2. INTRODUCTION

The incidence of type 2 diabetes mellitus (T2DM) is increasing in India, and has become a significant public health problem. The number of people with diabetes in India currently around 65.1 million is expected to rise to 109.0 million by 2035 [1]. The deleterious effect of diabetes mellitus on the retinal, renal, cardiovascular and peripheral nervous system are widely acknowledged. Less attention has been given to the effect of diabetes on cognitive functions. Although the progress is being made, the difficulty of detecting neurocognitive dysfunctions in patients with diabetes in the clinical setting may explain in part why the field of cognitive dysfunction in diabetes has not advanced similarly to other fields dealing with hyperglycemia associated end organ damage. Evidence from the previous studies have shown that type 2 diabetes is associated with cognitive impairment [2, 3]. Type 2 diabetes has been associated with decreases in psychomotor speed [4, 5], frontal lobe/executive function [5-7], verbal memory [8], processing speed [8], complex motor functioning [5], working memory [6, 7], immediate recall, delayed recall [9], verbal fluency [5, 10], visual retention [11], and attention [12]. The exact pathophysiology of cognitive dysfunction in diabetes is not completely understood but it is likely that hyperglycemia, vascular disease, hypoglycemia and insulin resistance play significant roles. This complication further lowers the quality of life in patients significantly and imposes enormous burden in terms of health and economic outcomes. We now have many kinds of antidiabetic medications, and each medication class has unique mechanisms of action and characteristics. To the best of our knowledge, there are no specific, well designed, clinical studies considering potential positive or negative effects of drug treatment on cognitive function in diabetic patients. The optimal level of blood glucose lowering and the best selection and combination of anti diabetic medications on cognitive performance will be explored in the present study.

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and pancreatic β-cell dysfunction which is linked to hyperglycemia and hyperinsulinemia. At the cellular level, type 2 diabetes mellitus is associated with mitochondrial dysfunction, increased oxidative stress, endoplasmic reticulum stress, vascular dysfunction, increased inflammation, and altered energy metabolism. These changes are also present in some common human neurological disorders, where they cause functional disturbances in neurons and in surrounding cells, ultimately leading to cell death [13]. In view of common mechanisms prevailing in type 2 diabetes and brain disorders, antidiabetic drugs might also positively affect brain-cell metabolism, which could be of clinical importance for treatment of brain complications in diabetes.

OVERVIEW OF MEMORY AND COGNITION

Cognition is one of the higher functions that our brain performs. Cognition is defined as “the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses” [14]. Memory is the retention, recording, and
process of retrieving knowledge. All knowledge gained from experience such as known facts, remembered events, gained and applied skills would be considered as memory [15] The “brain working memory” is defined as the ability to keep record of many bits of information at the same time and the recall of this information immediately if needed for subsequent thoughts [16]. When working memory is damaged, a wide range of cognition impairments occur and the patient will not be able to appropriately use his/her own information for thinking in different situations [15].

The majority of advanced cortical functions arise from association cortex. The main association areas are: (1) the parieto-occipitotemporal association area; (2) the prefrontal association area; and (3) the limbic association area [16].

Our knowledge about the mechanisms of thinking and remembering is little. It seems that each thought arises from simultaneous activation of many parts of the different areas in the brain such as cerebral cortex, limbic system, thalamus and reticular formation of the brainstem. The memory is the result of some events in the synaptic transmission by changing its basic sensitivity [16].

Constant neural activity that arises from traveling nerve signals to a temporary memory trace can create a “short term memory”. A temporary chemical or physical synaptic change that lasts for a few minutes up to several weeks makes an “intermediate long term memory”. Structural alterations in synapses occur when a “long term memory” is created and can be used weeks to years later [16]. The hippocampus and, to a lesser degree, the thalamus are responsible for deciding which thoughts are important enough to be saved as memories [16].

It is possible to acquire information about the patient’s cognitive, behavioral, linguistic, and executive functioning, and memory through Neuropsychological tests. These data can be used in the diagnosis of cognitive disorders and for localization of the abnormality in the brain, as well as, the assessment of therapeutic effects of any treatment modality on the cognitive dysfunction. Neurocognitive domains and some examples for their assessment are categorized in the Table 1.

