A REVIEW ON TYPE 2 DIABETES MELLITUS ASSOCIATED WITH COGNITIVE DISFUNCTION AND DEMENTIA AND FUTURE PERSPECTIVE

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ABSTRACT
Type 2 diabetes has previously been established as an independent risk for the development of both cognitive impairment and dementia. In their study, published in Neurology, the researchers wanted to investigate how inflammation, blood flow regulation in the brain and cognitive decline were related in people with the metabolic disorder. Diabetes mellitus affects millions of people, causing many complications. Recent studies have shown a link between diabetes and mild cognitive impairment (CI) in persons with earlier onset and greater severity of diabetes. Although the pathophysiology of CI is multifactorial, there is stronger evidence that lack of glycemic control resulting in hypo or hyperglycemia leads to CI among diabetic patients. With a growing geriatric population and increasing obesity trends in India, the prevalence of diabetes and the related CI, caregiving could be a challenge. Understanding the predisposing factors and the link between diabetes and CI or dementia can help improve the quality of life of diabetic individuals.

KEYWORDS: Cognitive impairment, metabolic disorder, hyperglycemia and dementia etc.

INTRODUCTION
Diabetes mellitus type 2 (also known as type 2 diabetes) is a long term metabolic disorder that is characterized by high blood sugar, insulin resistance, and relative lack of insulin.16]
Common symptoms include increased thirst, frequent urination and unexplained weight loss. Symptoms may also include increased hunger, feeling tired and sores that do not heal.[3] Often symptoms come on slowly.[6] Long-term complications from high blood sugar include heart disease, strokes, diabetic retinopathy which can result in blindness, kidney failure and poor blood flow in the limbs which may lead to amputations.[1] The sudden onset of hyperosmolar hyperglycemic state may occur; however, ketoacidosis is uncommon.[4,5]

Type 2 diabetes primarily occurs as a result of obesity and lack of exercise.[1] Some people are more genetically at risk than others.[6] Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes.[1] In diabetes mellitus type 1 there is an absolute lack of insulin, due to an autoimmune induced breakdown of the islet cells in the pancreas.[12,13] Diagnosis of diabetes is by blood tests such as fasting plasma glucose, oral glucose tolerance test, or A1C.[3]

Type 2 diabetes is partly preventable by staying a normal weight, exercising regularly and eating properly. Treatment involves exercise and dietary changes.[1] If blood sugar levels are not adequately lowered, the medication metformin is typically recommended.[14,7] Many people may eventually also require insulin injections.[9] In those on insulin, routinely checking blood sugar levels is advised; however, this may not be needed in those taking pills.[15] Bariatric surgery often improves diabetes in those who are obese.[8,16] Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity.[17] As of 2015 there were approximately 392 million people diagnosed with the disease compared to around 30 million in 1985.[18,11] Typically it begins in middle or older age,[6] although rates of type 2 diabetes are increasing in young people.[19,20] Type 2 diabetes is associated with a ten-year-shorter life expectancy.[10] Diabetes was one of the first diseases described.[21] The importance of insulin in the disease was determined in the 1920s.[22]

**Signs and symptoms:** The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger) and weight loss.[23] Other symptoms that are commonly present at diagnosis include a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections and fatigue.[13] Many people, however, have no symptoms during the first few years and are diagnosed on routine testing.[13] A small number of people with type 2 diabetes mellitus can develop a hyperosmolar hyperglycemic state (a condition of very high blood sugar associated with a decreased level of consciousness and low blood pressure).[13]
Complications: Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy.\textsuperscript{[10]} This is partly due to a number of complications with which it is associated, including: two to four times the risk of cardiovascular disease, including ischemic heart disease and stroke; a 20-fold increase in lower limb amputations, and increased rates of hospitalizations.\textsuperscript{[10]} In the developed world and increasingly elsewhere, type 2 diabetes is the largest cause of nontraumatic blindness and kidney failure.\textsuperscript{[24]} It has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia.\textsuperscript{[25]} Other complications include acanthosis nigricans, sexual dysfunction, and frequent infections.\textsuperscript{[23]}

