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# Literature review: Interconnection between Type 2 diabetes mellitus and ischemic stroke: Pathophysiology, risks, and management

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## Abstract

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), significantly elevates the risk of ischemic stroke through mechanisms involving chronic hyperglycemia, endothelial dysfunction, and a prothrombotic state. This review explores the interplay between T2DM and ischemic stroke, focusing on pathophysiological mechanisms, synergistic effects of comorbid conditions, and the implications of acute hyperglycemia in stroke outcomes. Chronic hyperglycemia in T2DM leads to oxidative stress, inflammation, and vascular changes that contribute to endothelial dysfunction, promoting atherosclerosis and increasing stroke risk. Furthermore, T2DM-associated prothrombotic states involve heightened platelet reactivity, altered coagulation factors, and impaired fibrinolysis, compounding the risk of thrombus formation and ischemic events. The coexistence of hypertension, dyslipidemia, and obesity further amplifies this risk, creating a cluster of interrelated metabolic abnormalities that exacerbate cerebrovascular damage.

Acute hyperglycemia during ischemic stroke worsens outcomes by increasing infarct size, disrupting the blood-brain barrier, and exacerbating inflammation and oxidative stress. Management of hyperglycemia in acute stroke remains challenging, as intensive glucose control may lead to hypoglycemia without significantly improving outcomes. Emerging therapeutic strategies, including the use of GLP-1 receptor agonists and SGLT2 inhibitors, show promise in reducing cardiovascular complications and stroke risk while addressing glucose regulation and comorbid conditions.

This review underscores the importance of integrated management strategies that address the multifactorial nature of T2DM and its complications to mitigate ischemic stroke risk and improve outcomes. Future research should focus on optimizing glycemic control strategies and exploring novel therapeutic interventions to target the complex interplay between T2DM and cerebrovascular disease.

**Keywords:** Type 2 diabetes mellitus; Ischemic stroke; Acute hyperglycemia; Endothelial dysfunction; Prothrombotic state

## 1. Introduction

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is a global health concern, profoundly impacting multiple organ systems and predisposing individuals to a wide array of complications, including ischemic stroke. The growing prevalence of T2DM—attributed to sedentary lifestyles, obesity, and poor dietary habits—has significantly increased the burden of cardiovascular morbidities globally (1). Epidemiological evidence underscores the heightened risk of stroke in individuals with T2DM, emphasizing the role of metabolic disturbances, vascular dysfunction, and

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prothrombotic states in its pathogenesis. Furthermore, acute hyperglycemia during ischemic stroke has been associated with larger infarcts, poorer functional outcomes, and increased mortality, highlighting its detrimental role in the acute stroke setting.

This literature review aims to explore the multifaceted relationship between T2DM, hyperglycemia, and stroke, with a particular focus on the mechanisms underlying vascular dysfunction, the synergistic effects of comorbid conditions, and the role of hyperglycemia as a prognostic factor in stroke outcomes. The review also examines therapeutic strategies for managing hyperglycemia in acute stroke, including traditional insulin-based approaches and emerging alternatives, as well as the challenges and limitations inherent in glycemic control during acute stroke.

By synthesizing findings from recent studies, this review seeks to provide a comprehensive understanding of the interplay between T2DM, hyperglycemia, and stroke, emphasizing the importance of tailored therapeutic interventions to improve patient outcomes. This knowledge is critical for developing strategies to mitigate the burden of stroke in individuals with diabetes and for optimizing acute stroke management protocols.

### 1.1. T2DM as a Risk Factor for Ischemic Stroke

#### *1.1.1. Overview of Risk Interactions*

T2DM contributes significantly to the overall risk of ischemic stroke, with various studies highlighting the associated risk with diabetes. Epidemiological studies reporting relative risks (RRs) between 1.3 and 4.9, highlighting a markedly increased stroke risk in individuals with T2DM compared to those without (2,3). T2DM also promotes inflammatory process , increases thrombotic potential, and also leads to vascular changes that predispose individuals to atherosclerosis, which can result in ischemic events (4). Glycemic control in T2DM is proven to be important, with studies showing uncontrolled T2DM patients having higher incidence of strokes compared to those with controlled diabetes approximately 4.71 times (5). Its impact is often compounded by coexisting conditions such as hypertension, dyslipidemia, and obesity, all of which are independent risk factors for stroke. This clustering of risk factors amplifies the pathogenesis of cerebrovascular disease, making T2DM a pivotal determinant of stroke incidence (6).