Table 1 Neurocognitive domains and some examples for their assessment [17, 18]

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Examples of assessments</th>
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<tr>
<td>Complex attention (sustained attention, divided attention, selective attention, processing speed)</td>
<td>Sustained attention: Maintenance of attention over time Selective attention: Maintenance of attention despite competing stimuli and/or distractors Divided attention: Attending to two tasks within the same time period Processing speed can be quantified on any task by</td>
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<td>Executive function (planning, decision making, working memory, mental flexibility)</td>
<td>Planning: Ability to find the exit to a maze; interpret a sequential picture Decision making: Performance of tasks that assess process of deciding in the face of competing alternatives (e.g., simulated gambling) Working memory: Ability to hold information for a brief period and to manipulate it (e.g., adding up a list of numbers or repeating a series of numbers or words backward) Mental/cognitive flexibility: Ability to shift between two concepts, tasks, or response rules</td>
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<td>Learning and memory [immediate memory, recent memory (including free recall, cued recall, and recognition memory), very-long-term memory (semantic, autobiographical), implicit learning]</td>
<td>Immediate memory span: Ability to repeat a list of words or digits. Note: Immediate memory sometimes subsumed under “working memory” (see “Executive Function”) Recent memory: Assesses the process of encoding new information (e.g., word lists, a short story, or diagrams) Free recall (the person is asked to recall as many words, diagrams, or elements of a story as possible Cued recall (examiner aids recall by providing semantic cues such as “list all the food items on the list” Recognition memory (examiner asks about specific items, e.g., “Was ‘apple’ on the list?”) Semantic memory (memory for facts) Autobiographical memory (memory for personal events or people) Implicit (procedural) learning (unconscious learning of skill)</td>
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<td>Language [expressive language (including naming, word-finding, fluency, and grammar and syntax) and receptive language]</td>
<td>Expressive language: Confrontational naming (identification of objects or pictures) Fluency [e.g., name as many items as possible in a semantic (e.g., animals) or phonemic (e.g., words starting with “f”) category in 1 min] Grammar and syntax (e.g., omission or incorrect use of articles, prepositions, auxiliary verbs) Receptive language: Comprehension, performance of actions/activities according to verbal command</td>
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Neuropsychological evaluation measures the cognitive abilities in the patient quantitatively, and its results must be interpreted in the setting of the patient's: Age, education, gender, and cultural background.

**OVERVIEW OF QUALITY OF LIFE**

Quality of life evaluation is one of the most significant indicators of patients' condition predicated by their health, both physical and psychological. There is no generally accepted definition of QOL. It can be explained as an individual’s ability to act in accordance with his/her public position and to enjoy life [19]. WHO defines QOL as an individual’s perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [20].

There are subjective (emotional status, life satisfaction, well-being) and objective (physical activity, occupational rehabilitation) criteria of QOL [20]. QOL assessment can be applied to all types of pathologies, including DM. This approach allows assessing the general condition of a patient against the background of prior disease, and the dynamics of this disease, against the background of basic and adjunctive therapy and/or changes in emotional state.

The following factors are evaluated quantitatively:

<table>
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<tr>
<th>Perceptual-motor (includes abilities subsumed under the terms visual perception, visuoconstructional, perceptual-motor, praxis, and gnosis)</th>
<th>Visual perception: Line bisection tasks can be used to detect basic visual defect or intentional neglect Visuoconstructional: Assembly of items requiring hand-eye coordination, such as drawing, copying, and block assembly Perceptual-motor: Integrating perception with purposeful movement (e.g., rapidly inserting pegs into a slotted board) Praxis: Integrity of learned movements, such as ability to imitate gestures (wave goodbye) or pantomime use of objects to command (“show me how you would use a hammer”) Gnosis: Perceptual integrity of awareness and recognition, such as recognition of faces and colors</th>
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<tr>
<td>Social cognition (recognition of emotions, theory of mind)</td>
<td>Recognition of emotions: Identification of emotion in images of faces representing a variety of both positive and negative emotions Theory of mind: Ability to consider another person’s mental state (thoughts, desires, intentions)</td>
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• Physical functioning (PF) reflects physical condition limiting physical activity (self-care, walking, mobility, stair climbing, weight lifting, etc.). Low rates indicate that physical activity is limited by patients’ health condition.
• Role-physical functioning (RP) assesses physical condition effects on daily role functioning (work, daily activity). Low rates indicate that daily activity is limited significantly by patients’ physical condition.
• Bodily pain (BP) and its impact on ability to perform daily activity including housework and tasks outside home. Low rates indicate that pain limits patients’ physical activity.
• General health (GH) was designed to examine patients’ self-assessment of current health condition and treatment perspectives. The lower is this score, the lower is the self assessment of general condition by the patient.
• Vitality (VT) supposes a sense of energy and activity or, in contrast, a sense of exhaustion. The low rates indicate patients’ fatigue and vitality decrease.
• Social functioning (SF) is defined by the degree of restrictions in social activities (communication) due to their physical and emotional status. Low rates indicate significant limitation of social contacts and reduction of communication in relation to both physical and emotional deterioration.
• Role-emotional functioning (RE) is determined by the emotional status and shows the degree in which it impedes daily activities (including time expenditure, a decrease in quality and extent of work, etc.). Low rates are interpreted as restrictions of daily activity related to emotional deterioration.
• Mental health (MH) characterizes the mood, the presence of depression or anxiety, and the common index of positive emotions. Low rates indicate depression, anxiety, and mental disturbances [21].