Cause

The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors.\textsuperscript{[24,26]} While some of these factors are under personal control, such as diet and obesity, other factors are not, such as increasing age, female gender and genetics.\textsuperscript{[10]} A lack of sleep has been linked to type 2 diabetes.\textsuperscript{[27]} This is believed to act through its effect on metabolism.\textsuperscript{[27]} The nutritional status of a mother during fetal development may also play a role, with one proposed mechanism being that of altered DNA methylation.\textsuperscript{[28]} The intestinal bacteriæ Prevotella copri and Bacteroides vulgatus have been connected with type 2 diabetes.\textsuperscript{[29]}

Lifestyle: Lifestyle factors are important to the development of type 2 diabetes, including obesity and being overweight (defined by a body mass index of greater than 25), lack of physical activity, poor diet, stress, and urbanization.\textsuperscript{[10,30]} Excess body fat is associated with 30\% of cases in those of Chinese and Japanese descent, 60–80\% of cases in those of European and African descent, and 100\% of cases in Pima Indians and Pacific Islanders.\textsuperscript{[13]} Among those who are not obese, a high waist–hip ratio is often present.\textsuperscript{[13]} Smoking appears to increase the risk of type 2 diabetes mellitus.\textsuperscript{[31]}

Dietary factors: Dietary factor also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.\textsuperscript{[32,33]} The type of fats in the diet are important, with saturated fats and trans fatty acids increasing the risk, and polyunsaturated and monounsaturated fat decreasing the risk.\textsuperscript{[26]} Eating a lot of white rice appears to play a role in increasing risk.\textsuperscript{[34]} A lack of exercise is believed to cause 7\% of cases.\textsuperscript{[35]} Persistent organic pollutants may play a role.\textsuperscript{[36]}
**Genetics:** Most cases of diabetes involve many genes, with each being a small contributor to an increased probability of becoming a type 2 diabetic.\(^\text{[10]}\) If one identical twin has diabetes, the chance of the other developing diabetes within his lifetime is greater than 90%, while the rate for nonidentical siblings is 25–50%.\(^\text{[13]}\) All of these genes together still only account for 10% of the total heritable component of the disease.\(^\text{[37]}\) The TCF7L2 allele, for example, increases the risk of developing diabetes by 1.5 times and is the greatest risk of the common genetic variants.\(^\text{[13]}\) Most of the genes linked to diabetes are involved in beta cell functions.\(^\text{[13]}\) There are a number of rare cases of diabetes that arise due to an abnormality in a single gene (known as monogenic forms of diabetes or "other specific types of diabetes").\(^\text{[13,10]}\) These include maturity onset diabetes of the young (MODY), Donohue syndrome, and Rabson–Mendenhall syndrome, among others.\(^\text{[10]}\) Maturity onset diabetes of the young constitute 1–5% of all cases of diabetes in young people.\(^\text{[38]}\)

**Medical conditions:** There are a number of medications and other health problems that can predispose to diabetes.\(^\text{[39]}\) Some of the medications include: glucocorticoids, thiazides, beta blockers, atypical antipsychotics,\(^\text{[40]}\) and statins.\(^\text{[41]}\) Those who have previously had gestational diabetes are at a higher risk of developing type 2 diabetes.\(^\text{[23]}\) Other health problems that are associated include: acromegaly, Cushing's syndrome, hyperthyroidism, pheochromocytoma and certain cancers such as glucagonomas.\(^\text{[39]}\) Testosterone deficiency is also associated with type 2 diabetes.\(^\text{[42,43]}\)

**Pathophysiology**

Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance.\(^\text{[13]}\) Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver and fat tissue.\(^\text{[44]}\) In the liver, insulin normally suppresses glucose release. However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood.\(^\text{[10]}\) The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion.\(^\text{[13]}\)

Other potentially important mechanisms associated with type 2 diabetes and insulin resistance include: increased breakdown of lipids within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system.\(^\text{[10]}\)
However, not all people with insulin resistance develop diabetes, since an impairment of insulin secretion by pancreatic beta cells is also required.\(^\text{13}\)

**Diagnosis**

The World Health Organization definition of diabetes (both type 1 and type 2) is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either:\(^\text{47}\) fasting plasma glucose $\geq$ 7.0 mmol/l (126 mg/dl) or with a glucose tolerance test, two hours after the oral dose a plasma glucose $\geq$ 11.1 mmol/l (200 mg/dl).