#### *1.1.2. Mechanisms of Endothelial Dysfunction*

Chronic hyperglycemia in T2DM leads to the formation and accumulation of Advanced Glycation End Products (AGEs), which contribute to oxidative stress and inflammation within the vascular walls. These AGEs bind to their receptor, RAGE (Receptor for Advanced Glycation End Products), activating pathways that cause endothelial dysfunction and accelerate the progression of atherosclerosis, further exacerbating vascular damage (7). Insulin resistance in T2DM amplifies platelet activation and adhesion, promoting thrombus formation and accelerating the growth of atherosclerotic plaques. Additionally, hyperinsulinemia stimulates the proliferation of vascular smooth muscle cells (VSMCs), which contribute to forming the core of an atherosclerotic, further accelerating the development and progression of atherosclerotic lesions (8).

T2DM is linked to chronic low-grade inflammation marked by elevated levels of inflammatory cytokines such as TNF-alpha and IL-6. These cytokines activate endothelial cells, increasing the expression of adhesion molecules that promote leukocyte adhesion and migration into the vascular wall, thereby contributing to the development of atherosclerosis (9). Hyperglycemia can induce Endothelial-to-Mesenchymal Transition (EndMT), a process where endothelial cells lose their typical characteristics and acquire mesenchymal-like properties. This transition is primarily driven by the activation of transforming growth factor-beta (TGF-β) signaling under hyperglycemic conditions, contributing to vascular remodeling and fibrosis (10).

These processes can lead to ischemic stroke by going into various pathway. Diabetes can activate Protein Kinase C (PKC) through the glycolysis process, which triggers the synthesis of diacylglycerol and subsequently activates PKC. This activation can lead to various responses, such as changes in cell proliferation and differentiation, disturbances in glucose and lipid metabolism, expression of pro-atherosclerotic genes, and impaired vasodilation mediated by nitric oxide (NO), all of which can contribute to vascular damage (11). This reduces blood flow to the brain during times of heightened demand, such as physical exertion or stress, raising the risk of ischemia. Additionally, endothelial dysfunction activates an inflammatory response, involving the release of cytokines and the recruitment of immune cells to the vascular wall, which further damages the endothelium and exacerbates vascular injury, thereby elevating the risk of stroke (12). Endothelial cells form the blood-brain barrier (BBB), protecting the brain from harmful substances. Dysfunction of the BBB compromises its integrity, allowing neurotoxic substances to enter, which can lead to neuronal damage and increased stroke risk. Additionally, BBB disruption contributes to edema, worsening post-stroke outcomes (13). Endothelial dysfunction disrupts the ability of blood vessels to adjust to changes in blood flow, resulting in inadequate

perfusion during ischemic events. This can worsen tissue damage and increase infarct size (12). Chronic endothelial dysfunction is linked to cognitive decline and long-term neurological deficits after an ischemic stroke. Persistent vascular damage and reduced cerebral perfusion can lead to ongoing cognitive impairment in ischemic stroke patients (14).

#### *1.1.3. Prothrombotic State in Diabetes*

Individuals with T2DM presents with heightened platelet activation, characterized by increased spontaneous aggregation and heightened sensitivity to activators like thrombin and collagen (15). This heightened platelet reactivity is linked to insulin resistance and hyperglycemia, which elevate glycoprotein (GP) Ib and IIb/IIIa levels on platelet surfaces, facilitating adhesion and aggregation (16). Additionally, chronic hyperglycemia leads to glycation of membrane proteins, reducing membrane fluidity and increasing intracellular calcium influx, both of which further promote platelet activation (17).

Hyperfibrinogenemia and hyperfibrinolisis are commonly observed in patients with T2DM. Elevated fibrinogen levels in T2DM promote the formation of blood clots by enhancing fibrinogen conversion into fibrin. These elevated levels result in the creation of thicker and denser fibrin clots, which are more resistant to breakdown. This makes these clots more stable and persistent, increasing the likelihood of thrombus formation and subsequent blockages in blood vessels. Furthermore, T2DM is often associated with elevated levels of plasminogen activator inhibitor-1 (PAI-1). PAI-1 inhibits the activation of plasminogen. The elevated activity of PAI-1 impairs the normal process of clot resolution, causing clots to remain in the bloodstream for longer periods. This prolongs the clotting process and further raises the risk of thrombotic events, which can lead to complications such as ischemic stroke, myocardial infarction, and other cardiovascular diseases in individuals with T2DM (18).