Quality of life in patients with insufficient glycemic index control has statistically lower levels comparing with those with constant glycemic index. Nevertheless, with a rise in Glycosylated hemoglobin rates (HbA1C), the results of SF-12, SF-36 survey become lower; with HbA1C above 8.1 %, the QOL score was statistically lower than in patients with HbA1C below 8 %. Moreover, the QOL score is lower in patients with complications of type-2 diabetes and in those undergoing insulin therapies. General health, physical functioning, social functioning, and patients’ psychical health are the most vulnerable functions [22].

PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENT

As diabetes is a heterogeneous disease that is easily compounded by hypertension, dyslipidemia and so on, it is considered to be a clinical condition that is modified by many factors. However, for cognitive dysfunction, the underlying conditions are blood glucose disorders, such as hyperglycemia and hypoglycemia, and insulin disorders, such as insulin resistance and insulin insufficiency, have been shown to lead to cognitive dysfunction. However, the exact pathophysiological mechanism of cognitive dysfunction
and cerebral damage in DM is not completely understood, but different causes such as hyperglycemia, vascular disease, hypoglycemia, and insulin resistance seem to play significant roles which can be seen in figure 1 reference [23].

**Figure 1: Possible Mechanistic Contribution to Cognitive Impairment seen in diabetes mellitus**

**THE ROLE OF HYPERGLYCEMIA**

Glucose is the main energy source of the brain. Although the brain needs glucose, too much of this energy source can be a bad thing. Both chronic and acute hyperglycemia seems to be the important factors for cognitive decline [24] though the effects of chronic hyperglycemia are more pronounced than those of acute hyperglycemia. High blood glucose levels can be detrimental to the brain’s functional connectivity, impairment in working memory and attention and it can lead to small-vessel disease, which restricts blood flow in the brain, causing cognitive difficulties. Hyperglycemia alters function through a variety of mechanisms including polyol pathway activation, increased formation of advanced glycation end products (AGEs), oxidative stress, diacylglycerol activation of protein kinase C, and increased glucose shunting in the hexosamine pathway [25]. These same mechanisms may be operative in the brain and induce the changes in cognitive function that have been detected in patients with diabetes [26].

Preclinical data confirmed that the high exposure of cerebral cortex to excessive glucose and the altered glucose uptake/metabolism in rat thalamus might contribute to
Introduction

hyperglycemia-related cognitive dysfunction [27]. A longitudinal study, that involved 200 diabetic patients, suggested that higher glucose levels could be a risk factor for dementia [28].

Although most data point to a detrimental role of hyperglycemia, a recent meta-analysis comparing the effect of intensive vs. standard glycemic control on cognitive decline in type 2 diabetic patients, suggests that intensive glycemic control should not be recommended for prevention of cognitive decline in diabetic patients because there is no evidence of its higher effectiveness in comparison to standard treatment [29]. A systematic review of 86 articles has further confirmed that the strength of the association between glycemic levels and cognitive function in diabetic people is weak [30].

THE ROLE OF HYPOGLYCEMIA

Neurons mainly rely on glucose as their energy source, and interruption of the supply of glucose causes neuronal damage and cognitive impairment [31]. If there isn’t enough glucose in the brain, for example, neurotransmitters, the brain’s chemical messengers, are not produced and communication between neurons breaks down. Hypoglycemia is the major, and most feared, complication of pharmacological therapies for diabetes that contributes to increased morbidity, reduced quality of life and limits treatment in many cases and in particular, hypoglycemic events, acute or recurrent, have been called into question in cognitive decline and dementia [32].