A random blood sugar of greater than 11.1 mmol/l (200 mg/dL) in association with typical symptoms\(^\text{23}\) or a glycated hemoglobin (HbA1c) of $\geq$ 48 mmol/mol ($\geq$ 6.5 DCCT %) is another method of diagnosing diabetes.\(^\text{10}\) In 2009 an International Expert Committee that included representatives of the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended that a threshold of $\geq$ 48 mmol/mol ($\geq$ 6.5 DCCT %) should be used to diagnose diabetes.\(^\text{48}\) This recommendation was adopted by the American Diabetes Association in 2010.\(^\text{49}\) Positive tests should be repeated unless the person presents with typical symptoms and blood sugars $>$11.1 mmol/l ($>$200 mg/dl).\(^\text{48}\)

Threshold for diagnosis of diabetes is based on the relationship between results of glucose tolerance tests, fasting glucose or HbA1c and complications such as retinal problems.\(^\text{10}\) A fasting or random blood sugar is preferred over the glucose tolerance test, as they are more convenient for people.\(^\text{10}\) HbA1c has the advantages that fasting is not required and results are more stable but has the disadvantage that the test is more costly than measurement of blood glucose.\(^\text{50}\) It is estimated that 20% of people with diabetes in the United States do not realize that they have the disease.\(^\text{10}\)

Diabetes mellitus type 2 is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.\(^\text{51}\) This is in contrast to diabetes mellitus type 1 in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas and gestational diabetes mellitus that is a new onset of high blood sugars associated with pregnancy.\(^\text{13}\) Type 1 and type 2 diabetes can typically be distinguished based on the presenting circumstances.\(^\text{48}\) If the diagnosis is in doubt antibody testing may be useful to confirm type 1 diabetes and C-peptide levels may be useful to confirm type 2 diabetes\(^\text{52}\) with C-peptide levels normal or high in type 2 diabetes, but low in type 1 diabetes.\(^\text{53}\)
Overview of Memory and Cognition

Cognition is defined as “the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses”.\textsuperscript{[54]}

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.\textsuperscript{[55]} Memory can be categorized into declarative and non-declarative memory. Declarative memory mostly corresponds to the learning and recalling new facts, events, and materials. Non-declarative memory refers to the many forms of memories that are reflective or incidental.\textsuperscript{[55]}

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.\textsuperscript{[56]} 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.\textsuperscript{[55]}

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.\textsuperscript{[56]}

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.\textsuperscript{[56]}

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.\textsuperscript{[56]} The hippocampus and to a lesser degree, the thalamus are responsible for deciding which thoughts are important enough to be saved as memories.\textsuperscript{[56]}

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.

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. In addition, reliability, validity, sensitivity and specificity of these tests are important aspects that should be considered.

Etiology of Cognitive Disorders

Dementia and cognitive dysfunction have many causes. Alzheimer’s disease (AD) and other degenerative diseases, vascular dementia, alcohol consumption and certain drug abuse are some of these etiologies. Memory loss and cognitive impairment etiology.\[57\]

Table 1: Memory loss and cognitive impairment etiology.