Individuals with T2DM frequently show alterations in circulating coagulation factors, such as elevated levels of factors VII and XII, which contribute to a hypercoagulable state. These changes are associated with underlying conditions like insulin resistance and dyslipidemia, which further increase the risk of thrombosis. Elevated factor VII levels promotes the initiation of the clotting cascade, while factor XII activation forms and develops thrombus. As a result, these coagulation factor imbalances in individuals with diabetes exacerbate the likelihood of clot formation, significantly raising the risk of thrombotic events such as ischemic stroke, myocardial infarction, and other cardiovascular complications (19).

Elevated levels of platelet-derived microparticles (PMPs) have been reported in T2DM patients, which contribute to thrombosis by enhancing platelet activation and releasing pro-inflammatory cytokines, promoting a prothrombotic state. Additionally, changes in erythrocyte properties occur in T2DM. Erythrocytes become rigid due to altered membrane composition, impair blood flow and increase resistance to fibrinolysis, contributing to the formation of dense thrombi that are harder to break down (15).

### 1.2. Synergistic Effect of Coexisting Conditions

#### *1.2.1. Hypertension*

Hypertension, in particular, interacts synergistically with hyperglycemia to cause arterial stiffness and increased cerebral blood pressure, compounding the risk of ischemic stroke. The combination of T2DM and hypertension plays a significant role in promoting endothelial dysfunction, which impairs the normal function of blood vessels. This dysfunction, along with increased arterial stiffness and enhanced platelet reactivity, creates a prothrombotic environment. As a result, individuals with both conditions are at a higher risk for thrombus formation, which can lead to ischemic events, such as stroke or heart attack (20). Research shows that T2DM and hypertension are closely linked to a higher risk of ischemic stroke. One study, for example, reported a hazard ratio (HR) of 4.151 for stroke risk in patients with both conditions, compared to those without either, emphasizing the increased risk when both factors are present (21).

#### *1.2.2. Dyslipidemia*

Dyslipidemia, which is commonly observed in individuals with T2DM, is characterized by elevated levels of low-density lipoprotein (LDL) cholesterol and triglycerides, along with reduced high-density lipoprotein (HDL) cholesterol. This lipid imbalance contributes to the development of atherosclerosis, a major precursor to ischemic stroke. The presence of dyslipidemia in diabetic patients worsens endothelial dysfunction and destabilizes arterial plaques, further increasing the risk of stroke. Together, these metabolic abnormalities significantly heighten the overall cardiovascular disease risk, ischemic stroke included (4).

*1.2.3. Obesity*

Obesity is strongly associated with insulin resistance and T2DM, contributing to systemic inflammation and worsening other components of metabolic syndrome, such as hypertension and dyslipidemia. Excess body weight leads to elevated blood pressure, altered lipid metabolism, and increased inflammation, all of which collectively raise the risk of stroke . Studies have shown that obese individuals with T2DM are more likely to experience ischemic strokes compared to those who are not obese (20).

Some studies reported cases of "obesity paradox" happening where overweight or mildly obese individuals with T2DM may have better outcomes regarding mortality and major adverse cardiovascular events (MACE) compared to those with normal weight. Some research indicate T2DM obese patients may experience less cardiovascular events despite their higher overall risk profile (22). While some studies suggest that overweight individuals may have a lower risk of stroke compared to underweight individuals, the overall relationship is complex and not universally applicable. The protective effects observed in certain studies may not hold true across all populations or types of strokes (23). This highlights the need for more research to fully understand this dynamic.

## 1.3. Heart Failure in T2DM and Its Connection to Stroke

*1.3.1. Mechanisms Underlying CHF in T2DM*

In T2DM, altered glucose metabolism causes a shift from glucose oxidation to increased fatty acid oxidation in the heart. This metabolic shift adversely affects cardiac contractility and function, leading to both systolic and diastolic dysfunction, even in the absence of coronary artery disease (CAD) (24). Both T2DM and heart failure are associated with endothelial dysfunction, which worsen vascular function and raises the risk of ischemic events. This dysfunction reduces nitric oxide availability, further leading to increased vascular inflammation and promoting the development of atherosclerosis (25). Chronic inflammation and oxidative stress are common in both T2DM and heart failure. These factors contribute to myocardial injury, worsening cardiac dysfunction and elevating the risk of heart failure (26). Autonomic neuropathy, a common complication in diabetic patients, can lead to cardiovascular issues by disrupting heart rate variability and increasing the risk of arrhythmias. Research indicates that impaired heart rate recovery is an independent predictor of heart failure in individuals with T2DM (27).