The damaging effects of hypoglycemia on the brain are known since 1930s, when insulin was discovered. It was early demonstrated that hypoglycemia-dependent brain damage was not uniform and the cortex and the hippocampus are the most involved areas. Today, oxidative stress and early ROS production have been suggested as a major mechanism contributing to neuronal death induced by hypoglycemia [33]. his mechanism has been confirmed in cultured hippocampal cells; indeed, under glucose deprivation, a rapid ROS increase due/linked to the activation of glutamate (NMDA and non-NMDA) receptors was observed [34] and was accompanied by an increase in inward calcium current. The latter is responsible for the activation of phospholipase A2 (cPLA2) and xanthine oxidase (XaO), which are calcium-dependent enzymes responsible for the synthesis of superoxide and other reactive species [33]. Mattson and others, in 1993 [35], evidenced that elevated calcium levels were associated to loss of mitochondrial trans-membrane potential, and consequently, mitochondrial damage. Mitochondrial uncoupling proteins (UCP) reduction is also involved in neuronal damage.

There is increasing evidence that hypoglycemia is associated with acute cognitive impairment and dementia [36]. The relationship between cognitive impairment and hypoglycemia appeared complex, with severe hypoglycemia associated with both poorer initial cognitive ability and accelerated cognitive decline [37]. Overall, the contribution of hypoglycemia to cognitive decline in diabetic patients is widely accepted, however, both the mechanisms and final validation is still lacking.

THE ROLE OF INSULIN RESISTANCE

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Insulin resistance (IR) is an important risk factor for the cognitive impairment in elderly patients with type-2 diabetes (T2D) [38]. Insulin resistance and type 2 diabetes mellitus may contribute to cognitive dysfunction through three indirect mechanisms. First, cognitive dysfunction in patients with type 2 diabetes has been correlated to inflammatory markers including C-reactive protein, α-1-antichymotrypsin, IL-6, and intercellular adhesion molecule 1 [39]. A second potential mechanism through which insulin resistance and type 2 diabetes could contribute to cognitive dysfunction is through the disruption of the hypothalamic-pituitary adrenal axis [40] and the increase in cortisol levels (hypercortisolemia) [41]. The third potential mechanism through which insulin resistance may indirectly contribute to cognitive dysfunction is by promoting the formation of senile plaques [42]. Blood glucose abnormalities and IR may be associated with acetylcholine (ACh) synthesis. ACh transferase, which is an enzyme responsible for ACh synthesis, is expressed in insulin-receptor-positive cortical neurons, and insulin regulates ACh transferase expression. Because ACh is a critical neurotransmitter in cognitive function, it may be relevant to neurocognitive disorders in diabetics [43].

THE ROLE OF VASCULAR DYSFUNCTION

Microalbuminuria, a marker of vascular dysfunction, predicted accelerated cognitive decline in T2DM subjects [44, 45]. These findings suggest that a deficit of vascular endothelial cells can lead to impairment of the functional coordination of the vascular supply in a timely response to the demand created by nervous activity. Neural activity requires a strong increase of cerebral blood flow and an acute increase in neuronal glucose. Hemodynamic neurovascular coupling coordinates these links (neurovascular units). Dysfunction of cerebral auto regulation with increasing age along with structural and functional alterations in cerebral blood vessels due to diabetes mellitus impairs the functioning of neurovascular units. These phenomena may induce functional deficits in neurons and increase neuronal degeneration and the susceptibility to hypoxia and ischemia. [46] Impaired neurovascular units would also induce BBB leakage [46]. T2D is a risk factor for atherosclerosis and small vessel disease, so it clearly increases the risk of multi-infarct dementia and mixed type dementia. Other risk factors of vascular disease contribute to the development of dementia in patients with T2D, probably by vascular involvement. It has been shown that in patients with T2D, presence of hypertension, signs of microvascular diseases such as lacuna, DR and micro-albuminuria or macrovascular complications such as cerebral infarcts increase the risks of dementia [47].

