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Review

The Role of Obstructive Sleep Apnea and Diabetes Mellitus in the Development of Cerebrovascular Complications: A Narrative Review

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Abstract

Background: Cerebrovascular accidents (stroke) remain a leading global cause of death and disability, with its burden increasingly overlapping the rising prevalence of obstructive sleep apnea (OSA) and diabetes mellitus (DM). These highly prevalent cardiometabolic conditions frequently coexist and may jointly amplify cerebrovascular risk through shared and interacting pathophysiologic pathways. This narrative review synthesizes current evidence on the independent and combined contributions of OSA and DM to cerebrovascular complications, with emphasis on mechanisms, stroke outcomes and implications for screening and integrated management. Methods: A narrative review was conducted using PubMed, MEDLINE, and the Cochrane Library to identify English-language articles published between January 2000 and December 2024. Search terms combined OSA or sleep-disordered breathing with stroke or cerebrovascular disease and DM or hyperglycemia. Secondary searches targeted mechanistic domains including intermittent hypoxia, insulin resistance, metabolic syndrome, atrial fibrillation, hypercoagulability, and bariatric surgery. Priority was given to systematic reviews and meta-analyses, randomized controlled trials, and large prospective cohort studies, with smaller studies included when mechanistically informative. Findings were synthesized thematically across OSA-related mechanisms, DM-related mechanisms, bidirectional interactions, combined risk through metabolic syndrome, stroke outcomes, and clinical management considerations. Results: OSA is associated with increased cerebrovascular risk through intermittent hypoxemia-related oxidative stress and inflammation, sympathetic activation with blood pressure surges and sustained hypertension, endothelial dysfunction and atherosclerosis, impaired cerebral autoregulation, arrhythmogenesis, particularly atrial fibrillation and prothrombotic changes. DM increases stroke risk via accelerated atherosclerosis, cerebral small vessel disease, endothelial injury, hypercoagulability, glycemic variability, and cardioembolic mechanisms. Evidence indicates that coexisting OSA and DM are common and associated with greater vascular injury markers, higher rates of cerebrovascular events, and poorer post-stroke recovery. Conclusions: OSA and DM contribute to cerebrovascular complications through convergent mechanisms centered on metabolic syndrome, obesity, inflammation, vascular dysfunction,

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and thrombosis. These findings support proactive screening and coordinated management strategies to reduce cerebrovascular risk and improve outcomes.

Keywords: obstructive sleep apnea; diabetes mellitus; stroke; cerebrovascular complications

1. Introduction

Cerebrovascular accident (CVA) or stroke represents one of the most significant global health challenges of the twenty-first century. According to the Global Burden of Disease 2021 study, CVA remains the second leading cause of death worldwide, accounting for approximately 7.3 million deaths annually, and the third leading cause of death and disability combined, responsible for over 160 million disability-adjusted life-years (DALYs) [1]. Each year, nearly 12 million individuals develop a new CVA, and more than 93 million people are living with the consequences of prior cerebrovascular events [1]. The global economic burden of CVA exceeds US$890 billion annually, representing 0.66% of global gross domestic product [1]. Perhaps most concerning is the fact that the absolute burden of stroke has increased substantially over the past three decades, with incident CVA rising by 70%, CVA-related deaths by 44%, and prevalence of CVA by 86% between 1990 and 2021, with the majority of this burden concentrated in low- and middle-income countries [1].

Obstructive sleep apnea (OSA) is a chronic sleep disorder characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, resulting in intermittent hypoxemia, sleep fragmentation, and excessive daytime somnolence. Population-based studies estimate that OSA affects 10–30% of adults, more so among those with cardiometabolic diseases [2]. Despite its high prevalence, OSA remains significantly underdiagnosed, with epidemiological surveys suggesting that 80–90% of affected individuals have not received a formal diagnosis [3].

Diabetes mellitus (DM) has reached pandemic proportions globally. Current estimates indicate that more than 530 million adults are living with diabetes, with projections suggesting this number will rise to 783 million by 2045 [4]. Type 2 DM accounts for approximately 90% of all cases and shares many risk factors with OSA, including obesity, sedentary lifestyle, and advancing age. Importantly, the coexistence of OSA and type 2 DM is exceedingly common: studies indicate that 58–86% of individuals with type 2 DM have some degree of OSA, while 15–30% of those with OSA have concurrent DM [5,6].

The relationship between OSA and DM is bidirectional. OSA promotes metabolic dysfunction through several mechanisms: intermittent hypoxemia in OSA triggers sympathetic activation and hypothalamic–pituitary–adrenal axis dysregulation, leading to elevated catecholamines and cortisol that impair insulin sensitivity and promote hepatic gluconeogenesis [1]. Chronic intermittent hypoxia also induces inflammatory remodeling of visceral adipose tissue, promoting a proinflammatory adipokine profile and further impairing insulin signaling [7,8]. These pathways contribute to nocturnal glucose dysregulation and β-cell dysfunction, ultimately increasing the risk of developing type 2 DM. Conversely, DM may worsen OSA through diabetic autonomic neuropathy affecting upper airway reflexes and central respiratory control, as well as through shared upstream drivers such as obesity [5].

Both OSA and DM independently increase the risk of CVA through multiple interrelated mechanisms. OSA mediates the increase in risk of CVA predominantly through ischemic pathways. A meta-analysis of prospective studies found that OSA was associated with a 2.24-fold increased risk of incident stroke, with this association particularly pronounced in men [9]. The mechanisms underlying this association include chronic

intermittent hypoxemia-generating reactive oxygen species and promoting endothelial dysfunction, blood pressure surges and sustained hypertension (HTN) from sympathetic overactivation, and cardiac arrhythmogenesis, particularly atrial fibrillation (AF), thus promoting cardioembolic events [10]. While OSA has been associated with both ischemic and hemorrhagic stroke in population studies, the preponderance of evidence suggests that the increased risk is driven primarily by ischemic stroke subtypes, with sleep-disordered breathing present in up to 72% of both ischemic and hemorrhagic stroke patients and predominantly obstructive in nature [11] Some data suggest that patients with ischemic stroke have higher apnea-hypopnea indices compared with hemorrhagic stroke patients, consistent with a stronger pathophysiological link between OSA and ischemic mechanisms [12].

