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Poor Outcome In Stroke Recovery As A Result Of Pathophysiological Changes From Diabetes Mellitus: A Brief Summary

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Abstract: **Stroke is a prominent cause of mortality and disability worldwide. The process of stroke recovery is mainly compromised by stroke severity. Restoration of synaptic connections, neuroplasticity and reparative angiogenesis are crucial for the brain's ability to remap neurons to damaged areas during post-stroke recovery. Diabetes is associated with increased risks of cardiovascular diseases such as stroke and alterations of metabolic function. Insulin receptor signaling pathways are essential parts in activation of synaptic plasticity mechanisms and insulin itself promotes formation of neural circuits after brain injury. Poor insulin signaling due to diabetes can contribute to decreased axonal sprouting and synaptogenesis resulting in poor recovery. Additionally, cerebral endothelial dysfunction caused by diabetes exacerbates existing cerebral microvascular lesions and cognitive decline. While the pathological state of microglia in the inflammatory response can increase neuronal degeneration and blood brain barrier dysfunction that could affect post-stroke cognitive impairment. This review serves to compile the foundational basis of the current correlation between stroke recovery and diabetes. Further research in this field is still needed to create better understanding of the underlying mechanisms for effective treatment of stroke recovery.**

Keywords: **Stroke recovery; Diabetes; Pathophysiology; Correlation.**

I. INTRODUCTION

In 2023 stroke had affected a total of 349,126 patients in Thailand and 36,214 of those incidences were fatal, most deaths were younger than 70 years old and more often were men than women. Those who are alive are most likely affected by some form of disability. On average, stroke is estimated to be prevalent in 1.88% of adults of 45 years and older, the majority of which were ischemic stroke, a stroke type that's much more common than hemorrhagic stroke [1]. Interestingly, within the same year, there are 3.3 million total diabetics in Thailand, and that number is growing by around 300 thousand patients per year, equivalent to a rate of 512.07 new diabetics for every 100 thousand people [2]. Approximately 30% of patients with stroke have type 1 diabetes mellitus or type 2 diabetes mellitus including those who are previously undiagnosed [3]. This is important because diabetics have 1.5-2 times the chance of stroke than non-diabetics [4]. The purpose of this research is to compile and identify potential key mechanisms caused by diabetes that can adversely delay stroke recovery.

II. WHAT IS STROKE

Stroke is ranked the second leading cause of death worldwide [5] and the fourth leading cause of disability [4][6][7]. The prevalence of stroke is highest in developing countries, with ischemic stroke being the most common type [8].

Strokes can be defined as a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal and at times global loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin [9] or alternatively, an abrupt neurological outburst caused by impaired perfusion through the blood vessels to the brain [8].

Stroke is classified into two types; *I.* Ischemic stroke is caused by deficient blood and oxygen supply to the brain [8] (blockage of blood flow) [9]. This is the most common type affecting 67-80% of stroke patients [9] or up to 87% according to another study [10]. Ischemic strokes can be classified into large- or small-vessel strokes. Large-vessel strokes can lead to profound neurological deficits and even death due to large area of brain infarction from embolism occlusion of carotid or proximal cerebral arteries. This is often the result of cardioembolism from atrial fibrillation, structural heart disease, atherosclerotic disease, or a hypercoagulable state [7]. Strokes resulting from vascular disease of end arterioles result in "lacunar" infarctions of deep brain structures. This includes brain regions supplied by end arterioles, such as the lenticular nucleus, internal capsule, thalamus, and pons [11]. These are called small-vessel strokes and are typically associated with small areas of brain infarction (often <1.5 cm) but result in highly morbid deficits due to their localization near prominent motor tracts. Lacunar strokes are usually associated with chronic hypertension or diabetes and are characterized by pathological thickening of the arterial media by fibrinoid deposition (lipohyalinosis) or obstruction of penetrating end arteries by intimal plaques [11][12]. *II.* Hemorrhagic stroke is caused by bleeding or leaky blood vessels (blood vessels rupture), causing leakage of blood in and around the brain [8]. This type of stroke is often associated with hypertension and it makes up the remaining percentage of stroke [10].