<table>
<thead>
<tr>
<th>Etiology</th>
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<tr>
<td>Degenerative disorders including Alzheimer’s disease</td>
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<td>Vascular dementia</td>
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<td>Depression and anxiety</td>
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<td>Hippocampal sclerosis</td>
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<td>Subdual and epidural hematomas</td>
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<td>Vitamin B12 deficiency</td>
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<td>Seizures</td>
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<td>HIV associated neurocognitive disorder</td>
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<td>Hashimoto’s encephalopathy</td>
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Association between Diabetes and Cognitive Decline

Cognitive dysfunction with its wide range, from mild cognitive impairment (MCI) through dementia, is one of the chronic complications of diabetes mellitus.\[58\] Both diabetes and cognitive impairment occur more commonly at older age. There is strong evidence that T2D increases the risk of dementia in the form of multi-infarct dementia, AD and mixed type dementia. There are some close associations between diabetes and vascular dementia of above 100%-160% compared to AD which is about 45% to 90%.\[58\] The long-term risk of dementia increases in patients with diabetes by a factor of two.\[59\] T2D also increases the risk
of progression of MCI to dementia.\textsuperscript{[59]} Even in pre-diabetic state; there is an increased risk of AD and dementia which are not related to the future development of diabetes.\textsuperscript{[58]} About 80% of people with AD may have diabetes or impaired fasting glucose.\textsuperscript{[60]} There is a faster deterioration of cognition in diabetic patients rather than non-diabetic elderly ones.\textsuperscript{[61]} Diabetes is associated with 1.5-2 fold increased risk of cerebrovascular accidents\textsuperscript{[62]} and the relative risk of stroke increases 1.15 (95\%CI: 1.08-1.23) for every 1\% increase in HbA1C.\textsuperscript{[63]}

In recent years, the relation of diabetes to memory disorders has been well established. In 2011, Wessels et al.\textsuperscript{[64]} published results of their comprehensive prospective study on a large sample size from 1992 to 2007. Patients in this cohort were examined at baseline and five follow-up assessments throughout the 15 years of study. During each evaluation, participants were given the Community Screening Interview for Dementia as part of a home visit. They followed up 1702 subjects and showed that diabetes reduced their cognitive capabilities via cardiovascular disruption.\textsuperscript{[64]} The results of the Edinburgh Type 2 Diabetes Study that was conducted for evaluation of this correlation were published in 2013. At baseline, any clinical and subclinical macrovascular diseases including cardiovascular event history, carotid intima-media thickness, ankle brachial index, and serum N-terminal probrain natriuretic peptide (NT-proBNP) were evaluated. Seven neuropsychological tests were also done at baseline, and after 4 years. They found that stroke and subclinical markers of cardiovascular and atherosclerosis are associated with cognitive decline in older patients with type 2 diabetes (T2D).\textsuperscript{[65]}

Recent research collaboration between Mayo Clinic and Shanghai was reported in 2015. In this study, involving a considerable number of patients, the effect of diabetes on the cognitive function of patients was strongly evident. This was, of course, irrespective of patients’ gender, age and possible cardiovascular risk factors.\textsuperscript{[66]}

In one study, the relationship between T2D and cognitive impairment had been evaluated and the subjects with diabetes had lower MMSE score than those without diabetes (P < 0.01).\textsuperscript{[67]} Diabetes was also associated with increased odds of cognitive decline as determined by MMSE scores [odds ratio (OR), 1.9; 95\%CI: 1.01-3.6]. Also, a statistically significant correlation between the duration of the disease and cognitive dysfunction was observed (P = 0.001). The same correlation was also found for the quality of diabetes control (P = 0.002).
In a different study that was carried out on 4206 subjects by Qiu et al., they investigated whether and the extent to which vascular and degenerative lesions in the brain mediate the association of diabetes with poor cognitive performance. They assessed cortical and subcortical infarcts and higher white matter lesion volume. They also evaluated neurodegenerative processes on magnetic resonance images. The results of this cross-sectional study showed that diabetic patients’ speed in processing and executive functions was markedly lower than others. However, their memory function score was not any better either.

The role of diabetes in neurodegeneration has been confirmed by neuroimaging and neuropathological studies. MRI studies have shown that T2D is strongly associated with brain atrophy. The rate of global brain atrophy in T2D is up to 3 times faster than in normal aging.

**Pathogenesis of Cognitive Impairment in Type 2dm**

Diabetes and diabetes-related CI continue to grow due to the increase in obesity and longevity of the modern-day human population, with significant effect on society. In this light, it is essential to understand the pathophysiological alterations that cause the development and progression of diabetes-related CI and also to devise treatments to reverse or prevent these complications.

