REVIEW OF SCIENTIFIC LITERATURE

3.0 REVIEW OF SCIENTIFIC LITERATURE

The existing literature on the following topics was reviewed.

- T2DM and cognitive dysfunction
- Structural and functional changes in the brain underlying cognitive dysfunction due to T2DM
- Effect of yoga on cognitive functions in T2DM patients

3.1 COGNITIVE DYSFUNCTION IN T2DM

In later life, people with diabetes in midlife have 19% more cognitive decline compared to those without diabetes. Poorly controlled diabetes was associated with a greater decline. The cognitive changes associated with diabetes develop slowly over time and are moderate in size (Rawlings et al., 2014; van den Berg et al., 2010). Elderly people with T2DM have a faster rate of cognitive decline (Allen et al., 2004). In addition, diabetes patients are more likely to suffer from dementia than non-diabetic individuals (Biessels et al., 2006). In people with type 2 diabetes, depression was more frequently associated with complications. Diabetes and depression are associated with greater deficits in executive function than diabetes or depression alone. The deficits in executive function result in poor diabetes management and emotional dysregulation. This in turn ends in a recursive cycle of hyperglycemia and depression (Black et al., 2018; Hussain et al., 2018). The presence of T2DM is associated with mild to moderate deficits in all cognitive abilities measured, with effect sizes that range from small to medium. Processing speed and divided attention/shifting had the largest effect sizes (Monette et al., 2014). Memory, information processing speed, attention, and executive functioning are especially affected by T2DM (Awad et al., 2004; van den Berg et al., 2010). Generally, other domains, such as visuoconstruction and language, are unaffected (Brands et al., 2007).

The cognitive impairments in patients with T2DM are related to endocrinological, metabolic and vascular abnormalities associated with T2DM (Biessels et al., 2006). The cognitive impairments in patients with T2DM are related to structural changes in the brain. It increases the burden of small-vessel disease and causes global brain atrophy. Patients with diabetes have microstructural lesions in their cerebral grey and white matter, which affect their structural and functional connectivity (Biessels & Reijmer, 2014; Manschot et al., 2006). Systemic insulin-

resistance diseases mediate brain Insulin/Insulin Growth Factor resistance and neurodegeneration. A dysregulated lipid metabolism can cause oxidative stress and toxic lipids, such as ceramides, to cross the blood-brain barrier to promote brain insulin resistance in people with T2DM, non-alcoholic steatohepatitis (NASH), visceral obesity, and metabolic syndrome. As a result of these changes, the brain undergoes atrophy with progressive cell loss, white matter fiber degeneration, and synaptic disconnection, resulting in learning and memory impairments (de la Monte, 2014).

3.2 CEREBRAL OXYGENATION AND WORKING MEMORY IN T2DM PATIENTS

There are several neuroimaging techniques used to study cerebral hemodynamics, providing insights into blood flow, oxygenation, and metabolism in the brain. The commonly used techniques are Functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Near-Infrared Spectroscopy (NIRS) and Transcranial Doppler Ultrasonography (TCD). Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique commonly used to assess cortical oxygenation levels by measuring the absorption of near-infrared light. It is portable and non-invasive, making it suitable for studying cerebral hemodynamics in various settings involving infants, children, and patients with mobility limitations (Scholkmann et al., 2014). Human functional neuroimaging studies indicated that the PFC is critical to the storage and manipulation of information in the working memory (D'Esposito et al., 1995). Also, studies with neuropsychological tests indicated that dorsolateral PFC (dlPFC) is necessary for working memory function (Barbey et al., 2013; Kane & Engle, 2002; Owen et al., 2005). fNIRS studies show that performing working memory tasks increases oxygen consumption, resulting in increased blood flow, resulting in higher OxyHb levels and lower DeoxyHb levels in healthy individuals (Bonetti et al., 2018). It has been found that, even at an early stage of cognitive decline, there was a clear abnormality in cerebral hemodynamics and oxygenation parameters (Beishon et al., 2017; Duarte et al., 2015; N. Mogi et al., 2004). T2DM patients had poorer executive and memory abilities during working memory tasks, associated with reduced activation in the middle frontal gyrus (MFG) and superior frontal gyrus (SFG) regions compared to healthy individuals (Y. Chen et al., 2014). Researchers have demonstrated that physical activity and exercise can prevent or delay the onset of age-related cognitive dysfunction and neurodegenerative diseases (Hamer & Chida,

2009). According to neuroimaging studies, moderate exercise improves executive function and is associated with increased prefrontal activation (Byun et al., 2014; Yanagisawa et al., 2010).