IMPAIRED NEUROGENESIS AND BLOOD–BRAIN BARRIER DYSFUNCTION

Neurogenesis in the hippocampus plays a role in learning and memory, and age-associated decline in neurogenesis has been reported [48]. Basic and animal experiments have indicated that a hyperglycemic environment induces the proliferation of adult neural progenitors, but is detrimental to their survival. The impaired neurogenesis in T2DM subjects may underlie an associated cognitive impairment and brain atrophy [49, 50]. T2DM reportedly induces changes in the permeability of the
blood–brain barrier [51]. The blood–brain barrier (BBB) consists of tight junctions between endothelial cells and astrocytic projections, which regulate paracellular and transcellular flow into the central nervous system (CNS), respectively.

Previous observations in brain tissue biopsied from AD subjects have indicated BBB breakdown in several respects [52, 53]. These include thinning of the endothelium, loss of mitochondria, and thickening of the basement membranes, the latter of which increase the accumulation of focal Aβ peptides. A break in the BBB also leads to potentially toxic substances and metabolites gaining access to the brain.[54, 55] Consequently, higher levels of peripheral proinflammatory cytokines may impact the degree of neuroinflammation. Mitochondrial dysfunction, vascular dysfunction, impaired neurogenesis, and blood–brain barrier dysfunction may also be involved in the mechanism underlying DM-associated cognitive dysfunction [56]

ROLE OF ANTIDIABETIC DRUGS ON COGNITIVE IMPAIRMENT

![Diagram showing effects of antidiabetic drugs on the periphery and brain](image)

**Figure 2: Effects of antidiabetic drugs on the periphery and brain**

Recent studies have shown that several antidiabetic drugs can promote neuronal survival and can lead to significant clinical improvement of memory and cognition. The action of some antidiabetic drugs on the periphery and brain is shown in figure 2.

Drug use is mainly based on the achievement of appropriate glucose blood level control maintaining HbA1c within the established limits found on current guidelines depending on patients’ risk. As above reported, treatment efficacy and appropriateness is mandatory not only for diabetes but also for a reduction in the risk of developing
cognitive impairment, although this latter point has been recently criticized [30]. On the other hand, drug effects on cognitive function in diabetic patients might not only be related to their efficacy against diabetes but also by their mechanism of action. Only few studies, up to date, have directly addressed the potential effects of antidiabetic drugs on cognitive impairment while several preclinical studies support their effectiveness. The following sections summarize the most relevant data on antidiabetic drugs and their potential role in the development of cognitive impairment.

DPP4 Inhibitors or Gliptins, metformin, sulfonylurea’s, alpha glucosidase inhibitors and insulin can improve glycemic control in the periphery and counteract organ complications in type 2 diabetes. These drugs also have favorable effects on the CNS. The mechanisms for the actions of these drugs in the brain are being investigated—they could act indirectly by positively affecting general whole-body metabolism and the vascular system in the brain.

**METFORMIN**

Metformin is a biguanide recommended as first-line antidiabetic therapy for the management of T2DM. Metformin has several effects that could benefit cognition through cerebrovascular or neurodegenerative mechanisms [57, 58], including decreasing advanced glycation end products [59, 60], inflammation, coagulation, and the prevention of the metabolic syndrome [61]. It is known that metformin possesses neuroprotective effects preventing apoptotic cell death in primary neurons [62], moreover, it effectively ameliorates impaired glucose uptake in insulin-resistant neuronal cells [63] it normalizes the reduction of cell proliferation and neuroblast differentiation in the sub granular zone of the hippocampal dentate gyrus in diabetic rats [64]. More recently, a study in the chronic L-methionine model of memory impairment, it prevents cognitive damage probably by normalizing oxidative stress in the hippocampus [65]. It has been shown that metformin prevents impairment of spatial reference memory associated with the HFD in rats [66]. Finally, a recent study evaluated in db/db mice, a mouse model of spontaneous diabetes with hyperinsulinemia, the effects of metformin on cognitive functions showing that the treatment for 6 weeks significantly ameliorates memory impairment including recovery of LTP and normalization of several brain molecular alterations such as RAGE and NF-κB [67].

Metformin effects were also previously linked to its ability in preventing brain mitochondrial dysfunction restoring learning behavior [68]. More recently, it has been shown that long-term treatment with metformin could decrease the risk of cognitive decline [69].