III. RISK FACTORS OF STROKE

A. Non-modifiable risk factors

Factors that could not be externally influenced which could include age, sex, ethnicity [13][14], TIA (Transient Ischemic Attacks) [15] and hereditary characteristics [16][17].

1. Age-specific stroke: The incidence of stroke increases with age [7][8], doubling after the age of 55 years [8][16] [18].

2. Gender-specific stroke: the occurrence of stroke in younger ages is higher in women, whereas incidence increases slightly with older age in men. Both brain infarction and intracerebral hemorrhage (ICH) are common in men, but cardioembolic stroke, a more severe form of stroke, is more prevalent among women [16].

3. Geographic and racial variation-specific stroke: varied environmental factors could affect stroke severity (for example: different exposures to environmental pollutants, such as lead and cadmium could influence stroke incidence) [19][20].

B. Modifiable risk factors

Risk factors that can be reduced if appropriate medical intervention is applied on time, this includes; hypertension, lack of physical exercise, alcohol and drug abuse, cigarette smoking, cholesterol/obesity, sedentary lifestyle, dyslipidemia, hyperlipidemia, hypercholesterolemia, hyperglycemia, diet management, and genetics, cardiac causes including atrial fibrillation and DM [4][7][8][21].

1. Total cholesterol: is associated with risk of stroke, whereas high-density lipoprotein (HDL) decreases stroke incidence [22].

2. Hypertension: one of the predominant risk factors for stroke [7][8]. In one study, BP of at least 160/90 mmHg and a history of hypertension were considered equally important predispositions for stroke [23].

3. Diabetes: a well-established risk factor for stroke [7][21], shown in some studies to be linked to 1.5-3 fold increased risk of stroke [24]. Epidemiologic studies have shown that DM is a well-established independent but modifiable risk factor for both ischemic and hemorrhagic stroke [25][26].

4. 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 [21]. It is important to highlight that the relationship between stroke outcomes and hyperglycemia is bidirectional: whilst high blood glucose may contribute to poor stroke outcomes, severe ischemic stroke may also be the cause of post-stroke hyperglycemia [27]

IV. PATHOPHYSIOLOGY OF STROKE

Stroke causes sudden paralysis or motor impairments, speech disturbances and/or loss of vision, among other neurological symptoms. This is most often due to interruption of blood flow caused by embolism to arteries supplying the brain [7]. There are two pathological mechanisms that could cause this interruption, which would cause either ischemic stroke or hemorrhagic stroke.

A. Ischemic stroke

Ischemic occlusion generates thrombotic and embolic conditions in the brain [28]. In thrombosis, the blood flow is affected by narrowing of vessels due to atherosclerosis. The build-up of plaque will eventually constrict the vascular chamber and form clots, causing thrombotic stroke [8]. In an embolic stroke, decreased blood flow to the brain region causes an embolism; the blood flow to the brain reduces, causing severe stress and untimely cell death (necrosis) [8]. Necrosis is then followed by disruption of the plasma membrane, organelle swelling and leaking of cellular contents into extracellular space [29], and loss of neuronal function [8].

B. Hemorrhagic stroke

In hemorrhagic stroke, stress in the brain tissue and internal injury cause blood vessels to rupture [8]. It produces toxic effects in the vascular system, resulting in infarction, classified into intracerebral and subarachnoid hemorrhage [30]. In subarachnoid hemorrhage, blood accumulates in the subarachnoid space of the brain due to a head injury or cerebral aneurysm [31]. Other key events contributing to stroke pathology are inflammation, energy failure, loss of homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, cytokine-mediated cytotoxicity, complement activation, impairment of the blood–brain barrier, activation of glial cells, oxidative stress and infiltration of leukocytes [32].