DM similarly increases stroke risk through mechanisms that promote vascular injury and thrombosis. Population-based studies demonstrate that DM approximately doubles the risk of ischemic stroke, with women experiencing a greater excess risk compared with men [13]. DM-associated risk of CVA occurs from accelerated atherosclerosis of large cerebral vessels, microvascular injury producing lacunar infarcts and white matter disease, a prothrombotic state characterized by elevated clotting factors and impaired fibrinolysis, and promotion of AF [14–17]. Recent Mendelian randomization studies have provided genetic evidence supporting a causal relationship between type 2 DM and cerebral small vessel disease, particularly lacunar stroke [15].

Central to understanding the convergence of OSA and DM on cerebrovascular risk is the concept of metabolic syndrome (MetS). MetS, defined by the clustering of central obesity, HTN, dyslipidemia (DLD), and insulin resistance, is highly prevalent among individuals with both OSA and DM. Large cohort and meta-analytic studies demonstrate that MetS confers a 1.5 to 2-fold higher incidence of stroke compared with individuals without the syndrome [18]. Importantly, obesity serves not only as a shared upstream driver of both OSA and DM but also as an independent risk factor for AF. Population data indicate that obesity increases AF risk by approximately 50%, with mechanisms including atrial structural remodeling, epicardial adipose tissue expansion and associated inflammatory cytokine release, and metabolic perturbations including insulin resistance [19,20].

When OSA and DM coexist, they appear to exert synergistic rather than merely additive effects on cerebrovascular risk. Patients with both conditions exhibit higher levels of inflammatory biomarkers, more pronounced endothelial dysfunction, and increased carotid intima-media thickness compared with those with either condition alone [6,21,22]. Large cohort studies have demonstrated that individuals with type 2 DM who develop OSA have substantially higher rates of cardiovascular and cerebrovascular events than matched patients with DM alone [23].

Beyond their role in stroke incidence, OSA and DM also adversely affect stroke outcomes. OSA is present in 44–95% of patients following stroke and transient ischemic attack, and its presence is associated with larger infarct volumes, poorer functional recovery, and increased mortality [24–26]. DM similarly worsens stroke prognosis: hyperglycemia at stroke onset is linked to larger infarcts, increased hemorrhagic transformation risk, and higher in-hospital mortality, while chronic DM is associated with impaired neurological recovery and a 50% higher risk of stroke recurrence [27–29].

This review synthesizes the current evidence on the pathophysiological mechanisms by which OSA and DM independently and synergistically increase stroke risk, with particular attention to the unifying role of metabolic syndrome and the contributions of obesity and insulin resistance. We examine the impact of OSA on stroke outcomes, discuss therapeutic and preventive implications including bariatric surgery, and outline clinical implications for screening and integrated management of these frequently coexisting conditions.

2. Methods

This narrative review was conducted to synthesize the available evidence on the role of OSA and DM in the development of cerebrovascular complications. We systematically searched PubMed, MEDLINE, and the Cochrane Library for English-language articles published from January 2000 through December 2024. The primary search strategy combined the following terms: ("obstructive sleep apnea" OR "sleep-disordered breathing") AND ("stroke" OR "cerebrovascular disease" OR "transient ischemic attack") and ("diabetes mellitus" OR "type 2 diabetes" OR "hyperglycemia") AND ("stroke" OR "cerebrovascular disease"). Secondary searches included terms for specific mechanistic pathways, including "intermittent hypoxia," "insulin resistance," "metabolic syndrome," "atrial fibrillation," "hypercoagulability," and "bariatric surgery." Reference lists of identified articles were hand-searched to identify additional relevant publications.

Studies were selected based on their relevance to the pathophysiological mechanisms linking OSA and DM to stroke risk, epidemiological data on disease associations, and clinical implications for screening and management. Priority was given to systematic reviews and meta-analyses, randomized controlled trials, and large prospective cohort studies. Case reports and small case series were generally excluded unless they provided unique mechanistic insights. Two authors independently reviewed titles and abstracts, with disagreements resolved by consensus.

The data extracted from included studies were organized into thematic sections addressing: (1) mechanisms by which OSA increases stroke risk; (2) the role of bariatric surgery as a therapeutic intervention; (3) OSA's impact on stroke outcomes; (4) mechanisms linking DM to stroke; (5) the bidirectional relationship between OSA and DM; (6) combined effects of OSA and DM on cerebrovascular risk through the framework of metabolic syndrome; and (7) clinical implications for screening and management.

Key findings from landmark studies are summarized in Table 1.

Table 1. Landmark studies on the role of OSA and Diabetes on Stroke Risk and Outcomes.

Title	Reference	Study Population and Design	Main Result
Role of Obstructive Sleep Apnea in Risk of Stroke			
Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome	Ryan et al., 2005 [30]	Prospective experimental human study with controlled intermittent hypoxia in OSA patients	Intermittent hypoxia in OSA selectively activates inflammatory pathways (NFκB)
Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension	Pedrosa et al., 2011 [31]	Cross-sectional study of 125 patients with hypertension undergoing polysomnography	OSA was the most common secondary cause of resistant hypertension
Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation	Gami et al., 2007 [32]	Retrospective cohort of 3542 adults undergoing polysomnography with 4.7-year follow-up.	OSA independently predicted incident atrial fibrillation
How does obstructive sleep apnea alter cerebral hemodynamics?	Gregori-Pla et al., 2023 [33]	Prospective physiologic study using cerebral perfusion and oxygenation monitoring in severe OSA	Apneas caused cyclic cerebral hypoxia and hypo-/hyperperfusion