**SULFONYLUREAS**
Sulfonylureas have been widely used for the treatment of T2DM. They stimulate insulin-secreting cells in the pancreas by binding to ATP-sensitive potassium channels to increase insulin release. The blood-glucose-lowering effects of this class are relatively strong. There are no preclinical and molecular studies on the possible mechanisms involved in cognitive function regulation by these drugs; however, among sulfonylureas, glyburide and glipizide have been shown to act as mTOR (mammalian target of rapamycin) inhibitors [70]. Considering the role of mTOR pathway in memory and learning and its suggested role in neurodegenerative disorders including AD [71, 72], such drugs might have beneficial effects in the prevention of cognitive decline in diabetic patients. A recent study reported that glimepiride protects neurons against Ab-induced synapse damage and by reducing synapse damage could delay the progression of cognitive decline in AD [73].

**ALPHA-GLUCOSIDASE INHIBITORS**

This class of medications inhibits a-glucosidase to delay the absorption of carbohydrates, thereby lowering postprandial glucose. An animal study demonstrated the improvement of spatial memory and learning in a senescence-accelerated prone mouse model [74].

**INSULIN**

Exogenous insulin is used as a treatment for type 2 diabetes patients when hyperglycaemia is uncontrolled by OHAs. Insulin receptors are expressed in a wide range of brain areas including the hippocampus, hypothalamus, cortex, and olfactory bulbs [75]. Peripheral insulin enters into the brain across the blood–brain barrier through the active transport system [76]. Insulin has several roles in the central nervous system other than the regulation of glucose metabolism. Insulin is involved in feeding behavior, learning and memory, neuroprotection, and vasodilation [75]. Insulin inhibits tau phosphorylation through the glycogen synthase kinase 3-b pathway [77]. Insulin deficiency and/or IR in the brain contributes to the development of AD pathologies such as synaptic loss, limited dendritic arborisation and cognitive dysfunction [78]. There are, however, controversial reports in the literature on the effect of insulin alone or in combination with OHA on cognitive function in diabetes. Several molecular mechanisms have been proposed regarding insulin and its protective effects (glycemic control) and risks (anabolic effect including weight gain, inhibition of lipolysis, and enhanced lipogenesis) on cognition in patients with diabetes [79].

**DIPEPTIDYL PEPTIDASE IV INHIBITORS (GLIPTINS)**

Dipeptidylpeptidase-4 (DPP-4) inhibitors are a new class of oral hypoglycemic agents used in monotherapy or in combination with other antidiabetic compounds such as metformin, TZDs and sulfonylureas. They work by suppressing the enzyme DPP4 that normally degrades endogenous GLP-1, thereby increasing the concentration of biologically active GLP-1. Gliptins bind reversibly and competitively to DPP-4 indirectly enhancing incretin’s action. Sitagliptin, vildagliptin, saxagliptin, alogliptin, teneligliptin and
linagliptin are already marketed drugs. Several preclinical studies have been conducted to assess the role of gliptins on cognitive functions.

A large number of animal studies have shown the neuroprotective effects of DPP4 inhibitors in experimental rodent models of AD and vascular dementia [80]. Treatment with sitagliptin significantly improved the working and reference memories in diabetic rats [81, 82]. Recent data showed that Sitagliptin improves recognition memory and hippocampal neurogenesis in high-fat-fed mice [83]. Accordingly, Vildagliptin prevents neuronal insulin resistance, brain mitochondrial dysfunction, learning and memory deficit in rats with insulin resistance induced by high-fat diet [81, 84]. A recent study showed that Vildagliptin treatment also ameliorates cognitive deficits in the STZ-induced rat model of AD [85]. Furthermore Vildagliptin treatment ameliorates memory and learning impairment in a STZ-induced diabetic rat model [86]. Recently, Rizzo et al. reported that DPP4 inhibitors have protective effects on cognition compared with SUs in a human clinical study [87].

A benefit of DPP-4 inhibitors is that they are available for oral administration, while all GLP-1 receptor agonists are only injectable formulations. DPP4 inhibitors have a relatively low risk of hypoglycemia and body weight gain [88]. Hypoglycemia has been suggested to be a risk factor for cognitive decline and dementia, as is IR induced by weight gain. The beneficial features of DPP4 inhibitors (low risk of hypoglycemia and weight gain) suggest that treatment with DPP4 inhibitors may have advantages in terms of cognitive preservation [89].

**COMBINATION THERAPIES**

Patients with T2DM often require multiple drug use to achieve proper disease control. In a randomized double-blind trial that enrolled subjects with T2DM receiving metformin monotherapy or add-on therapy with either rosiglitazone or glyburide, it was demonstrated that both drugs induce a statistically significant cognitive improvement, which was related to a better glycemic control [90]. Another study evaluated cognitive impairment in patients with AD and T2DM treated with either oral antidiabetic drugs or combination of insulin with other diabetes medications, showing a significant slowing in cognitive decline after 12 months in patients treated with drugs’ combination [91]. Similarly, a prospective cohort study showed that addition of sulfonylureas to metformin therapy decreases the risk of dementia in T2DM patients [92].