V. POST-STROKE IMPAIRMENTS

After the stroke, Most stroke patients experience reduction in quality of life (QOL), patients often suffer from residual impairments of function and difficulties in performing activities of daily living (ADL) [33]. ADL includes the basic tasks that a person performs to function on a daily basis, which include bathing, dressing, eating, grooming, toileting, and transferring [34]. ADL limitations are defined when a person needs assistance with at least one task and when a person shows inability to complete any ADL alone [35]. Difficulties performing ADL mainly comes from having disabilities which can include hemiparesis, hemianopsia, dysphasia, dysphagia and bladder or bowel incontinence, weakness of limbs, postural imbalance, gait, loss of dexterity and various conditions associated with functional limitations [5][36]. In addition to potential neurological problems such as impairment of intellectual reasoning and memory, specific neuropsychological disturbances (in speech, gnostic and practic functions) which may contribute to post-stroke cognitive impairment (PSCI) and emotional reactions [36].

VI. GENERAL FACTORS IN OVERALL POST-STROKE RECOVERY

After an acute decline, patients may experience varying recovery post-stroke [37]. Various predictors associated with long-term functional deficits and mortality after stroke in patients with diabetes have been reported [38].

A. Severity of stroke

The extent of brain damage caused by stroke will directly impact the degree of physical and cognitive impairments [39].

B. Physical factors

Initial impairments: factors like muscle strength, coordination and sensation significantly improves recovery [39]. Exercise and rehabilitation: regular exercises and physical therapy are vital to regaining impaired functions [39].

C. Emotional and psychological factors

A patient's attitude and emotional response to disabilities and changes in lifestyle can affect their willingness to actively engage in activities that can improve their recovery [39].

D. Social and environmental factors

Having appropriate accommodations, support from close relatives and easy access to healthcare services are crucial in increasing the likelihood of recovery [39].

E. Therapeutic factors

Availability to optimal therapy from professionals within a nearby timeframe after stroke is recommended for effective treatment [39].

F. Other important factors

Physiological factors from during and after stroke which subsequently influence post-stroke recovery can drastically vary between each individual [39]. For instance, a negative association was observed between patients' age and functional gain after rehabilitation [40], a healthy diet can provide nutrients necessary for healing and stroke prevention, quitting destructive lifestyles such as smoking [39]. Besides the aforementioned factors, co-morbidities like DM are one of the biggest factors in determining stroke recovery.

VII. DIABETES MELLITUS (DM)

DM is known to have complex pathogenesis and varied presentation. Any classification of this disorder is arbitrary and is often influenced by physiological conditions at the time of diagnosis [41]. The classification currently used is based on both the etiology and the pathogenesis of disease and is useful in the clinical assessment of disease and for deciding the required therapy [41]. The 4 main types of DM are: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and DM caused by specific conditions, pathologies or disorders (Secondary DM) [42].

T1DM (insulin-dependent DM) is an autoimmune disorder characterized by T-cell-mediated destruction of pancreatic β-cells resulting in insulin deficiency and hyperglycemia [43][44]. Idiopathic diabetes, also referred to as ICA-negative or type 1B diabetes, includes the forms of diabetes which are similar to T1DM in presentation but characterized by variable nonimmune β-cell dysfunction without any observed HLA association characterized by severe but varying degrees of insulin deficiency (insulinopenia) which can exhibit episodic patterns concomitant with varying degrees of severity and episodic DKA (diabetic ketoacidosis) [45].

T2DM (non-insulin dependent DM) is characterized by insulin resistance and β-cell dysfunction [43], in this case DKA may occur during severe stress conditions (ex.infections or other pathophysiological scenarios). T2DM progresses slowly and asymptomatically, its symptoms include severe hyperglycemia, weight loss, growth impairment, blurred vision, polyuria, and polydipsia in the advanced stages of the disease [41].

GDM is defined as any degree of glucose intolerance or DM diagnosed at the onset or during pregnancy [41].

In this review, mechanisms behind DM's influence on stroke outcomes will be separated into two parts based on mechanisms within DM itself and the ones in hyperglycemia, as a diabetic co-morbidity, affect stroke recovery.