Table 1. *Cont.*

Title	Reference	Study Population and Design	Main Result
Relationship between sleep-breathing events induced nocturnal blood pressure surge and sympathetic nervous activity in patients with obstructive sleep apnea	Sun et al., 2025 [34]	Cross-sectional study of OSA patients with polysomnography, BP monitoring, HRV, and norepinephrine	Nocturnal BP surges correlated with elevated sympathetic activity in OSA
Evaluation of Fibrinolytic Inhibitors: Alpha-2-Antiplasmin and Plasminogen Activator Inhibitor 1 in Patients with Obstructive Sleep Apnoea	Zakrzewski et al., 2016 [35]	Cross-sectional case-control study OSA patients	OSA patients had elevated α2-antiplasmin and PAI-1, indicating impaired fibrinolysis
Therapeutic and preventive implications: Bariatric Surgery			
The effect of bariatric surgery on ischemic stroke risk Obstructive Sleep Apnea: The Effect of Bariatric Surgery After Five Years-A Prospective Multicenter Trial	Williams et al., 2021 [19] Peromaa-Haavisto et al., 2024 [36]	Retrospective matched national claims cohort with up to 5-year follow-up Prospective cohort with baseline, 1-year, and 5-year sleep recordings after laparoscopic Roux-en-Y gastric bypass	Bariatric surgery significantly reduced 1- and 5-year ischemic stroke risk AHI decreased from 28 to 9 events per hour, with 55% achieving remission at 5 years
Impact of OSA on stroke outcomes			
Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up	Sahlin et al., 2008 [37]	Prospective cohort of stroke rehabilitation patients with 10-year follow-up	OSA independently increased long-term mortality
Effect of upper airway obstruction in acute stroke on functional outcome at 6 months	Turkington et al., 2004 [38]	Prospective cohort of acute stroke patients studied within 24 h and followed 6 months	Severity of early airway obstruction predicted higher mortality, dependency, and worse disability
Impact of DM on Stroke Outcomes			
Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes	Peters et al., 2014 [13]	Systematic review and meta-analysis of 64 prospective population-based cohort studies; 775,385 individuals; 12,539 strokes	DM associated with ~2× increased stroke risk (RR 2.28 in women, 1.83 in men); women with DM have 27% greater excess stroke risk than men (RRR 1.27; 95% CI 1.10–1.46)
Causal Impact of Type 2 Diabetes Mellitus on Cerebral Small Vessel Disease: A Mendelian Randomization Analysis	Liu et al., 2018 [15]	Two-sample Mendelian randomization using GWAS summary data; 5 CSVD phenotypes including lacunar stroke (n = 2191/27,297) and radiological markers	T2DM causally associated with lacunar stroke (OR 1.15; 95% CI 1.04–1.28; $p = 0.007$) and lower fractional anisotropy (OR 0.78; 95% CI 0.66–0.92; $p = 0.004$)

Table 1. *Cont.*

Title	Reference	Study Population and Design	Main Result
Stress Hyperglycemia and Prognosis of Stroke in Nondiabetic and Diabetic Patients: A Systematic Overview	Capes et al., 2001 [27]	Systematic review and meta-analysis of 32 cohort studies; patients with ischemic or hemorrhagic stroke; outcomes: in-hospital/30-day mortality and functional recovery	Admission hyperglycemia (>6–8 mmol/L) associated with 3.07× increased mortality (95% CI 2.50–3.79) in non-diabetics; 1.41× increased risk of poor functional recovery (95% CI 1.16–1.73) in non-diabetic stroke survivors
Type 2 diabetes is associated with a worse functional outcome of ischemic stroke	Tziomalos et al., 2014 [28]	Prospective cohort study of consecutive ischemic stroke patients; comparison of outcomes by diabetes status	T2DM independently associated with ~2× higher risk of significant disability or death at discharge (OR 2.23; 95% CI 1.25–3.98) despite similar initial stroke severity
Diabetes As an Independent Risk Factor for Stroke Recurrence in Ischemic Stroke Patients: An Updated Meta-Analysis	Zhang et al., 2021 [29]	Systematic review and meta-analysis of 27 population-based studies; ischemic stroke survivors; follow-up for recurrent stroke	DM associated with 50% greater hazard of recurrent stroke (pooled HR 1.50; 95% CI 1.36–1.65; I^2 = 61%); lacunar stroke subgroup HR 1.65 (95% CI 1.41–1.92)
Risk of Ischemic and Hemorrhagic Stroke in Individuals With Type 1 and Type 2 Diabetes: A Nationwide Cohort Study in Sweden	Mavridis et al., 2025 [39]	Nationwide cohort study using Swedish National Diabetes Register (2005–2019); 47,720 T1DM and 686,158 T2DM patients matched to 2.2 million controls	T1DM: ischemic stroke HR 2.54 (95% CI 2.36–2.73), hemorrhagic stroke HR 1.88 (95% CI 1.57–2.26); T2DM: ischemic stroke HR 1.37 (95% CI 1.35–1.38), no significant hemorrhagic stroke risk
Long-term glycemic variability and risk of stroke in patients with diabetes: a meta-analysis	Ren et al., 2022 [40]	Meta-analysis of cohort studies examining HbA1c and fasting glucose variability in diabetic patients	Greater long-term variability in HbA1c and fasting glucose associated with ~1.8-fold higher stroke risk compared with lowest variability

3. Mechanisms by Which Obstructive Sleep Apnea Increases the Risk of Stroke

OSA is a chronic sleep disorder defined by recurrent episodes of partial or complete upper-airway obstruction during sleep, resulting in reduced airflow, oxygen desaturation, and sleep fragmentation [7]. OSA frequently coexists with type 2 diabetes mellitus (T2DM), and its prevalence increases with cardiometabolic disease burden [2,5]. OSA is strongly associated with major cardiovascular diseases—including ischemic heart disease (IHD), stroke or transient ischemic attack (TIA), heart failure, and AF—in individuals with T2DM, independent of traditional factors [23].

There are several pathophysiological mechanisms that increase the risk of developing cerebrovascular accidents in the setting of OSA.

Chronic Intermittent Hypoxemia and Oxidative Stress: Each episode of apnea (complete cessation of breathing) or hypopnea (partial cessation of breathing) in OSA results in transient hypoxemia followed by rapid reoxygenation. These cyclical oxygen perturbations result in the generation of reactive oxygen species and widespread oxidative stress, inflicting significant damage to various tissues, notably the vascular endothelium [30]. The endothelial injury induced by oxidative stress is a key trigger in atherogenesis, promoting the formation and destabilization of atherosclerotic plaques and predisposing individuals to cerebrovascular events [21,30]. Pro-inflammatory cytokines, such as TNF-α and acute phase reactants including C-reactive protein (CRP), are elevated in OSA and are implicated in further promoting endothelial dysfunction, systemic inflammation, and atherosclerosis progression [8,30].

***Blood Pressure Surges and Sustained Hypertension*:** Apneic episodes are associated with marked surges in sympathetic nervous system activity, leading to transient increases in blood pressure during apneas and arousals [10]. Over months to years, this chronic sympathetic overactivity contributes to persistent, often nocturnal, HTN—a key modifiable stroke risk factor [31]. Epidemiological research confirms the independent association between OSA and the development of HTN; and the severity of OSA correlates with both the incidence and resistance of HTN, especially evident in non-dipper overnight blood pressure profiles [2,31,41]. Aldosterone may contribute to HTN in OSA, particularly in patients with resistant HTN. Mineralocorticoid excess can promote sodium and water retention, amplify sympathetic and renin–angiotensin–aldosterone system activity, and worsen endothelial dysfunction, thereby sustaining elevated blood pressure. Aldosterone may also worsen OSA via overnight rostral fluid shift and parapharyngeal fluid accumulation, increasing upper airway collapsibility during sleep [42,43].