**COMBINATION WITH A NON-PHARMACOLOGICAL APPROACH**

Many studies have demonstrated that exercise and a healthy diet ameliorate cognitive decline [93]. A recent report from the FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) demonstrated that a multidomain intervention including diet, exercise, and vascular risk monitoring improved cognition in an elderly population at risk of dementia, including those with DM [94]. The combination of a pharmacological approach and a non-pharmacological approach could be more efficacious than either approach alone.
OTHER FACTORS INFLUENCING COGNITIVE FUNCTIONS IN T2DM

![Diagram showing factors influencing cognitive impairment in type 2 diabetes]

**Figure 3: Risk factors of cognitive impairment in type 2 diabetes.**

It has been reported that lifestyle-related diseases in middle age, such as hypertension and dyslipidemia, increase the future incidence of dementia [95], and risk factors for cardiovascular events readily accumulate in diabetic patients. Thus, diabetes mellitus plays a central role in cognitive decline.

There have also been a large number of studies on an association between hypertension and cognitive function [96], and antihypertensive therapy is thus also important for the prevention of dementia. A recent meta-analysis found that renin–angiotensin system blockers, especially angiotensin II receptor blockers, were effective in preventing cognitive decline [97]. Although an association between hypercholesterolemia and cognitive impairment is still the subject of much debate, statins are thought to be useful in preventing dementia. However, they are considered to achieve this through a range of actions other than cholesterol lowering, including anti-inflammatory and vascular endothelial stabilizing actions [98].

A growing quantity of the literature reveals that physical activity influences brain function mainly frontal lobe mediated cognitive process such as planning, scheduling, and working memory [99-101]. Cross-sectional studies have shown that physically active individuals tend to exhibit better neurocognitive function relative to inactive individuals.
Prospective observational studies have reported similar findings, demonstrating that individuals who maintain greater levels of physical activity show improvements in neurocognitive function compared to their sedentary counterparts. [102, 103].

Exercise improves cognitive functions by regulating the physiological parameters including glycemic control, fasting blood-glucose level, and lipid profile. Moreover, it can restore the endothelial function and reduces the arterial stiffness, enhancing neurotrophic factors, increased BDNF and growth factors like IGF-1[104], increased levels of catecholamines, neurogenesis, enhanced functions of cortical region, increased hippocampus perfusion, increased synaptic plasticity, vascular functions, and cerebral blood flow. It has been documented that infusion of BDNF enhances learning [105].

Gender differences in treatment outcomes might influence the progress of DM and the onset of complications. Both genetic and hormonal factors are involved to influence such a progression. It has been suggested that very likely women arrive later and in worse conditions to DM diagnosis, receive diagnostic and therapeutic supports in a lesser measure reaching therapeutic goals to a lesser extent [106]; this was confirmed by a pooled analysis showing that females had smaller reductions in HbA1c and were less likely to reach glycemic goals than males [107]. It was highlighted a gender difference in the onset of cognitive impairment; a large (6892 patients) multicenter prospective population-based cohort study in patients aged 65 or older indicated that men have a significantly (P = 0.02) higher probability to return to normal cognitive functioning (36% vs 39%) and women more likely to have continuing cognitive disorder (58% vs 53%).

A cross-sectional analysis of 2629 community-dwelling older adults shown that a greater proportion of older women, compared to men, had cognitive impairment (15.8% vs. 7.3%, respectively) [108]

Although age remains the main risk factor for cognitive decline and dementia, it is increasingly recognized that a substantial number of cases with dementia may be attributable to obesity as one of the risk factor[109]. Obesity was associated with significantly worse cognitive performance, but only in men [110] One late-life study actually reported an inverted U-shaped association showing that both low and high BMI was associated with worse cognition [111].