3.3 EFFECT OF YOGA ON COGNITIVE FUNCTIONS IN T2DM PATIENTS

Yoga may be as effective or even more effective than exercise at improving a variety of health-related outcomes in both healthy and diseased populations (Ross & Thomas, 2010). Studies show that yoga may have positive effects on a variety of factors related to managing type 2 diabetes. Yoga may lower oxidative stress, decrease sympathetic activation and improve nervous system function, enhance pulmonary performance, sleep, quality of life and reduce medication (Innes & Selfe, 2016). Many studies show that yoga helps in improving glycemic parameters such as glycated hemoglobin (HbA1c), fasting blood glucose (FBG) and post prandial blood glucose (PPBG) in T2DM patients (Nagarathna et al., 2012; Thind et al., 2017). Interventional studies involving healthy individuals showed that yoga had the strongest effect on attention and information processing speed, followed by executive function and memory. The acute effect of yoga was strongest on memory, followed by attention, processing speed and executive function (Gothe et al., 2019). In another study involving healthy individuals, yoga practice improved attention and concentration, remote memory, mental balance, delayed and immediate recall, verbal and visual retention (Nangia & Malhotra, 2012). There are only a few studies that investigated the effect of yoga on cognitive functions in T2DM patients. The study by Mohan et al. showed that yoga significantly reduced FBS and HbA1c in the participants and improved mini-mental state examination (MMSE) scores significantly as well (Mohan et al., 2015). In another study investigating electrophysiological evidence, yoga was found to improve the latency and amplitude of P300 and N200 cerebral evoked potentials, which assess higher cognitive functions (Kyizom et al., 2010). Nagothu et al. demonstrated the improvement in cognition using Addenbrooke's cognitive examination revised battery after regular yoga practice in combination with oral hypoglycemic agents in T2DM patients (Nagothu et al., 2017; Nagothu, Reddy, Archana, et al., 2015). A single-group study by Satish & Lakshmi demonstrated that yoga practice improves attention, but no significant improvement in processing speed and cognitive flexibility (Satish & Lakshmi, 2016). It has been found that yoga influences cerebral hemodynamics (Bellissimo et al., 2020). There is evidence that yoga techniques increase cerebral blood flow to the frontal lobes of the dorsal medial and prefrontal cortex, as well as the sensorimotor cortex (Cohen et al., 2009).

3.4 SUMMARY OF SCIENTIFIC LITERATURE REVIEW

Table 1. Summary of studies assessing cognitive functions in T2DM patients

Study (Author, Year)	Sample size	Experimental Design	Outcome Measures	Findings	Conclusions
Benichou et al., 2018	25 studies involving 1356 T2DM patients and 1576 healthy controls	Meta-analysis	HRV parameters	T2DM patients had Lower values of RR interval, RMSSD, SDNN, pNN50, LF, HF LF/HF ratio did not differ with healthy controls	A significant decrease in HRV was found in T2DM patients with T2DM. As a result of altered glucose metabolism affecting HRV, sympathetic and parasympathetic activity was reduced, resulting in cardiac autonomic neuropathy.
Biessels and Reijmer, 2014	MRI studies from the years 2000 to 2014	Review	Findings with brain MRI that may underlie cognitive dysfunction in diabetes.	MRI findings of structural abnormalities namely, brain atrophy and microstructural lesions.	Diabetes type 2 increases the burden of small-vessel disease and causes global brain atrophy. Patients with diabetes have microstructural lesions in their cerebral grey and white matter, which affect their structural and functional connectivity
Biessels et.al, 2006	14 longitudinal studies included a population of various ethnic origins - white, black, Asians and Hispanic	Systematic Review	To examine the strength of the correlation between diabetes and dementia	The risk of Alzheimer's disease and vascular dementia increases in patients with diabetes mellitus.	Diabetes increases the risk of dementia. The various mechanisms for cognitive decline are - vascular pathology, glucose toxicity leading to microvascular abnormalities and accelerated brain aging