Cardiac Stress and Arrhythmogenesis: The negative intrathoracic pressure and the intermittent hypoxemia seen in OSA impose mechanical and metabolic stress on the myocardium and epicardial adipose tissue [8]. Such repetitive insult promotes structural heart changes, such as atrial enlargement and fibrosis, and facilitates the development of AF, which is recognized as a potent etiological factor for cardioembolic stroke [44,45]. Cohort data indicate an increased incidence of AF in OSA patients, and this risk is further amplified in those with concurrent risk factors like obesity or DM [32,46].

Impaired Cerebral Blood Flow Regulation: OSA-induced changes in arterial blood gases (O_2 and CO_2) alter cerebral autoregulation. After an apneic episode, the abrupt restoration of breathing can result in surges and drops in cerebral blood flow, entropy in autoregulatory mechanisms, and transient cerebral ischemia [33,47]. Particularly, patients with moderate to severe OSA lack the normal buffering protection against these fluctuations, predisposing them to small vessel disease and increased ischemic risk [37,47].

***Autonomic Dysfunction and Sympathetic Overdrive*:** OSA is characterized by pronounced activation of the sympathetic nervous system, contributing to both blood pressure variability and increased heart rate. The chronicity of this overactivation leads to persistently elevated vascular tone and hypertensive surges, compounding stroke risk. Frequent arousals during sleep further exacerbate sympathetic overdrive, creating a feedback loop of vascular stress [10,34,48].

Hypercoagulability and Thromboembolic Risk: OSA is associated with a prothrombotic and hypercoagulable state [35]. Recurrent hypoxemia elevates hematocrit, increases platelet aggregability, and enhances levels of clotting factors, which can collectively promote thrombosis. This facilitates both local and embolic cerebrovascular events, thereby amplifying stroke risk [35,49].

4. Impact of OSA on Stroke Outcomes

***Poorer Recovery and Functional Outcomes*:** While OSA is primarily recognized as a risk factor for stroke, it may also negatively influence post-stroke prognosis. Growing evidence indicates that OSA is highly prevalent in the subacute phase following stroke, with estimates ranging from 44% to 95% of stroke patients affected. Previous studies have demonstrated that post-stroke patients with sleep apnea exhibit significantly greater impairments in activities of daily living (ADLs), higher levels of delirium and depressed mood, and increased ADL dependency compared to those without sleep apnea; these differences remained after accounting for age, sex, body mass index, and comorbid ischemic heart disease [50]. Additionally, the severity of upper airway obstruction in the first 24 h after stroke independently predicts increased disability at 6 months, as shown by lower Barthel index scores, and a higher rate of institutionalization and dependency. The pathophysiology is multifactorial: OSA-related intermittent hypoxemia, fluctuations in cerebral blood flow, and blood pressure lability may exacerbate neurological injury in the vulnerable penumbral tissue after stroke, further impeding recovery. These studies collectively support that sleep-disordered breathing is not just a concurrent morbidity, but a key determinant of poorer cognitive and functional outcomes after stroke [38].

Epidemiology and Increased Risk of Recurrence and Mortality: *OSA* is now recognized as an independent predictor of stroke irrespective of other traditional risk factors such as HTN, DM, or obesity [23,51]. Both cross-sectional and longitudinal studies show that patients with stroke are more likely to have undiagnosed or untreated OSA; and severity of OSA independently predicts both incident and recurrent stroke [51,52]. A prolonged ten-year follow-up cohort study reported that survivors of stroke with moderate to severe OSA (apnea-hypopnea index $\geq$ 15) had a significantly increased risk of early mortality, independent of age, obesity, smoking status, blood pressure, DM, and cognitive impairment [37]. Similar results have been observed across multiple patient populations and in patients with both type 1 and type 2 DM [23,53,54]. Previous studies also established that greater severity of upper airway obstruction in acute stroke is independently associated with both increased mortality and higher rates of dependency at 6 months, with each unit increase in the respiratory disturbance index leading to a significant rise in risk [38]. Notably, Sahlin's work differentiates between obstructive and central sleep apnea, reported that only OSA (not central sleep apnea) is independently related to excess mortality after stroke, suggesting a unique pathophysiological role for OSA-related mechanisms, such as nocturnal hypoxemia and cardiovascular stress [37]. Although the cited studies did not directly quantify the rate of recurrent stroke, elevated long-term mortality in OSA underscores its substantial contribution to adverse post-stroke outcomes.

5. Therapeutic and Preventive Implications: Bariatric Surgery

Obesity occupies a central position in the pathophysiology linking OSA to adverse cerebrovascular outcomes. As a shared upstream driver of OSA severity and multiple cardiometabolic risk factors, including HTN, AF, and a prothrombotic state, obesity modulates the vascular and cerebrovascular risk and therefore represents a rational therapeutic target for metabolic intervention [24–26]. Consistent with this framework, OSA in the presence of a body mass index (BMI) $\geq$ 35 kg/m^2 is recognized as an eligibility criterion for bariatric weight loss surgery, reflecting the established contribution of sleep-disordered breathing to cardiometabolic risk [55]. Bariatric surgery has been shown to substantially improve OSA severity, with remission (defined as normalization of the apnea–hypopnea index (AHI < 5 events/hour)), occurring in approximately 45–65% of patients within 1–5 years after surgery [36]. Nevertheless, moderate-to-severe OSA persists in 20–35% of cases, underscoring the contribution of other anatomical and neuromuscular factors, beyond obesity

to residual disease. Improvements in OSA severity following surgery correlate closely with reductions in BMI, neck circumference, and visceral adiposity, and are accompanied by increased pharyngeal cross-sectional area and improved pulmonary mechanics [3]. Beyond its effects on sleep-disordered breathing, bariatric surgery is also associated with favorable cardiovascular outcomes. Large population-based studies demonstrate a significantly lower risk of ischemic stroke at both 1 and 5 years among patients undergoing metabolic and bariatric surgery compared with matched, surgery-eligible nonsurgical controls [19,56]. In this context, bariatric surgery may represent an effective strategy to mitigate stroke risk by addressing obesity-driven OSA and its downstream cardiometabolic consequences, complementing conventional approaches to cardiovascular risk reduction.

