INTRODUCTION

1.0 INTRODUCTION

1.1 EPIDEMIOLOGY OF DIABETES

In 2021, the worldwide prevalence of diabetes was estimated to be 10.5% (536.6 million) among people aged 20-79. It is expected that number will rise to 12.2% (783.22 million) by 2045 (International Diabetes Federation, 2021). There was a similar prevalence of diabetes among men and women, with the highest prevalence observed among those aged 75 to 79 years old. In 2021, urban prevalence (12.1%) was greater than rural prevalence (8.3%), and high-income countries (11.1%) were higher than low-income countries (5.5%). From 2021 to 2045, middle-income countries will have a rise in diabetes prevalence (21.1% compared with 12.2% in high-income countries). From USD 966 billion in 2021, diabetic-related health expenditures are expected to reach USD 1,054 billion by 2045. Over 74 million adults in India are living with diabetes, which is the second highest in the world, after China and it is projected to increase to 134 million by the year 2045. A further 40 million adults in India are at high risk of type 2 diabetes.

Diabetes mellitus is a major lifestyle disorder manifested in high glucose levels and glucose intolerance caused by insulin deficiency or impaired insulin action. Depending on their etiology and clinical presentation, diabetes mellitus can be divided into two types: type 1 diabetes (T1DM) and type 2 diabetes (T2DM). T1DM occurs when an autoimmune reaction destroys insulin-producing cells in the pancreas. An insulin shortage causes chronic hyperglycemia in people with T1DM. Insulin resistance (IR) and relative insulin deficiency characterize T2DM. IR occurs when insulin target tissues are unable to respond adequately to circulating insulin, such as skeletal muscle, liver tissue, and adipose tissue (Cho et al., 2018).

1.2 T2DM AND COGNITION

In recent years, cognitive impairments and dementia (including Alzheimer's disease) have been recognized as common complications and comorbidities of T1DM and T2DM. Diabetics are associated with a 1.25–1.9-fold higher risk for cognitive dysfunction, including Alzheimer’s disease (AD) (Relative risk of 1.53) and vascular dementia (Relative risk of 2.27). It is estimated that 7% of people aged 60–64 are affected by Mild cognitive impairment (MCI) and that 25% may develop cognitive impairment as they get older. It has been found that the risk

of converting mild cognitive impairment to dementia is 1.53 times higher in individuals with diabetes (Xue et al., 2019).

T2DM has been associated with cognitive dysfunction, and studies have established a link between T2DM and major neurocognitive disorders (Cheng et al., 2012). Studies show that individuals with T2DM have a nearly 50% increased risk of major neurocognitive disorders compared to individuals without T2DM (Biessels et al., 2014). Brain imaging studies show that T2DM is associated with both degenerative and vascular brain damage, which is likely to contribute to abnormalities in brain functional and structural connectivity leading to cognitive dysfunction (Biessels & Reijmer, 2014; Brundel et al., 2014).

The severity of deficits in cognitive functioning in adults with type 2 diabetes can be roughly divided into three stages: diabetes-associated cognitive decline, MCI, and dementia. Diabetic-associated decline refers to subtle changes in cognitive functions that are not likely to interfere with daily life activities or diabetes management. These declines will probably begin in pre-diabetic stages, and they will progress very slowly over many years, at a rate up to 50% faster than normal cognitive aging (Biessels & Despa, 2018).

Working memory (WM), a cognitive ability that enables one to actively maintain and manipulate information and forms an essential part of the human memory system (Baddeley, 2010), is implicated along with other cognitive functions such as attention, executive function, verbal memory, information processing speed (Manschot et al., 2006; Zhang et al., 2014), language and visuospatial abilities (Bangen et al., 2015). It has been found that higher cognitive functions such as executive function, language, planning, and problem-solving rely on WM.

1.3 RISK FACTORS FOR COGNITIVE DYSFUNCTION IN DIABETES MELLITUS

Diabetes-related complications, such as glucose and insulin imbalances, microvascular and macrovascular complications significantly predispose patients to the progression of MCI and dementia. Additionally, several risk factors for cognitive dysfunction in diabetes were identified, such as hypertension, dyslipidemia, depression, age, duration of diabetes, genetic factors and educational level of patients with diabetes (Ehtewish et al., 2022).

Neurodegeneration has been suggested as a mechanism linking diabetes to an increased risk of AD. However, the underlying pathology of AD consisting of amyloid protein buildup and abnormal tau phosphorylation is still being investigated as a mechanism of cognitive

impairment in diabetes. Other mechanisms may also include advanced glycation end products (AGE) and vascular endothelial dysfunction, dysglycemia, insulin dysregulation, and neuroinflammation (Biessels & Despa, 2018).

T2DM is associated with dysfunction of cardiac autonomic regulation which affects both sympathetic and parasympathetic activities. This is observed with decreased heart rate variability (HRV) in T2DM patients (Benichou et al., 2018). A higher resting state HRV parameters are linked with better cognitive performance. The studies show that in populations without dementia or stroke, HRV parameters can be considered as early biomarkers for the measurement of cognitive impairment (Forte et al., 2019).

The other important aspect linked to poor cognition and an increased risk of dementia in diabetics is depression (Chow et al., 2022). Studies found a high prevalence of depression among T2DM patients and more often associated with the presence of T2DM complications (Hussain et al., 2018). A combination of diabetes and depression leads to greater impairments in executive functions than either condition alone. Consequently, diabetes is not properly managed, so hyperglycemia persists, as well as poor emotion regulation occurs as a result. This causes a vicious cycle of depression and hyperglycemia (Black et al., 2018). Rumination is a part of depressive symptoms predicting the onset of depression in individuals (Nolen-Hoeksema, 2000). Rumination is a way of coping with depressive situations by involving oneself in self-reflection and repetitive attention to negative emotions (Treynor et al., 2003).