Black et al., 2018	Studies involving diabetes with depression	Review	Effect of diabetes and depression on Executive function	Executive function performance of individuals with comorbid conditions was poorer compared to individuals with either diabetes or depression alone.	Diabetes and depression are associated with greater deficits in executive function than diabetes or depression alone. The deficits in executive function result in poor diabetes management and emotional dysregulation. This in turn ends in a recursive cycle of hyperglycemia and depression.
Cheng et al., 2012	19 studies including 6184 subjects with diabetes and 38,530 subjects without diabetes	Meta-analysis	The relative risk for AD, VD and MCI	Diabetes had a higher risk for AD (relative risk (RR):1.46, 95% CI:1.20–1.77), VD (RR: 2.48, 95% CI:2.08–2.96), any dementia (RR: 1.51, 95% CI:1.31–1.74) and MCI (RR: 1.21, 95% CI: 1.02–1.45) than those without.	Diabetes was associated with a higher risk of AD, VD, any form of dementia, and MCI than those without diabetes.
Garcıa-Casares et al, 2014	25 subjects with T2DM aged 45–65 years and 25 control subjects	Cross-sectional study	Executive functions, attention, information processing speed, and verbal memory, APOE 4 allele	It was found that reduced grey matter density in the orbital and prefrontal cortex, temporal (middle gyrus, parahippocampus, and uncus) and cerebellum regions were associated with poor executive and memory functioning.	Compromised executive and memory functions in T2DM compared to controls without T2DM.
Hussain et al., 2018	43 studies with 10,270 diabetes patients	Meta-analysis	Prevalence of depression	Prevalence of depression in T2DM patients was found to be 38% (95% CI: 31%–45%), Presence of complications with an odds ratio of 2.33, 95% CI: 1.62–3.36, $p < 0.00001$	The study found that 38% of T2DM patients suffered from depression. In people with type 2 diabetes, depression was more frequently associated with complications.
Luchsinger et al, 2007	918 Age > 65 699 –	Longitudinal cohort study for	Measures of learning and memory,	Having diabetes increases the risk of having an amnestic or non-amnestic MCI. There was	Diabetes was related to a higher risk of amnestic and non-amnestic Mild Cognitive Impairment (MCI)

	Nondiabetic, 219 -diabetic	10 years, every 18 months follow-up	orientation, abstract reasoning, language, and visuospatial ability	an 8.8% risk of MCI attributable to diabetes for the entire sample	
Manschot et al., 2006	113 T2DM subjects with hypertension, 51 nondiabetic control subjects	Cross-sectional study	Compared the cognition and brain magnetic resonance imaging (MRI) between type 2 diabetic patients and nondiabetic control subjects and assessed the relationship between cognition and MRI findings and blood pressure and metabolic control	Cortical and subcortical atrophy, deep White Matter Lesion (WML) and infarcts were more prevalent in T2DM than in control subjects. Cognitive performance was poor in the following domains - memory, attention, information processing and executive function. It was found that cognitive function was inversely related to WMLs, atrophy, and infarctions. HbA1c and diabetes duration are moderately correlated with impaired cognition. The strongest association was found with age.	The cognitive impairments in patients with type 2 diabetes are related to structural changes in the brain. These changes are indicative of a vascular etiology, although the increased cortical brain atrophy and the relation with age are also suggestive of other mechanisms such as accelerated brain ageing.
Monette et al., 2014	25 studies with nondemented T2DM adult patients	Meta-analysis – effect size	General cognitive functioning; Attention, Working memory, Fluency, Processing speed (learning and immediate recall, delayed recall)	The presence of type 2 diabetes is associated with mild to moderate deficits in all cognitive abilities measured, with effect sizes that range from small to medium. Processing speed and divided attention/shifting had the largest effect sizes	T2DM leads to mild to moderate cognitive decline in all domains.