6. Diabetes Mellitus and the Increased Risk of Stroke

DM (both type 1 and type 2) is a well-established risk factor for stroke. Epidemiological studies indicate that adults with DM are about twice as likely to experience a stroke compared to those without DM [13]. This elevated risk applies to both ischemic strokes and (to a lesser extent) hemorrhagic strokes. Notably, recent cohort data suggest that individuals with type 1 diabetes mellitus (T1DM) may have an even higher relative risk of stroke (e.g., >2-fold for ischemic stroke) than those with T2DM when compared to non-diabetic controls [39]. The mechanisms by which DM predisposes to stroke are multifactorial, involving both chronic vascular damage and acute pathophysiological changes. DM contributes to stroke risk through endothelial dysfunction, atherosclerosis, HTN, small vessel disease, hypercoagulability, and cardioembolic factors. We also examine the impact of DM on stroke severity, outcomes, and recurrence.

7. Pathophysiological Mechanisms Linking Diabetes to Stroke

Endothelial Dysfunction and Atherosclerosis: Chronic hyperglycemia in DM causes injury to the vascular endothelium, the inner lining of blood vessels. High glucose levels trigger oxidative stress and inflammation in endothelial cells, impairing their function. One consequence is reduced bioavailability of nitric oxide, a key vasodilator and anti-thrombotic molecule produced by healthy endothelium. Diminished nitric oxide and other endothelial changes lead to loss of normal vascular tone control and a pro-inflammatory, "sticky" endothelium prone to attracting immune cells and platelets [14]. Over time, this endothelial dysfunction promotes the development of atherosclerosis—the buildup of fatty plaques in arterial walls. DM is often characterized by chronic low-grade inflammation and DLD (high triglycerides, low HDL, small dense LDL particles), which accelerate atherosclerotic plaque formation in both extracranial and intracranial arteries. Indeed, macrovascular complications of DM are typified by earlier and more extensive atherosclerosis in arteries supplying the heart, brain, and limbs [14]. In cerebral circulation, such plaque buildup can narrow or occlude critical arteries (like the carotids and intracerebral arteries), directly increasing the risk of ischemic stroke due to thrombotic or thromboembolic events.

Hypertension and Vascular Injury: DM and HTN commonly coexist, and each condition exacerbates the other's impact on the vasculature. Persistent hyperglycemia contributes to arterial stiffness by promoting collagen cross-linking (via advanced glycation end-products) and reducing the elasticity of blood vessels. This stiffness, along with diabetic nephropathy-related fluid retention, often leads to elevated blood pressure in people with DM. Conversely, HTN accelerates diabetic vascular damage by imposing high shear stress on already-compromised endothelial walls. The combination of DM and high blood pressure greatly increases the risk of stroke. In DM, the small arteries and arterioles are particularly vulnerable: hyperglycemia-induced damage to these vessels (including in the brain) causes hyaline arteriosclerosis and makes them less responsive to autoregulation

of blood flow. Thus, patients with DM not only have a higher prevalence of HTN, but the deleterious effects of high blood pressure on the brain's vasculature are more pronounced, compounding stroke risk.

Cerebral Small Vessel Disease: Beyond large-artery atherosclerosis, DM also injures the microcirculation in the brain. Chronic hyperglycemia causes thickening of capillary basement membranes and perivascular fibrosis in the cerebral microvasculature, analogous to changes seen in diabetic retinopathy and nephropathy [14]. These changes are part of cerebral small vessel disease and can lead to lacunar infarcts (small, deep ischemic strokes) as well as diffuse white matter damage. Supporting this, genetic evidence from a Mendelian randomization study indicates that T2DM may be causally associated with an increased burden of small vessel ischemic disease, particularly lacunar stroke subtype [15]. Diabetic microangiopathy in the brain can manifest as multiple tiny infarcts, white matter hyperintensities on MRI, and breakdown of the blood–brain barrier. These small vessel changes not only cause lacunar strokes (which account for a significant fraction of ischemic strokes) but also contribute to vascular cognitive impairment. In summary, diabetes-induced microvascular pathology in the brain is another pathway elevating stroke risk.

Hypercoagulability in Diabetes Mellitus: DM is known to create a prothrombotic (hypercoagulable) state that favors clot formation, further raising the risk of ischemic stroke. Multiple abnormalities in coagulation and fibrinolysis have been documented in people with DM For example, DM is associated with elevated plasma levels of several clotting factors (such as fibrinogen, factor VII, factor VIII, and von Willebrand factor) and increased activation of platelets [16]. At the same time, key endogenous anticoagulant and fibrinolytic factors are impaired: levels of protein C (an anticoagulant) are often reduced, and plasminogen activator inhibitor-1 (PAI-1) is elevated, leading to slower breakdown of clots [16]. Platelets in individuals with DM tend to be hyperreactive—they aggregate more easily and secrete more prothrombotic mediators. The endothelial dysfunction mentioned above also contributes to this state by reducing anti-thrombotic surface properties. The net effect of these changes is that people with DM have blood that clots more readily and clots that are more resistant to lysis. This increased coagulation tendency means that an atherosclerotic plaque or arterial injury is more likely to precipitate an obstructive thrombus, and circulating clots (emboli) can form more easily, potentially occluding cerebral arteries.

Insulin Resistance and Stroke Risk: Insulin resistance, characterized by impaired cellular response to insulin signaling, represents an independent risk factor for CVA even in people without DM. Insulin resistance promotes risk of CVA through multiple mechanisms, including acceleration of atherosclerosis, enhanced platelet activation and thrombosis, and exacerbation of endothelial dysfunction. Studies have demonstrated that insulin resistance is associated with increased stroke risk in both populations with and without DM, with individuals with insulin resistance showing approximately 45% higher risk of ischemic stroke compared to insulin-sensitive controls [57]. Furthermore, insulin resistance adversely affects stroke outcomes and recovery, independent of diabetes status.