**Hypoglycemia vs. Hyperglycemia**

Hypoglycemia is the number-one reason for temporary or short-term CI. A normal and controlled glycemic level is defined as 4 to 7 mmol/L or 72 to 126 mg/dL. Levels can fluctuate in this range, and the diabetic patient can function adequately; but when levels fall below 4 mmol/L, cognitive deficits can be seen. When the brain does not have a sufficient amount of glucose to function, typically defined as <3.5 mmol/L or 63 mg/dL, certain symptoms can present and should be immediately corrected. It is possible for these short-term hypoglycemic states to result in permanent brain damage. Even repeated bouts of mild hypoglycemia have been shown to cause CI. Marked decreases in IQ were measured over a 6-year time period in one particular study. Many studies have been done on the effects of hypoglycemia and CI. The Edinburgh Type 2 Diabetes Study showed that severe hypoglycemia was linked to cognitive impairment later in life. The Fremantle Diabetes Study was able to document dementia and cognitive decline.
A recent 7-year follow-up study done in Taiwan used 1 million random subjects as the largest sample size to date. The study found that many different parameters were statistically significant predictors of dementia. Among the parameters studied, female gender, older age, insulin use, and previous episodes of hypoglycemia all put the patients in the study at high risk for dementia. Cases with previous episodes of hospitalized hypoglycemia resulted in a three-fold increase in dementia by the end of the study.\(^{[74]}\)

Hyperglycemia, when prolonged, can also have negative effects such as neuropathy, retinopathy, nephropathy and CI. Brain imaging using MRI of patients with hyperglycemia for long periods of time can show visible lesions. These lesions represent damage to the neurons, which in turn translates to CI in that patient. A decrease in white matter volume in particular has been linked to reduced processing of information and loss of executive function.\(^{[72]}\) A tighter glycemic control can help to prolong or even to some extent prevent the CI that can occur with T2DM.

**Microvascular Changes**

The common microvascular complications in diabetes include diabetic nephropathy, neuropathy, and retinopathy. Cerebral microvascular changes as seen in diabetic retinopathy can be the most common complication of T2DM. Predominantly, microvascular disease has been shown to affect the thalamus, basal ganglia, and white matter.\(^{10}\) An increased severity of microvascular changes shows a worse prognosis with regard to mental flexibility, verbal fluency, and processing speed. This was seen more in men than in women. The decline in processing speed was also found with hypertensive retinopathy.\(^{[75]}\) Executive-functioning deficits are also a concern because of the involvement of frontal subcortical atrophy.\(^{[76]}\)

**Macrovascular Changes**

The most noted macrovascular complications in diabetes include coronary artery disease, peripheral arterial disease, and stroke. Atherosclerosis is a leading cause of acute coronary syndrome as well as cerebrovascular accident and is accelerated by hyperglycemia secondary to T2DM. Macrovascular changes can affect heart and brain function by occlusion and ischemia. Cognitive impairment related to stroke alone could be directly linked to prolonged periods of hyperglycemia.\(^{[72]}\) In addition, diabetes promotes hyperglycemia when not properly controlled, which combined with hypertension and hyperlipidemia, can result in cognitive decline from brain structure atrophy due to large deposits of amyloid and other fatty products.\(^{[75,76]}\) Figure 1 shows the probable mechanisms leading to CI during diabetes.\(^{[77]}\)
Figure 1: Possible Mechanistic Contribution to Cognitive Impairment Seen in Diabetes Mellitus.