Rawlings et al, 2014	**13351** black and white adults aged 48 to 67 years n=1779 (Diabetes) 11,572(non-diabetes)	Prospective cohort study	DSST DWRT WFT HbA1c HDL	The cognitive decline, over 20 years, was 19% higher in individuals with diabetes in midlife compared to those without diabetes. Those with prediabetes showed a significantly greater decline in cognitive function. The decline was greater in participants with poorly controlled diabetes than in participants with well-controlled diabetes	In later life, people with diabetes in midlife have 19% more cognitive decline compared to those without diabetes. Poorly controlled diabetes was associated with a greater decline.
Van den Berg et al, 2009	68 -T2DM, 38-control	RCT, assessment at baseline and after 4 years	Neuropsychological assessments – Cognitive domains: abstract reasoning, memory, information processing speed, attention and executive function	Cognitive decrements are moderate in size and cognitive decline over 4 years is largely within the range of what can be viewed in normal ageing.	The cognitive changes associated with diabetes develop slowly over time and are moderate in size.

Table 2. Summary of studies assessing cerebral oxygenation and working memory in T2DM patients

Study (Author, Year)	Sample size	Experimental Design	Outcome Measures	Findings	Conclusions
Barbey et al., 2013	Subjects with brain injury-199; healthy - 54	Investigatory study	Working memory performance using N-back task. WMS and the WAIS	An important neuropsychological finding of this study is that verbal and spatial knowledge manipulation requires the dlPFC	The dlPFC region is a core component of the working memory that manipulates verbal and spatial information.
Beishon et al., 2017	26 studies (11-TCD, 8-fNIRS, 5-fMRI, 2-PET)	Systematic Review	Cerebral hemodynamics – Cerebral blood flow, Oxygenation	Compromised cerebral hemodynamics in early stages of cognitive decline.	Even at an early stage of cognitive decline, there was a clear abnormality in cerebral hemodynamics and oxygenation parameters.
Bonetti et al., 2018	11 fNIRS studies with healthy individuals	Review	Oxygenation changes with cognitive tasks	Increase in OxyHb and decrease in DeoxyHb in the PFC region during WMT and VFT	Performing working memory tasks increases oxygen consumption, resulting in increased blood flow, resulting in higher OxyHb levels and lower DeoxyHb levels.
Chen et al., 2014	30 diabetic patients, 37 healthy controls	Cross-sectional study	N-back task performance, brain activation through fMRI	T2DM patients had poorer executive and memory abilities than control subjects. Further, under different WM loads, the brain activation patterns in T2DM patients changed, with less activation of the inferior left frontal gyrus when under low load and less activation of the left middle frontal gyrus (MFG)	T2DM patients had reduced activation in MFG and SFG regions compared to healthy individuals during the working memory task.

				and superior frontal gyrus (SFG) when under high load.	
Chung et al., 2007	10 healthy college students	Investigatory study	N-back task performance and Heart rate	An increase in blood oxygen saturation was observed after 40% oxygen administration, as well as a positive effect on the performance of n-back tasks and a decrease in heart rate.	Transient oxygen administration improves cognitive functioning
Duarte, 2015	121 subjects (51-T2DM, neurologically intact patients with T2DM)	Cross-sectional study	BOLD (Blood Oxygenation Level-Dependent) response to visual motion stimuli.	The fMRI response profile of patients with T2DM shows significantly impaired neurovascular coupling.	fMRI study shows that T2DM patients have compromised neurovascular coupling.
Endo et al., 2013	13 young (age,23+-1) subjects (8 female, 5 male)	Experimental study	With and without Dynamic exercise (ergometer) of different intensity and PFC oxygenation, Stroop test results before and after the cessation of the exercise. HR and MAP	Heart rate (HR) and mean arterial pressure (MAP) not influenced by exercise, remain the same during Stroop tests. The total period of the Stroop test was (improves cognition) shortened after dynamic exercise. No change in test scores. Average OxyHb is increased during dynamic exercise, with no change during low intensity exercise. DoxyHb remained near the baseline in all the exercises. Similar response from Right and Left PFC.	Moderate intensity exercise increases PFC oxygenation, while low intensity exercise does not. In addition, moderate exercise improves response time.