Cardiac Factors and Cardioembolic Stroke: DM often coexists with or contributes to cardiac conditions that can cause cardioembolic strokes. Notably, DM is an independent risk factor for AF, the most common arrhythmia linked to stroke. Population studies and meta-analyses have shown that patients with DM have approximately a 30–40% higher risk of developing AF compared to those without DM [17]. AF can lead to formation of thrombi in the heart (particularly the left atrial appendage), which can embolize to the cerebral circulation and cause ischemic stroke. DM may promote AF through mechanisms such as atrial fibrosis, autonomic dysfunction, and shared risk factors (e.g., HTN and obesity). In addition, DM is frequently associated with coronary artery disease (CAD) and heart failure. A history of myocardial infarction or significant left ventricular dysfunction in patients

with DM can lead to mural thrombus formation in the heart, another potential source of emboli to the brain. Thus, DM contributes to stroke risk not only via direct vascular injury but also indirectly by increasing the prevalence of cardioembolic sources of stroke (like AF and ischemic cardiomyopathy). It is worth noting that DM is included as a risk factor in stroke risk scoring systems for AF (e.g., CHA2DS2-VASc score), underlining its recognized role in cardioembolic stroke risk stratification.

Glycemic variability: Beyond average glycemia, glycemic variability (fluctuations in glucose over time) may contribute to cerebrovascular risk. In a meta-analysis, greater long-term variability in glycated hemoglobin (HbA1c) and fasting glucose was associated with an approximately 1.8-fold higher risk of stroke compared with the lowest variability [40]. This may be especially relevant in patients with OSA, which has been associated with increased glucose variability [58]. As continuous glucose monitoring (CGM) becomes more widely used, CGM-derived metrics (for example, glucose variability indices and time spent in and out of target range) may help refine risk assessment beyond HbA1c alone and may partially explain heterogeneity in stroke risk and outcomes among patients with DM [58].

8. Impact of Diabetes on Stroke Outcomes

DM not only predisposes individuals to stroke but also adversely affects stroke severity and outcomes when strokes occur. Clinical studies have observed patients with DM tend to have worse outcomes and higher complication rates after stroke than in people without DM [59]. One important factor is hyperglycemia at the time of stroke onset. Elevated blood glucose is common during acute stroke in people with DM (and can occur as a stress response in others), and it has been linked to larger infarct sizes, increased neuronal damage, and a higher risk of hemorrhagic transformation of an ischemic stroke. A meta-analysis of stroke patients found that admission hyperglycemia was associated with markedly increased in-hospital mortality, especially in patients without DM (a more than three-fold higher risk of death vs. normoglycemia) [27]. In patients with DM, who often present with high glucose, persistent hyperglycemia in the acute phase impairs the brain's ability to withstand ischemia—exacerbating processes like lactic acidosis, edema, and reperfusion injury. This can translate into more severe neurologic deficits and complications (such as increased intracranial pressure) in the days following the stroke. Moreover, chronic hyperglycemia can lead to poor collateral circulation development. Some data suggest that while baseline stroke severity (e.g., NIH stroke scale score on admission) may be similar between people with and without DM, people with DM have a lower likelihood of favorable recovery. For instance, a prospective study found that T2DM was independently associated with worse functional outcomes at discharge (approximately double the risk of significant disability or death) despite similar initial stroke severity [28]. Thus, DM appears to impair post-stroke neurological recovery, potentially due to factors like aggravated brain injury, comorbidities, and less effective rehabilitation (perhaps from diabetic complications affecting mobility or healing).

Another concerning aspect is that patients with DM have a higher risk of stroke recurrence. DM contributes to the progression of atherosclerosis and small vessel disease even after an initial stroke, and it often clusters with other uncontrolled risk factors, creating a milieu for recurrent events. A comprehensive meta-analysis of longitudinal studies in stroke survivors demonstrated that DM is associated with about a 50% greater hazard of recurrent stroke compared to non-diabetic patients with prior stroke [29]. In other words, a stroke patient with diabetes is significantly more prone to have another stroke in subsequent years. This emphasizes the need for aggressive secondary prevention in people with DM. Furthermore, in-hospital and long-term mortality after stroke are higher in patients with DM than those without DM, reflecting both the acute impact of hyperglycemia and the

chronic multi-organ burden of DM. Even among stroke patients without a known history of DM, those who experience stress hyperglycemia during the acute event tend to have poorer outcomes, suggesting that hyperglycemia itself (whether due to undiagnosed DM or acute stress) is a mediator of brain injury [27].

In summary, DM plays a powerful role in increasing stroke risk through multiple interrelated mechanisms. It damages large and small blood vessels, promotes thrombosis, and often co-occurs with other deleterious conditions like HTN and AF. When strokes occur in patients with DM, they are more likely to be severe and to result in worse functional outcomes, with an elevated chance of recurrence. These insights underscore the importance of diligent management of DM and associated cardiovascular risk factors to prevent stroke. They also highlight the need for careful monitoring and aggressive treatment (e.g., control of blood glucose, blood pressure, and use of antithrombotic therapy) in the acute stroke setting and afterward, to improve outcomes for patients with DM.

9. Combined Effects of Obstructive Sleep Apnea and Diabetes Mellitus on Cerebrovascular Risk

Inflammatory and Oxidative Stress Pathways: Patients with both OSA and DM show a more adverse inflammatory and atherogenic profile than those with either condition alone. In T2DM cohorts, the presence of OSA is associated with higher CRP and more atherogenic lipid indices, translating into about a 6-percentage-point higher predicted 10-year CAD risk on the UKPDS engine compared with T2DM patients without OSA [6]. Reviews integrating biomarker studies report that comorbid OSA and DM are characterized by higher circulating pro-inflammatory cytokines and unfavorable adipokine patterns than isolated OSA or DM, consistent with a more unstable vascular milieu that favors plaque rupture and ischemic cerebrovascular events [22].

Synergistic Vascular Damage: Patients with T2DM who subsequently develop OSA have a substantially higher burden of vascular events than matched patients with DM alone, with adjusted hazard ratios of 1.54 for composite cardiovascular disease and 1.57 for stroke or transient ischemic attack in a large U.K. primary care cohort [23]. A systematic review and meta-analysis including 582,267 participants similarly found that the coexistence of DM and sleep disorders increased the risk of cardiovascular disease events by 27 percent and stroke by 28 percent compared with DM without sleep disorders [60]. Contemporary reviews in populations with DM conclude that OSA and DM exert synergistic effects on cardiovascular complications, describing this overlap as a distinct high-risk phenotype that accelerates macrovascular disease and worsens cerebrovascular prognosis [5].