Inflammatory Changes
Obesity and T2DM can be associated with some systemic inflammation; this inflammation is believed to increase the risk for vascular disease. It is also thought that the inflammation is directly related to CI because inflammation of the brain itself is much like inflammatory changes seen in dementia. Although most studies have not focused on this link between inflammatory cytokines and CI, some information has been documented. Increases in interleukin (IL)-6, tumor necrosis factor (TNF), and C-reactive protein (CRP) have all been linked to lower cognitive functions.\(^\text{[75]}\)

Diabetes and Cognitive Impairment
Mild Cognitive Impairment: Mild CI is defined as the predementia state that is associated with an increased risk for developing dementia. Mild CI helps to identify individuals who may progress further to CI.\(^\text{[75]}\) Mild CI is characterized as memory complaints without a severe effect on activities of daily life.\(^\text{[78]}\) Diabetes has been linked to a 1.5-fold increase in the development of mild CI, thus putting diabetic patients at greater risk for dementia. Multiple longitudinal studies have demonstrated that T2DM is directly linked to mild CI and dementia and affects numerous cognitive domains. Mild CI can lead to a decrease in memory, language, verbal memory, executive functioning, abstract reasoning, and information-processing speed.\(^\text{[75]}\)
Dementia and Alzheimer's Disease: Dementia is associated with a decrease in memory, communication and reasoning. In 2014, more than 5 million people in the U.S. had Alzheimer's disease, with 1 in 9 persons aged ≥65 years suffering from the disease. The most common type of dementia is late-onset Alzheimer's disease (LOAD), followed by VaD. LOAD accounts for 70% to 90% of all cases of dementia. There is a 50% to 100% increase in the development of LOAD and VaD in patients with T2DM compared to those without. The most common type of dementia is late-onset Alzheimer's disease (LOAD), followed by VaD. Regions of the brain that are linked to LOAD are particularly high in insulin receptors. There can also be an increase of protein deposition in the brain in LOAD and T2DM that can be seen in the pancreas as well. Overall, there is increased incidence of LOAD with T2DM.

Translation to Clinical Practice

Screening: With T2DM being such a complex, chronic metabolic disorder, it requires intact cognition. Independent diabetic self-care is imperative for successful patient outcomes. Glycemic control relies on patient awareness of the condition even at home and is assisted by healthcare professionals with education on self-monitoring of blood glucose (SMBG), insulin dosing, and other pharmacologic interventions that depend upon compliance. Because the disease is associated with other comorbidities, it is part of diabetic care to have many annual screenings. For example, the presence of proteinuria is assessed to monitor kidney function, ophthalmoscopic examinations are performed to look for diabetic retinopathy, and monofilament tests are done to evaluate for diabetic neuropathy. In addition to the conditions already mentioned, as well as many others, CI is now on the rise as yet another commonly associated comorbidity. For clinicians, the Mini-Mental State Examination (MMSE) or another cognitive screening tool should be on the forefront of diabetic patient care. Some recommendations have been made to assist healthcare providers in treating the T2DM patient with regard to the increasing potential for cognitive impairment.

Sending written instructions and materials home for patients who are unable to remember them has been shown to be effective. For others, whose CI prevents reading comprehension, visual aids and even video depictions have been proven helpful for patient compliance with treatment.

Mental Status Screenings: Different studies have shown trends between specific cognitive screening tools and forms of dementia due to the characteristics of each subtype of dementia.
For example, Alzheimer's disease in the initial stage can be characterized by loss of episodic memory, while VaD has a severe impairment of executive functioning. Frontotemporal dementia has early impairments on letter fluency, and Lewy body dementia has a loss of attention and abstract reasoning. A screening tool that could pick up Alzheimer's disease might not detect frontotemporal dementia. Mental status screening tools should not only detect the CI, but also identify the most likely etiology. Although the MMSE is the most widely used, others, such as the Addenbrooke's Cognitive Examination-Revised (ACE-R), help to distinguish Alzheimer's disease specifically from other subtypes. Clinicians should take into account the many different types of screening tools to be performed.\textsuperscript{[81]}

**Pharmacologic Management:** For insulin-dependent diabetes mellitus (IDDM), strict glycemic control and SMBG are the preferred method of management, according to the ADA. When monitoring after an episode of hypoglycemia, a patient and provider should attempt to identify the cause and prevent any further hypoglycemic episodes due to their strong link to CI and dementia. Monitoring blood glucose before and after meals to prevent future events is recommended.\textsuperscript{[82]} Overall, well-controlled glycemic levels are what give the patient the best possibility for positive outcomes.