1.4 HEMODYNAMICS AND COGNITION

In the brain, cerebral blood flow (CBF) is maintained through tight coordination with neuronal activity and metabolism. Neurons' energy demands increase when they become activated, leading to increased cerebral blood flow. A neurovascular unit represents the interaction between neurons, vascular cells (endothelial, pericytes, smooth muscle cells) and glial cells (astrocytes and microglia) in the brain on an anatomical and metabolic level. This system is responsible for ensuring that the brain receives continuous oxygen, glucose, and other nutrients. A series of inflammatory responses are triggered as a result of conditions such as stroke, diabetes, hypertension, dementia, as well as aging. It is found that all of these conditions lead to the escalation of inflammatory responses in the brain which aggravates the brain damage. Tight regulation and maintenance of neurovascular coupling are therefore essential to maintaining brain homeostasis (Venkat et al., 2016). It has been hypothesized that altered

cerebral hemodynamics may contribute to cognitive declines (Brundel et al., 2012). A decreased CBF impairs neurovascular coupling and causes neuronal injury and death. T2DM may disrupt the cerebral microenvironment, including both vascular dysfunction and astrocytic dysfunction. A significant role for astrocytes is thought to play in the regulation of local CBF. Increased oxidative stress is observed in astrocytes grown in high glucose environments. A prolonged state of hyperglycemia impairs astrocytic gap junction communication. Astrocytic trafficking of metabolites and signaling molecules may be disrupted in T2DM and result in changes in brain function and cognitive decline (M. Mogi & Horiuchi, 2011).

Neuroimaging studies have identified that the prefrontal cortex (PFC) region plays a prominent role in working memory (Barbey et al., 2013; Kane & Engle, 2002). The level of neuronal activity in the PFC, which relates to glucose metabolism, reflects the efficiency with which individuals can perform cognitive activities. An increase in neuronal activity is linked to an increase in regional blood flow to transport glucose and oxygen to meet the increased metabolic needs. As a result, the levels of oxyhemoglobin (OxyHb), deoxyhemoglobin (DeoxyHb), and total hemoglobin (TotalHb) in the brain change (Heeger & Ress, 2002). Efficient cerebral oxygenation is essential for cognitive processes to be intact and its deficiency results in lower cognitive performance (Chung et al., 2007, 2008; Turner et al., 2015). A study by Chen et al. (2014) on functional Magnetic Resonance Imaging (fMRI) and working memory has shown that T2DM patients exhibited reduced activation in PFC regions compared to control subjects and this diminished activation was associated with increasing WM task difficulty (Y. Chen et al., 2014).

1.5 ROLE OF YOGA IN IMPROVING COGNITIVE FUNCTIONS

Besides medications, non-pharmacological approaches such as physical exercise, yoga, computer-based training, nutrition, brain stimulation, sleep, and music are gaining importance in treating cognitive deficits. Most of these approaches are still evolving and may be utilized as adjuvant therapy tools in the early stages because they are cost-effective and relatively safe without any side effects, and have minimum risk of interaction with prescription medications (Sachdeva et al., 2015). Yoga has been one such non-pharmacological approach gaining popularity as a form of complementary and alternative medicine worldwide and its therapeutic benefits are being explored in various clinical conditions.

Yoga is a way of life that aims to bring harmony and wellness to one's physical, mental,

emotional, and spiritual selves. Both as an art and science, with 5,000 years old tradition, yoga has eight limbs: social ethics (*yama*), individual ethics (*niyama*), postures (*asana*), breath regulation (*pranayama*), control of senses (*pratyahara*), concentration (*dharana*), meditation (*dhyana*) and state of bliss (*samadhi*) (Iyengar, 1995). Yoga therapy involves the application of yoga practices, especially asanas, pranayama and meditation, to treat ailments through the prevention or alleviation of structural, physiological, emotional and psychological sufferings (Woodyard, 2011). The therapeutic effect of yogic practices showed structural and physiological benefits, including enhanced muscular strength and body flexibility, improved respiratory and cardiovascular function, and chronic pain (Büssing et al., 2012). Moreover, the benefits of yoga on emotional and psychological health include recovery from addiction, stress reduction, overcoming anxiety and depression, enhanced sleep quality, and improved overall well-being and quality of life (Büssing et al., 2012; Taneja, 2014). A meta-analysis shows that the long-term and immediate effect of yoga practice is associated with moderate improvements in cognitive functions such as attention, memory, executive function and processing speed (Gothe & McAuley, 2015). Another review involving cross-sectional studies with adult and older adult populations indicates the beneficial effect of yoga on brain anatomy and/or function; it may mitigate age-related neurodegeneration to sustain or further decline in cognitive health (Gothe et al., 2019).

Besides pharmaceutical treatment, non-pharmacological approaches such as exercise, diet, yoga, Tai Chi, mindfulness, and cognitive training are increasingly popular as alternative methods of treatment for cognitive improvement due to their safety and fewer side effects. Many studies have shown that yoga improves cognitive functions in healthy and clinical populations. However, there are only a few studies that address cognitive function in T2DM patients. Moreover, the cognitive performance was observed with neuropsychological tests, without investigating the underlying actions of yoga. To the best of our knowledge, yoga has not been studied for its effect on working memory and associated prefrontal oxygenation in T2DM patients. With the aforementioned context in mind, we designed this study with the assumption that yoga practice would enhance working memory performance and associated PFC activation in T2DM patients. In the current study, we assessed the impact on working memory performance and associated PFC oxygenation changes after a twelve-week integrated yoga intervention.