10. Role of Metabolic Syndrome in Compounding Risk of Stroke with Both OSA and Diabetes Mellitus

OSA and DM frequently coexist and, when present together, they produce a more severe cardiometabolic and cerebrovascular risk profile than either condition alone. Patients with both disorders exhibit higher levels of inflammatory biomarkers, more pronounced endothelial dysfunction, and increased carotid intima–media thickness, indicating a more aggressive vasculopathic phenotype [6,21–23]. These shared abnormalities lead to impaired cerebrovascular reactivity and increase the likelihood of future ischemic events, underscoring that the combination of OSA and DM exerts synergistic rather than additive vascular harm [6,21–23].

This amplified cerebrovascular vulnerability is best understood through the framework of metabolic syndrome (MetS), which links these overlapping conditions. MetS is highly prevalent among individuals with OSA and DM and is defined by central obesity, HTN, DLD, and insulin resistance, each of which independently increases stroke risk [18].

Large cohort and meta-analytic studies show that MetS confers a 1.5 to 2-fold higher incidence of stroke compared with individuals without the syndrome [18]. OSA promotes metabolic dysfunction by increasing sympathetic activity, impairing insulin sensitivity, and promoting visceral adiposity, while DM accelerates DLD, oxidative stress, and endothelial injury [7,61]. When these abnormalities converge, they create a metabolic and inflammatory environment that magnifies cerebrovascular injury beyond what either condition produces alone [7,61].

Together, these findings indicate that MetS is not a passive comorbidity but the central pathophysiologic substrate through which OSA-related intermittent hypoxemia and diabetes-related hyperglycemia interact to worsen vascular injury. By integrating chronic inflammation, oxidative stress, atherogenic DLD, HTN, and pro-thrombotic tendencies, MetS creates biologic conditions that place individuals with both OSA and DM at disproportionately increased risk of ischemic stroke and cerebrovascular complications [7,18,61].

Adiposity-Driven Cardiac and Vascular Remodeling in Metabolic Syndrome: Visceral adiposity is a central component of MetS and a key mechanism through which OSA and DM interact to worsen cerebrovascular risk. Individuals with both disorders commonly exhibit increased visceral fat, which drives systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis [62,63]. This visceral fat expansion is closely associated with greater epicardial adipose tissue (EAT), a metabolically active depot linked to higher cardiometabolic risk [64,65].

EAT secretes inflammatory cytokines, adipokines, and free fatty acids that promote oxidative stress and vascular injury [64–66]. In OSA, higher EAT volume correlates with disease severity and adverse metabolic parameters, while in DM, EAT contributes to insulin resistance, DLD, and coronary artery calcification [63,66,67]. Both visceral adiposity and EAT have also been associated with increased carotid intima–media thickness, a marker of subclinical atherosclerosis that predicts future cardiovascular and cerebrovascular events.

Beyond its atherogenic effects, obesity is also an independent risk factor for AF, a major contributor to cardioembolic stroke risk. Large population-based cohort studies and meta-analyses demonstrate a graded association between increasing body mass index and incident AF, with obesity conferring approximately a 1.5–2-fold higher risk compared with normal-weight individuals [20,68]. Visceral adiposity plays a central role in this relationship by promoting atrial structural remodeling, local and systemic inflammation, autonomic dysfunction, and atrial fibrosis, all of which increase susceptibility to AF [69]. In the setting of OSA and DM, obesity-related AF risk may be further increased by intermittent hypoxemia, sympathetic activation, and metabolic inflammation, providing an additional mechanistic link between metabolic syndrome and stroke.

Thus, visceral fat accumulation, as a key manifestation of MetS in individuals with OSA and DM, amplifies cerebrovascular vulnerability through convergent pathways of inflammation, lipotoxicity, atrial remodeling, and accelerated arterial remodeling.

Dyslipidemia and Atherogenic Lipoprotein Profiles: DLD is a core component of MetS and a major contributor to cerebrovascular risk in patients with coexisting OSA and DM. MetS is characterized by elevated triglycerides, reduced HDL cholesterol, and an excess of small dense LDL particles, an atherogenic profile strongly linked to stroke risk [70]. In DM, insulin resistance drives overproduction of VLDL and impairs clearance of triglyceride-rich lipoproteins, promoting formation of small dense LDL that more readily penetrates the arterial wall and oxidizes [71].

OSA further exacerbates this dyslipidemic state. Intermittent hypoxemia and sympathetic activation alter hepatic lipid metabolism, resulting in higher triglyceride levels and lower HDL cholesterol independent of obesity [72]. Meta-analysis reports that OSA is

associated with significantly higher triglycerides and non-HDL cholesterol, and that lipid abnormalities worsen with increasing apnea severity [72].

When DLD from MetS is combined with OSA and DM, the result is a markedly pro-atherogenic lipoprotein environment. Elevated triglycerides, reduced HDL, and small dense LDL particles accelerate endothelial dysfunction and plaque growth, contributing to the higher incidence of ischemic stroke observed in individuals with metabolic clustering of vascular risk factors [18,70,71].

Hypertension and Hemodynamic Stress in the Metabolic Syndrome Phenotype: HTN is one of the most consequential components of MetS and is the strongest modifiable risk factor for both ischemic and hemorrhagic stroke. Large global studies consistently demonstrate that elevated blood pressure accounts for more population attributable stroke risk than any other factor, including DM or DLD [73,74]. Within the MetS phenotype, central obesity, insulin resistance, and sympathetic overactivity promote sodium retention, activation of the renin–angiotensin–aldosterone system, and impaired nitric oxide bioavailability. These mechanisms together create a sustained prohypertensive environment [75]. These hemodynamic disturbances are worsened when OSA and DM coexist.

OSA contributes to resistant HTN through chronic sympathetic activation, intermittent hypoxia, impaired nocturnal blood pressure dipping, and large swings in intrathoracic pressure that increase left ventricular afterload [10,48]. DM accelerates arterial stiffness, endothelial dysfunction, and microvascular rarefaction, which amplify systolic pressure and increase pulsatile load on cerebral vessels. When these abnormalities converge within the MetS framework, the result is persistently elevated central blood pressure, increased vascular shear stress, and impaired cerebral autoregulation. These processes promote small vessel disease and lacunar infarction and increase overall susceptibility to stroke [73,74].

11. Clinical Implications

The coexistence of OSA and DM has meaningful clinical implications because these disorders share multiple cardiometabolic risk factors and produce additive harmful effects on vascular biology. Early identification and simultaneous treatment are essential to reduce stroke risk and improve long-term cardiovascular outcomes [76,77].