Heeger and Ress, 2002	-	Review	Influence of fMRI signal on neuronal activity	The linear transform model, a common assumption in the interpretation of fMRI studies, is a reasonable and useful approximation.	fMRI signal changes indicate the changes in hemodynamics due to alterations in neuronal activity
Kane and Engle, 2002	-	Review	Executive-attention framework for guiding future research on both PFC function and cognitive control	Executive-attention framework is based on the constructs of working-memory capacity, general fluid intelligence, and prefrontal cortex function.	The review confirms the view that dorsolateral PFC circuitry is critical to executive-attention functions
Mogi et al., 2011		Review	Neurovascular coupling in Type 2 diabetics	Diabetes induced microvascular complications, such as disruption of the Blood Brain Barrier (BBB) plays a role in cognitive impairment	In T2DM, cognitive impairment may be due to disruption in BBB leading to poor neurovascular coupling.
Owen et al., 2005	24 studies	Meta-analysis	Neuroimages of activation of brain areas due to N-back working memory paradigm	The regions activated robustly were the lateral premotor cortex; dorsal cingulate and medial premotor cortex; dlPFC, vlPFC, frontal poles; and medial and lateral posterior parietal cortex.	N-back working memory paradigm shown to activate frontal and parietal cortical regions
Tanida et al., 2012	19 healthy female subjects, fNIRS study	Experimental	Working memory performance, PFC oxygenation	Evoked cerebral blood oxygenation changes in the lateral prefrontal cortex during the Sternberg test (ST)	In healthy participants, oxygenation increases in the PFC region while performing working memory tasks

Table 3. Summary of studies assessing the effect of yoga in T2DM patients

Study (Author, Year)	Sample size	Experimental Design	Outcome Measures	Findings	Conclusions
Bellissimo et al., 2020	20 healthy participants (10 male,10 female)	Experimental	Heart rate (HR), Stroke volume (SV), Cardiac output (CO), OxyHb and DeoxyHb in the PFC region following different yogic breathing techniques	Increase in OxyHb in the PFC region following fast yogic breathing. No significant changes in HR, SV and CO.	According to this study, fast yoga breathing stimulates cerebral brain oxygenation in the PFC region and may improve brain blood flow in a healthy and clinical population
Brunner et al., 2017	43 young participants (8 male, 35 females)	Within-subject design, 6 sessions (60 min each) of asanas and mindful meditation	Digit span and Letter-number sequencing, Mind full Attention Awareness Scale (MAAS)	Improvement in WM functioning and attentive mindfulness was observed	Yoga with mindfulness meditation may enhance attentive mindfulness and improve WM functioning
Bussing et al., 2012	26 studies	Review	Physical and mental health related outcome measures	A review of review literature on the effect of yoga on several physiological and psychological factors found that yoga could be an effective adjunct treatment method.	Yoga may enhance patient self-efficacy, self-competence, physical fitness, and group support, and it may also be effective as a supportive adjunct to mitigate medical conditions, although it has not yet been proven as a stand-alone treatment for medical conditions.

Cohen et al., 2009	4 subjects	Pre-Post study	CBF following 12-week Iyengar yoga program	Greater CBF in the right PFC following 12 weeks of Iyengar yoga program	This study found a training effect of yoga that enhances the activation in the prefrontal cortex
Eyre et al., 2017	81 participants with MCI	Randomized control trial	Comparison of Kundalini yoga (KY) and Memory enhancement training (MET)	KY group showed short- and long-term improvements in executive functioning as compared to MET, and broader effects on depressed mood and resilience	Kundalini yoga is found more effective in improving executive function compared to memory enhancement training.
Gothe and McAuley, 2015	15 RCTs, 7 acute exposure studies	Meta-analysis	Attention, Memory, Executive function and Processing speed	Interventional studies showed that yoga had the strongest effect on attention and information processing speed, followed by executive function and memory. The acute effect of yoga was strongest on memory, followed by attention, processing speed and executive function.	Immediate and long-term yoga practice positively affects the cognitive domains namely memory, executive function, attention and processing speed.
Innes et al., 2016	13 – Non randomized and 12-randomized control trials with 2170 adult participants.	Systematic Review	Effect of yoga practice on specific health outcomes pertinent to the management of T2DM	A positive effect on glycaemic control, insulin resistance, lipid profiles, body composition, and blood pressure. Improves the function of the nervous system, pulmonary performance, mood, sleep, and quality of life, and reduces the need for medications. Reduces	Studies show that yoga may have positive effects on a variety of factors related to managing type 2 diabetes. Yoga may lower oxidative stress, decrease sympathetic activation and improve nervous system function, enhance pulmonary performance, sleep, quality of life and reduce medication.