Some studies recently have argued that insulin significantly increases the prevalence of dementia and should be avoided, if possible. A documented decrease in the incidence of dementia is seen with the use of oral hypoglycemic agents, such as metformin. The use of HMG-CoA reductase inhibitors (statins) has been proven to significantly decrease the risk for dementia as well.\textsuperscript{[77]} Another drug class to consider is the peroxisome proliferator-activated receptors (PPARs) because of their efficacy in reducing inflammatory response, enhancing insulin sensitivity, and improving glucose metabolism.\textsuperscript{[83]} For example, rosiglitazone, a PPAR-\(\gamma\) agonist, has been shown to maintain performance on attention tasks and delayed recall. Other recent studies have shown negative effects of rosiglitazone in patients with Alzheimer's disease with regard to objective cognitive performance.\textsuperscript{[83]} More studies and research would benefit the medical community on this dispute.

**Investigational Therapies:** Another pharmacologic intervention to consider is noninvasive intranasal insulin. The administration of intranasal insulin is argued to be more efficacious because it delivers drugs directly to the brain faster.\textsuperscript{[83]} It has also been demonstrated to improve memory in normal adults. Glucagon-like peptide-1 (GLP-1), a stimulator of insulin secretion via oral glucose, has been studied as well. A study in the animal-subject phase
showed that cognitive deficits and insulin resistance had been improved by GLP-1. Two specific analogues were reviewed, extendin-4 and Val (8)-GLP-1(7–36). GLP-1 intranasal administration demonstrated improved glycemic control.[83] Further studies would be needed to support these claims. Weighing the risks and benefits for all diabetic patients to achieve the best glycemic control while keeping pharmacologic management to an affordable cost for the patient is the preferred treatment on an individual basis.

CONCLUSION
With the rising number of diabetic patients in India, the complications that accompany this metabolic disease process will play a key role in the future of healthcare, both for patients and providers. Providers need to be aware of the increasing prevalence of dementia as well and to recognize the link between two major ailments diabetes and dementia. With the strong ties between the two with regard to hypo and hyperglycemia, micro and macrovascular changes and other physiological changes in the body, clinicians need to be prepared to treat the whole patient. By using screening techniques to identify dementia early and detect cognitive impairment, patients can have a better chance at managing their diabetes at home with the assistance of medical providers. If clinicians can guide their patients to glycemic control in a healthy range, counsel them in pharmacologic interventions and educate them on diabetes and all of its complications, then patients will have opportunities for better outcomes.

REFERENCES


7. Maruthur, NM; Tseng, E; Hutflless, S; Wilson, LM; Suarez-Cuervo, C; Berger, Z; Chu, Y; Iyoha, E; Segal, JB; Bolen, S. "Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis". Annals of Internal Medicine, 19 April 2016; 164: 740–51. PMID 27088241. doi:10.7326/M15-2650. (Subscription required (help)).


20. Imperatore, Giuseppina; Boyle, James P.; Thompson, Theodore J.; Case, Doug; Dabelea, Dana; Hamman, Richard F.; Lawrence, Jean M.; Liese, Angela D.; Liu, Lenna L. "Projections of Type 1 and Type 2 Diabetes Burden in the U.S. Population Aged <20 Years Through 2050". Diabetes Care, December 2012; 35(12): 2515–2520. ISSN 0149-5992. PMC 3507562 Freely accessible. PMID 23173134. doi:10.2337/dc12-0669.


32. Malik, VS; Popkin, BM; Bray, GA; Després, JP; Hu, FB. "Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk". Circulation, 2010-03-23; 121(11): 1356–64. PMC 2862465 Freely accessible. PMID 20308626. doi:10.1161/CIRCULATIONAHA.109.876185.


34. Hu, EA; Pan, A; Malik, V; Sun, Q. "White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review". BMJ (Clinical research ed.), 2012-03-15; 344: e1454. PMC 3307808 Freely accessible. PMID 22422870. doi:10.1136/bmj.e1454.