Screening and Diagnosis: Screening is central to this approach. Validated screening tools such as the STOP-BANG and Berlin questionnaires can be used to identify individuals at high risk for OSA in clinical practice [78,79]. Definitive diagnosis is established by overnight polysomnography, the gold-standard diagnostic modality, while home sleep apnea testing may be appropriate in selected patients with a high pretest probability and without significant cardiopulmonary comorbidities [76]. Individuals with metabolic syndrome who exhibit obesity, resistant HTN, or symptoms suggestive of sleep-disordered breathing should be evaluated for possible OSA, while those with moderate to severe OSA should be systematically assessed for components of metabolic syndrome [10,76].

Lifestyle Modification: Lifestyle modification remains a cornerstone of management. Weight loss achieved through structured dietary intervention and increased physical activity improves insulin sensitivity, lowers systemic inflammation, and reduces the severity of OSA [80]. Cardioprotective dietary patterns such as the Mediterranean and DASH diets further reduce blood pressure and are associated with lower stroke risk [11,81].

Pharmacologic Interventions: Pharmacologic therapies complement these lifestyle strategies. Evidence-based DM treatments, including sodium glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists, improve cardiovascular outcomes and reduce markers of vascular injury in high-risk populations [82]. The SURMOUNT-OSA trial demonstrated that tirzepatide produces substantial improvements across multiple cardiometabolic domains relevant to OSA. Treatment was associated with

marked reductions in body weight, with mean weight loss of approximately 15–20%, translating into significant decreases in body mass index in patients with obesity-related OSA. These changes were accompanied by pronounced improvements in OSA severity, with reductions in apnea–hypopnea index of approximately 20–30 events per hour, representing a clinically meaningful attenuation of sleep-disordered breathing. In addition, tirzepatide therapy resulted in modest but statistically significant reductions in systolic blood pressure, on the order of 5–7 mmHg, further supporting its role in mitigating cardiovascular risk. Collectively, these findings highlight the potential of tirzepatide to address both the mechanical and metabolic contributors to OSA within the broader metabolic syndrome phenotype [83].

Continuous Positive Airway Pressure Therapy: Continuous positive airway pressure therapy remains a foundational treatment for moderate to severe OSA and improves oxygenation, sympathetic tone, and blood pressure regulation [10]. Importantly, CPAP may also confer dual benefit by modestly improving glycemic control in patients with coexisting OSA and T2DM. A recent meta-analysis of randomized controlled trials demonstrated a statistically significant reduction in HbA1c of approximately 0.24% with CPAP therapy, with greater improvements observed among patients with higher baseline HbA1c and good nightly adherence [84]. These findings suggest that effective treatment of sleep-disordered breathing can partially mitigate diabetes-related metabolic burden, likely through reductions in intermittent hypoxemia, sympathetic activation, and insulin resistance [85]. However, variability across randomized trials indicates that glycemic benefit is not universal and is strongly influenced by treatment adherence, supporting CPAP as an adjunct rather than a standalone glycemic therapy. Recent studies have also highlighted the importance of CPAP treatment to reduce blood pressure in those with OSA and uncontrolled HTN [86,87].

Bariatric Surgery: For selected patients with severe obesity (BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with obesity-related comorbidities including severe OSA), bariatric surgery represents a highly effective intervention. Meta-analyses demonstrate 60–80% reductions in OSA severity and approximately 30–40% reductions in long-term stroke risk following bariatric surgery [3,19]. Current guidelines recognize severe OSA as a qualifying comorbidity for bariatric surgery eligibility, reflecting the substantial metabolic and cardiovascular benefits achievable through sustained weight loss in this population.

Integrated Care and Long-Term Management: Long-term follow-up is necessary to maintain benefit. Monitoring continuous positive airway pressure adherence, glycemic control, lipid levels, and blood pressure trends allows clinicians to adjust treatment strategies over time. Reports also highlight the role of hyperglycemia even in inpatient settings in contributing to cardiovascular risk [88], thus management of OSA even in inpatient settings will be helpful in reducing cardiovascular risk. Coordinated care involving sleep medicine, endocrinology, cardiology, and primary care offer the greatest opportunity to reduce the cerebrovascular risk faced by individuals at the intersection of OSA, DM, and MetS.

The convergence of OSA and DM creates a spectrum of cerebrovascular risk that necessitates a stratified, personalized approach to screening intensity and therapeutic intervention. Patients presenting with multiple high-risk features including severe OSA (apnea-hypopnea index > 30 events/hour), poorly controlled diabetes (HbA1c > 8%), metabolic syndrome with visceral adiposity, resistant hypertension requiring multiple antihypertensive agents, and elevated inflammatory biomarkers—represent a particularly vulnerable phenotype characterized by accelerated vascular injury and heightened stroke risk [18]. These individuals warrant intensive multimodal intervention with aggressive CPAP titration, optimization of pharmacologic diabetes management (preferentially with agents demonstrating cardiovascular benefit such as GLP-1 receptor agonists or SGLT2 inhibitors) [82], close blood pressure monitoring, and consideration of bariatric

surgery in appropriate candidates [19]. Conversely, patients with mild OSA (apnea-hypopnea index 5–15 events/hour) and well-controlled DM (HbA1c < 7%) without additional metabolic syndrome features may be managed effectively with targeted lifestyle modification, periodic reassessment for disease progression, and selective use of CPAP therapy guided by symptoms and cardiovascular comorbidities [76]. Between these extremes lies a broad intermediate-risk population in whom shared decision-making, informed by individual patient preferences, treatment tolerability, and evolving biomarker profiles, should guide the intensity and sequencing of interventions. This risk-stratified framework optimizes resource allocation, tailors treatment burden to anticipated benefit, and acknowledges the heterogeneity of metabolic and sleep-disordered phenotypes within the OSA–diabetes population. As our understanding of precision medicine advances, future approaches may incorporate comprehensive biomarker panels including measures of systemic inflammation (high-sensitivity C-reactive protein, interleukin-6), advanced glycation end products, endothelial dysfunction markers, and sleep-specific hypoxemia burden metrics to further refine risk prediction and identify individuals most likely to derive maximal cerebrovascular benefit from aggressive intervention [22]. Such personalized, risk-stratified care represents the evolution from one-size-fits-all treatment protocols toward individualized therapeutic strategies that balance clinical benefit, patient burden, and healthcare resource utilization in the management of this complex, high-risk population.

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