*1.3.2. Cardioembolic Stroke from Congestive Heart Failure (CHF)*

T2DM frequently leads to CHF due to myocardial fibrosis, autonomic dysfunction, and metabolic disturbances like hyperlipidemia. CHF predisposes patients to cardioembolic strokes by creating conditions for blood stagnation and thrombus formation (28). Patients with T2DM have a higher likelihood of developing atrial fibrillation (AF), a significant contributor to cardioembolic strokes. AF raises the risk of thrombus formation in the left atrial appendage, which can then embolize and block cerebral arteries, leading to ischemic strokes (29). Both T2DM and chronic heart failure (CHF) contribute to endothelial dysfunction, which is marked by impaired vascular function and heightened inflammation. This dysfunction promotes atherosclerosis and increases the likelihood of thrombus formation, thus elevating the risk of stroke (30). Additionally, CHF results in reduced cardiac output and blood flow stagnation, especially in the left atrium, further increasing the risk of thrombus formation. These effects are compounded by the metabolic dysregulation seen in T2DM (31).

*1.3.3. Therapeutic Implications*

Recent trials have demonstrated the efficacy of SGLT2 inhibitors like empagliflozin and GLP-1 receptor agonists like liraglutide in reducing CHF incidence and subsequent stroke risk. These drugs provide dual benefits by improving glucose control and cardiovascular outcomes (Regina et al., 2023). Anticoagulation is the main preventive therapy for cardioembolic stroke, with warfarin significantly reducing ischemic stroke risk in patients with chronic nonvalvular atrial fibrillation (AF) compared to aspirin. While warfarin increases the risk of intracranial hemorrhage, it lowers the overall risk of ischemic or hemorrhagic stroke (30).

## 1.4. Acute Hyperglycemia During Ischemic Stroke

*1.4.1. Pathophysiological Impact of Acute Hyperglycemia*

Acute hyperglycemia is a common phenomenon during the early phase of acute stroke. Stroke triggers a general stress response that involves the activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated serum glucocorticoid levels, sympathetic nervous system activation, and catecholamine release. This increase in stress hormones enhances aerobic glycolysis, glucose release from gluconeogenesis and glycogenolysis, while inhibiting

glucose storage by insulin. This leads to increased secretion of glucocorticoids and catecholamines, resulting in acute hyperglycemia (28).

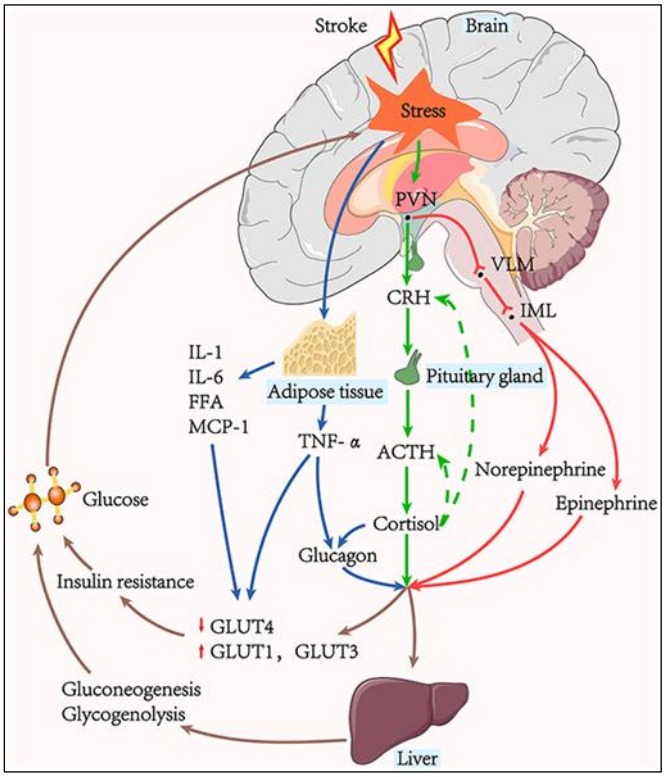


**Figure 1** Stress induced hyperglycemia pathway

Stress-induced hyperglycemia is primarily caused by hepatic gluconeogenesis, glycogenolysis, and insulin resistance. During acute ischemic stroke, the sympathoadrenal system and HPA axis are activated. Stressors trigger the adrenal medulla to release catecholamines via the PVN-VLM-IML pathway, while the HPA axis stimulates the adrenal cortex to produce cortisol. Cortisol can then stimulate glucagon release, alongside TNF-α secreted from surrounding tissues. Glycemic hormones like catecholamines, cortisol, and glucagon act on the liver to promote gluconeogenesis and glycogenolysis. This hyperglycemia further amplifies the stress response and increases pro-inflammatory factor release, perpetuating a harmful cycle (32).