VIII. HOW DM PATHOPHYSIOLOGICALLY AFFECTS STROKE RECOVERY

There are several explanations for the association between diabetes duration and stroke, including an increased risk of atherosclerotic lesions [21][46] and more severe endothelial dysfunction with an increased duration of diabetes [47]. Subsequently, Diabetes increases cardiovascular disease risks, including stroke, through systemic metabolic and inflammatory effects that alter the structure and function of blood vessels and modulate immune function [7]. These alterations could also play an important part in large artery atherosclerosis, cerebral small vessel disease (SVD) and cardiac embolism, which are reported to be the three main causes of ischemic stroke [48].

A. Diabetic pathophysiology impedes neuroplasticity and stroke recovery

Post-stroke recovery of ADL in patients with diabetes seems to be poorer than that in patients without diabetes possibly due to impaired neurogenesis, neuroplasticity, and angiogenesis in diabetes and the detrimental effects of hyperglycemia [33]. Reparative angiogenesis is important for good functional recovery after stroke [49] and impaired angiogenesis has been reported in patients with diabetes after stroke [50].

Cerebral endothelial dysfunction: It has been proven that neurogenesis and synaptic reorganization are important for functional improvement after stroke [51]. DM slows the patient's stroke recovery trajectory, exacerbates post-stroke cognitive decline, and increases the risk of post-stroke dementia even when adjusting for stroke severity and age [52]. Interestingly, in diabetic patients without stroke, structural and functional imaging studies demonstrate an increased burden of preexisting cerebral microvascular lesions, which alters imaging features of regional connectivity [53].

Insulin resistance: Besides cellular metabolism and regulation of nutrient intake, insulin also affects cognition and neural plasticity [54]. Studies have shown that diabetic humans and animal models of type 1 and 2 diabetes have impairments in cognitive function, synaptic plasticity, synaptogenesis, and neurogenesis [55]. Insulin plays an important role in the formation of neural circuits and synaptic connections, and it facilitates and promotes neuroplasticity [56] thereby promoting

recovery after brain injury [57]. Activation of insulin receptor and insulin-like growth factor (IGF) receptor signaling pathways improves recovery from brain injury by activating neuronal antioxidant defense and engaging synaptic plasticity mechanisms [57][58]. Brain insulin resistance (BIR) in diabetes is a critical modulator of alterations in neural metabolic functions, restorative processes, and susceptibility to neurodegeneration in human patients and animal models of disease [59]. Poor insulin signaling in neurons may contribute to decreased synaptogenesis and axonal sprouting after stroke, leading to poor ADL recovery [60]. Although no results are available on human trials of intranasal insulin in post-stroke recovery, it has been shown to be safe and effective at improving cognition in small human studies of patients with Alzheimer's Disease (AD) [61].

Inflammation: Both hyperglycemia and diabetes mellitus are associated with a higher risk of PSCI and dementia [7]. It is thought that diabetes may exacerbate initial stroke damage by altering the activation of apoptotic or inflammatory signaling pathways [62] however, some research has no consensus on this topic [63]. Additionally, the duration of inflammatory response, late aberrant neurogenesis, and baseline brain pathologies were noted to affect the severity of PSCI [64]. DM and MetS are closely linked with inflammation, cognitive decline and AD in human epidemiological studies [65][66]. Chronic hyperglycemia leads to pro-inflammatory microglial proliferation via the endothelin-1 system [67]. Inflammatory cells and cytokines stimulated by stroke or neurodegeneration have both beneficial and detrimental effects [7]. Activation of microglia seems to play an important role in the inflammatory response [69]. Activated macrophages or microglia help brain recovery by clearing debris and stimulating trophic factors, but in pathological states, these cells can also lead to neural injury and impede repair [70]. Diabetic patients suffer increased neuronal injury and degeneration due to increased susceptibility to binge biogenic failures, BBB dysfunction and increased M1 pro inflammatory microglial/macrophage polarization [7]. Studies have also linked M1 microglial and macrophage polarization with reduced neurogenesis, atonal regeneration and synaptic density [71].

