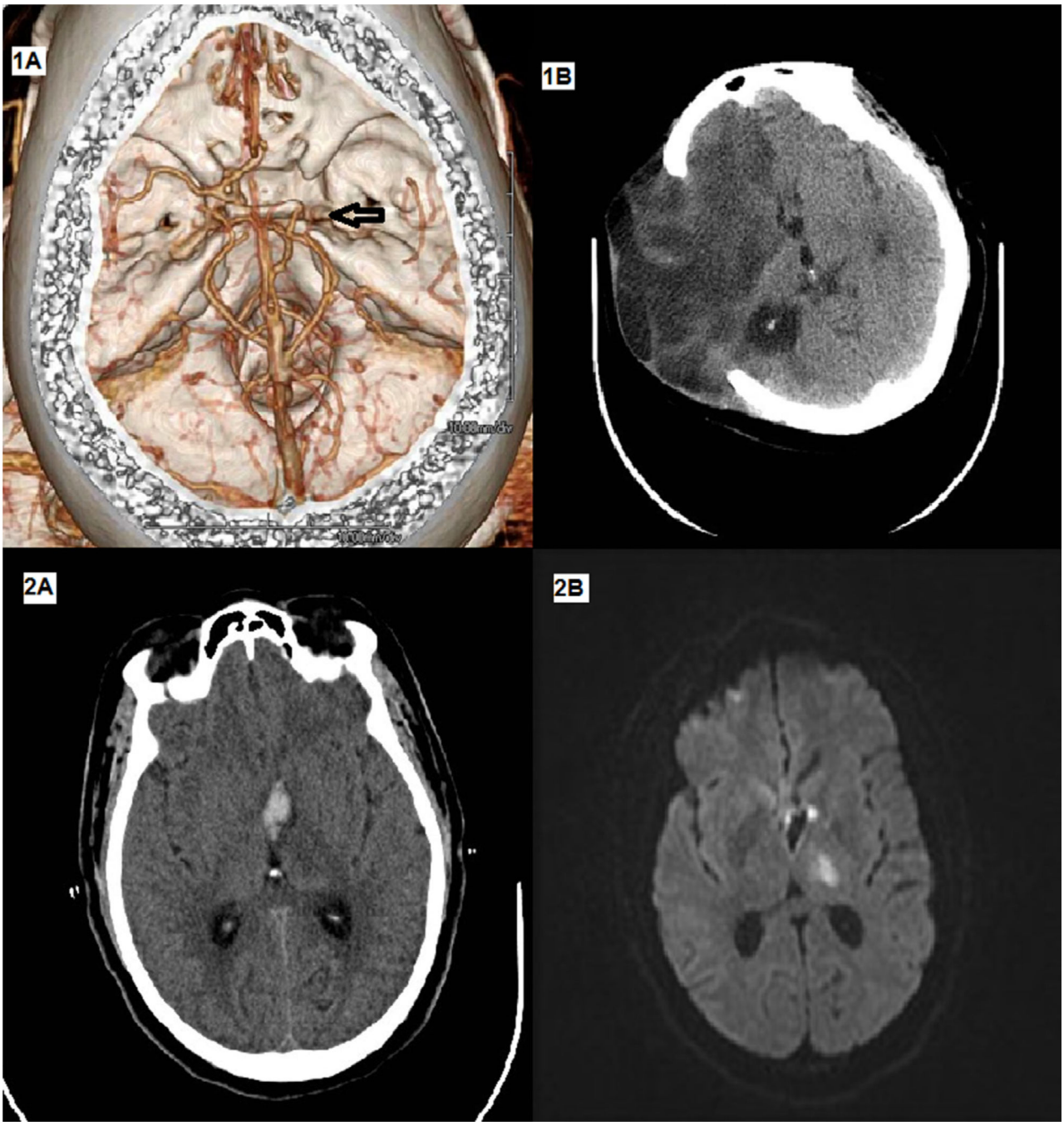

FIGURE 2.

Microvascular and macrovascular stroke complications of diabetes. Patient A with history of uncontrolled diabetes (glucose is 490 mg/dL and hemoglobin A1C is 10.5% at presentation) and smoking presented with an occlusion of right ICA extending to right MCA causing acute infarct (A, arrow). Subsequently, patient A developed malignant MCA syndrome due to severe swelling and received hemicraniectomy despite the fact this patient received tPA in the first place (B). Patient B with history of uncontrolled diabetes (glucose is 434 mg/dL and hemoglobin A1C is 11.3% at presentation) presented with acute intracerebral hematoma in

the left genu of internal capsule and medial aspect of left thamalus (C) and acute ischemic stroke (lacunar infarct) in the left thalamus(D). ICA, internal carotid artery; MCA, middle cerebral artery.

TABLE

Risk of diabetes to strokes.

	Odds ratio/relative risk/hazard ratio		
Study	**Ischemic stroke**	**Intracerebral hematoma**	**All strokes**
O'Donnell et al[3]	1.60 (1.29–1.99)	0.87 (0.60–1.24)	1.36 (1.10–1.68)
The Emerging Risk Factors Collaboration[4]	2.27 (1.95–2.65)	1.56 (1.19–2.05)	
Wolf et al[5]			Male: 1.40
			Female: 1.72
Khoury et al[6]	Black: 3.2 (2.4–3.9)		
	White: 3.8 (3.3–4.3)		
Cui et al[7]	Male: 2.22 (1.58–3.11)	Male: 0.75 (0.35–1.6)	Male: 1.64 (1.21–2.23)
	Female: 3.63 (2.41–5.48)	Female: 0.58 (0.18–1.86)	Female: 2.19 (1.53–3.12)
Iso et al[8]	Male: 1.8 (1.0–3.2)		
	Female: 2.2 (1.2–4.0)		
Manolio et al[9]			2.47 (1.74–3.50)
Karapanayiotides et al[10]	1.34 (1.11–1.62)	0.63 (0.45–0.90)	
Janghorbani et al[11]	Type I DM: 6.3 (4.0–9.8)	Type I DM: 3.8 (1.2–11.8)	Type I DM: 4.7 (3.3–6.6)
	Type II DM: 2.3 (2.0–2.6)	Type II DM: 1.0 (0.7–1.4)	Type II DM: 1.8 (1.7–2.0)

DM, diabetes mellitus.