Higher education level in a protective factor for the cognitive impairment in elderly patients with type-2 diabetes [38] People with a higher level of education will continue to perform at a higher level of cognitive functioning than their lower educated peers, which may delay the onset of impairment in the future [112]. A number of population-based studies have explored the relationship of cognitive function to age and education. Cross-sectional studies, using a variety of measures, have found decreases in cognitive function at older ages and higher scores in those with higher levels of education.[113, 114] Longitudinal studies have shown a decline in cognitive function with age that is most rapid after age 70,[115]. A Prospective study by S Roy has reported a weakly positive relationship between cognitive impairment and to the level of education [116]. The pathogenic mechanisms present with advancing age and with diabetes may have
been acting synergistically resulting in some of the observed neurobehavioral impairment, taking notice of this fact patients of all age groups were included in our study.

Hence life style risk factors like smoking, exercise, diet, cardiovascular risk factor like hypertension and dyslipidemia, diabetic specific variables like hyperglycemia, hypoglycemia, insulin resistance and insulin deficiency, macro and microvascular changes all contribute to the relationship between type 2 diabetes mellitus with cognition.

Our previous research suggested that Indian population with diabetes have higher prevalence of cognitive impairment than its western counterpart [117, 118]. People with cognitive impairment have difficulty in communicating and ability to think clearly and logically and are at increased risk of developing dementia [119, 120] or Alzheimer’s [121] in their later stage which increases the financial and personal costs with an adverse impact on health care expenditure and on families. Cognitive impairment also affects their quality of life [122]. Knowledge of the effectiveness of antidiabetic therapies on cognitive functions and quality of life in diabetes patients may help in delaying the occurrence of dementia and may bring down the social and economic burden of the disease and could even assists the physicians in making decisions about alternative drug therapies and process the regulatory approvals.

A large number of animal studies have demonstrated the effects of antidiabetic drugs on cognitive dysfunction and dementia but studies in humans have generated conflicting results. In the GPRD study (General Practice Research Database) conducted in United Kingdom the authors reported that long term use of Metformin were at a greater risk of developing Alzheimer’s Disease (AD) / Dementia than those not taking Metformin and also reported that there is no relationship between sulfonylurea use and risk of developing AD [123]. Similar results observed in a cross sectional study conducted in Australia, that individuals with self reported T2DM using Metformin had lower cognitive performance on the Mini Mental State Examination than those not taking metformin and also reported that there is no relationship between sulfonylurea use and risk of developing AD [123]. Similar results observed in a cross sectional study conducted in Australia, that individuals with self reported T2DM using Metformin had lower cognitive performance on the Mini Mental State Examination than those not taking metformin [124]. Conversely, in the Taiwanese study people with T2DM who used sulphonylureas had a lower incidence of dementia over 8 years of follow up compared with those who did not receive medications [92]. The same study has reported that the combination of a sulphonylureas and metformin had an even greater reduction in the 8 year hazard of developing dementia compared with no medication or single agent therapy with either drug class. Similarly in a study of 365 people with T2DM in the population based Singapore Longitudinal Aging Study, the use of metformin was associated with less cognitive impairment both cross-sectionals and after 4 years compared with those who were not receiving Metformin [69]. With these reports, we hypothesize that antidiabetic drugs modulate differently on cognitive functions and quality of life in diabetes patients. Few human studies have also examined the role of DPP4 inhibitors in preventing T2DM related cognitive impairment. To our knowledge, no studies were conducted in an Indian population, which may differ in lifestyle changes including dietary habits, level of physical activity when compared with Western population. In the current study we will be focusing
mainly on the influence of DPP4 inhibitors/Gliptins a new class of oral hypoglycemic agents on cognitive functions and quality of life in Indian population. Several preclinical models have demonstrated the neuroprotective effects of DPP4 inhibitors [85, 125]. Gliptins bind reversibly to DPP4 to increase the action of Incretin’s that, among other actions, increases pancreatic beta cell sensitivity to glucose and reduces alpha cell glucagon secretion[126]. The beneficial feature of DPP4 inhibitors (low risk of hypoglycemia and weight gain) suggests that treatment with DPP4 Inhibitors may have advantages in terms of cognitive preservation and also they are available for oral administration unlike GLP-1 receptor agonists which are available only as injectable formulations. In one retrospective study conducted in Italy, of 240 older people with T2DM and mild cognitive impairment (MCI) the use of DPP4 (n=120) is protected against worsening of cognitive functions independent of improved glucose control [87] but this require confirmation in randomized trials. The present study will be carried out to find out the impact of antidiabetic medications mainly focusing on Gliptins (mono and combination therapy) on cognitive functions and quality of life in type-2 diabetes mellitus patients with and without comorbidities hypertension and/or dyslipidemia in Indian population.