IX. HOW ACUTE HYPERGLYCEMIA PATHOPHYSIOLOGICALLY AFFECTS STROKE RECOVERY

Many retrospective studies have found compelling associations between admission blood glucose and infarct growth, poor outcome and hemorrhagic conversion [72]. Studies in stroke patients have demonstrated greater infarct growth in patients with hyperglycemia or DM or both using serial MRI [73][74]. Patients with higher plasma glucose levels at admission had more severe functional deficits 6 months after stroke [38]. Chronically elevated blood glucose level increases the risk of microstructural changes in the white matter tracts, and poor metabolic control accelerates cognitive decline [75]. eGFR <60 ml/min/1.73m^2 was associated with severe white matter lesion and poor survival in patients with acute stroke [38]. The detrimental effects of hyperglycemia in patients with diabetes may cause further cerebral damage after stroke, which may also contribute to poor ADL recovery. Hyperglycemia further aggravates the stroke consequences through augmented reperfusion injury by increasing oxidative stress, stimulating systemic inflammation and increasing barrier permeability [21].

After focal cerebral ischemia, glucose is anaerobically metabolized to lactic acid [76], and the production of lactate increases, leading to irreversible neuronal injury and consequent expansion of the infarct core into the penumbra. Metabolic abnormalities in diabetes can aggravate this process, as hyperglycemia causes an elevation of lactate and H^+production, facilitating further cerebral damage [33]. Hyperglycemia triggers free radical production, endonuclease activation, glutamate release, and alteration of intracellular Ca^+ regulation [77]. It can also decrease the activity of tissue plasminogen activator, leading to impaired recanalization, delayed reperfusion, and increased infarct size [8] and additionally leads to alterations in brain energy and neurotransmitter homeostasis, consequently causing brain injury and dysfunction [78]. Chronic systemic hyperglycemia in diabetes causes impaired glucose transport and cell-to-cell metabolic interactions, along with changes in the activities of key enzymes involved in glycogen metabolism [78].

X. DISCUSSION

Although the underlying mechanism behind diabetes and stroke are still unclear, there have been improvements regarding the research in the correlation between stroke outcomes and diabetes comorbidities. Subsequently, the trends regarding certain pathways and comorbidities have pointed towards the likelihood of being a determined cause of poor post-stroke outcomes. For instance, inflammation, immune dysfunction, endothelial dysfunction and neuronal injury caused by comorbidities of diabetes and diabetes itself has been associated as major contributors in impeding many neurological functions like synaptability and cortisol remapping that was linked to improved recovery. Despite that, not all studies have

reached a consensus on the specific causes of poor stroke recovery and further research is needed to fully determine appropriate treatments and correctly define the mechanisms of stroke for diabetic stroke patients.

XI. CONCLUSION

In conclusion, though the specific are inconclusive, diabetes can impede stroke recovery by deteriorating neuroplasticity and neurogenesis which are crucial for recovery through remapping damaged neurons and exacerbating stroke outcomes. By altering metabolic functions, reducing endothelial plasticity and promoting other comorbidities such as hypertension and hyperglycemia, diabetes can increase stroke recurrence, neuronal injury, stimulate large artery atherosclerosis, cerebral small vessel disease (SVD) and cardiac embolism thereby worsening potential recovery following stroke treatments and intensify stroke severity. Therefore, it is best to avoid conditions that could increase the risk of stroke in the first place. From what had been gathered in this review, those with comorbidities such as high cholesterol and diabetes run the risk of microvascular diseases that could worsen stroke outcomes. Reducing the risks by constantly monitoring and regulating glucose levels or cholesterol levels, reducing harmful lifestyle choices such as smoking, regularly exercising and strictly following professional medical guidelines is recommended to reduce the risk of stroke, stroke recurrence, severe stroke outcomes and lessen the affliction caused by comorbidities.

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