### *1.4.2. Prognostic Implications*

Acute hyperglycemia is associated with larger infarct sizes, reduced salvage of the ischemic penumbra, and poorer functional recovery. Hyperglycemia at hospital admission is an independent predictor of larger ischemic damage, worse functional and cognitive outcomes, and a higher risk of mortality (33). Persistent hyperglycemia at both 6 and 24 hours after stroke onset is associated with an increased risk of mortality within 30 days (34). This condition can worsen the patient's post-stroke condition by increasing lactate production in the brain, reducing penumbra tissue salvage, enlarging the infarct area, increasing oxidative stress, triggering systemic inflammation, and enhancing blood-brain barrier permeability. Hyperglycemia in patients with intracerebral hemorrhage (ICH) can lead to poor outcomes by exacerbating hematoma expansion and perihematoma edema. Studies in rat models have shown that hyperglycemia results in more significant brain edema and increased neuronal death around the hematoma. Hyperglycemia following ICH also activates the sympathetic nervous system, leading to hormonal and metabolic changes that worsen the condition (28).

### *1.4.3. Challenges in Glycemic Control*

In the acute stroke setting, hyperglycemia is commonly managed with subcutaneous insulin using a sliding scale. Normalizing blood glucose within the first 48 hours of hospitalization has been shown to offer survival benefits for patients experiencing ischemic stroke (28). While insulin therapy is commonly employed to manage hyperglycemia, excessive insulin use may lead to hyperinsulinemia, which has been linked to increased cardiovascular risks, including exacerbation of atherosclerosis. This underscores the need for careful glucose management strategies (Després et al.,

1996). The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial assessed the effectiveness of intensive insulin therapy versus standard treatment for hyperglycemia in acute ischemic stroke (AIS) patients. The trial found that although intensive treatment targeting lower glucose levels (80-130 mg/dL) was feasible, it did not significantly improve functional outcomes compared to standard treatment (80-179 mg/dL) at 90 days post-stroke. This suggests that while managing hyperglycemia is important, overly aggressive glucose control may not lead to better outcomes and could increase the risk of hypoglycemia (35).

Alternative therapy emerges addressing insulin drawbacks in several clinical trials. While intravenous insulin is effective for rapid glucose management, subcutaneous insulin serves as a viable alternative in acute settings. Research indicates that subcutaneous insulin protocols can effectively maintain blood glucose levels below 200 mg/dL in most patients, minimizing the risks linked to rapid intravenous administration. This method may be more suitable for patients who do not need immediate or aggressive glucose reduction (36). Medications like albiglutide, dulaglutide, and exenatide present potential alternatives to insulin for managing hyperglycemia post-stroke. These agents work by enhancing insulin secretion, suppressing glucagon release, and slowing gastric emptying, helping to regulate blood glucose levels effectively while minimizing the risk of hypoglycemia often associated with insulin therapy (37).

## 2. Conclusion

Type 2 diabetes mellitus (T2DM) is a significant contributor to the pathogenesis of ischemic stroke, driven by mechanisms such as endothelial dysfunction, a prothrombotic state, and vascular remodeling. The presence of comorbid conditions, including hypertension, dyslipidemia, and obesity, amplifies the risk, underscoring the complex interplay between metabolic abnormalities and cerebrovascular disease. Acute hyperglycemia, whether stress-induced or due to poorly controlled diabetes, exacerbates stroke outcomes by increasing oxidative stress, reducing penumbra tissue salvage, and worsening infarct size.

Current management strategies, including insulin therapy, aim to control hyperglycemia during the acute stroke phase. However, evidence from clinical trials suggests that overly aggressive glucose control may not yield significant functional benefits and could increase the risk of hypoglycemia. Emerging therapies, such as GLP-1 receptor agonists and other novel agents, show promise in managing hyperglycemia with fewer adverse effects, providing a potential alternative to traditional insulin-based approaches.

This review highlights the critical importance of glycemic control in mitigating the risks and improving outcomes of ischemic stroke in T2DM patients. While progress has been made in understanding the pathophysiological mechanisms and therapeutic approaches, further research is needed to develop personalized strategies that address the multifactorial nature of hyperglycemia in stroke patients. Optimizing treatment protocols will be essential in reducing the burden of stroke and improving long-term outcomes in this ever-vulnerable present world population.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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