				oxidative stress, decreases sympathetic activity, and improves nervous system function.	
Jayawardena et al., 2018	18 studies with 842 participants in total (30 to 78 years of age)	Systematic review and meta-analysis	The benefit of yoga practice compared to physical exercise in T2DM	Reduction in FBG, PPBG, HbA1c and Body mass index (BMI) in the yoga group compared to the Exercise group. No difference in lipid parameters, blood pressure and other body composition measures.	Yoga reduces glycemic parameters more effectively than physical exercise, although no differences are observed in lipid levels and blood pressure.
Kyizom et al., 2010	60 T2DM participants (30 yoga)	Experimental study	Latency and amplitude of N200 and P300	Significant improvement in latency and amplitude in the yoga group compared to control.	Yoga improves latency and amplitude of P300 and N200, cerebral evoked potentials, which measure cognitive improvement.
Mohan et al., 2015	30 T2DM participants without a control group	Case study	HbA1c, FBS, MMSE score	The study showed that yoga significantly reduced FBS and HbA1c in the participants. MMSE scores improved significantly for these patients following yoga as well.	Improvement in cognition following yoga practice in T2DM
Nagarathna et al., 2012	YG, n=141 CG, n=136	RCT	blood glucose, HbA1c, lipid profile Medication score	Reduction in PPBG, HbA1c, triglycerides, LDL, total cholesterol and dose of oral hypoglycemic medication in the yoga group	Yoga is more effective than exercise in lowering blood sugars and improving lipid profile in T2DM patients
Nangia et al., 2012	19 – yoga, 19- controls	Experimental	Digit Symbol Test (DST),	Yoga practitioners showed better performance in DST,	Yoga practice improves attention and concentration, remote memory, mental

			PGI memory scale, (PGIMS), Mental Health questionnaire	improved scores in the PGI memory scale and Mental Health questionnaire	balance, delayed and immediate recall, verbal and visual retention.
Nagothu, Reddy, Archana et al., 2015	20 T2DM participants (10 yoga)	Case-control study	HbA1c, Addenbrooke's Cognitive Examination - Revised battery (ACE-R)	Decreased HbA1c and better ACE-R scores in the yoga group.	Improvement in cognition following yoga practice in T2DM.
Ross and Thomas, 2010	81 studies comparing yoga and exercise	Review	Physical and mental health related outcome measures	Various physiological and psychological health parameters indicate that yoga may be as effective as exercise.	Yoga may be as effective or even more effective than exercise at improving a variety of health-related outcomes in both healthy and diseased populations.
Sachdeva et al., 2015	10 studies	Review	Non-pharmacological therapies and their outcome	Various non-pharmacological methods were discussed keeping the cognitive health as an outcome.	There is a possibility that non-pharmacological interventions such as exercise, yoga, music, computer training, brain stimulation, etc. could contribute to maintaining and possibly improving optimal cognitive functioning.
Thind et al., 2017	23 studies with 2473 adult T2DM	Systematic review and meta-analysis	Glycemic control (i.e. HbA1c, FBG, or PPBG). Secondary outcomes - lipid profile,	Compared with controls, yoga participants were successful in improving their HbA1c, FBG, PPBG, lipid profile, blood pressure, body mass index, waist/hip ratio and cortisol level	Many studies show that yoga helps in improving glycaemic parameters such as HbA1c, FBG and PPBG.

			and diastolic blood pressure, body composition, and fasting cortisol		
Vizcaino et al., 2016	29 studies	Systematic review and meta-analysis	Yoga as complementary therapy for T2DM – HbA1c, FBG, PPG	Reduction in FBG in yoga practice compared to standard care alone. The effect on PPG and HbA1c was not consistent	There was a reduction in fasting glucose with three months of yoga practice, but there were no consistent effects on postprandial glucose or HbA1c.