Expert Consensus on Cognitive Dysfunction in Diabetes

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[Abstract] The incidence of diabetes is gradually increasing in China, and diabetes and associated complications, such as cognitive dysfunction have gained much attention in recent time. However, the concepts, clinical treatment, and prevention of cognitive dysfunction in patients with diabetes remain unclear. The Chinese Society of Endocrinology investigated the current national and overseas situation of cognitive dysfunction associated with diabetes. Based on research both in China and other countries worldwide, the Expert Consensus on Cognitive Dysfunction in Diabetes was established to guide physicians in the comprehensive standardized management of cognitive dysfunction in diabetes and to improve clinical outcomes in Chinese patients. This consensus presents an overview, definition and classification, epidemiology and pathogenesis, risk factors, screening, diagnosis, differential diagnosis, treatment, and prevention of cognitive dysfunction in patients with diabetes.

Key words: diabetes; cognitive dysfunction; antidiabetic agents

Diabetes and cognitive dysfunction are chronic conditions that are widely prevalent worldwide; patients with diabetes are at a significantly high risk of cognitive dysfunction. Patients with cognitive impairment have reduced diabetes self-management ability and higher care dependency, which exacerbates progression of diabetes and thereby creates a vicious cycle. Cognitive impairment is increasingly being diagnosed in many patients with diabetes, and its prevalence is expected to increase over the forthcoming decades. However, there is limited awareness among medical practitioners regarding this subject and a lack of guidelines for optimal management, diagnosis, and treatment. The Chinese Society of Endocrinology has organized experts from related professions in China to review the epidemiology, definition, risk factors, screening, diagnosis, treatment, and prevention of diabetes-related cognitive dysfunction, based on the results of various national and overseas clinical studies, as well as management opinions and the current trends in China. Relevant recommendations have been provided to guide physicians in the comprehensive standardized management of cognitive dysfunction in diabetes and improve clinical outcomes in Chinese patients. This guideline will be updated and improved following accumulation of the results reported by further clinical studies.

1 OVERVIEW

Key tips: 1. Patients with diabetes are at a significantly high risk of cognitive dysfunction. 2. Cognitive dysfunction is increasingly being diagnosed as an increasingly prevalent complication of diabetes.

Epidemiological investigations have shown that the prevalence of diabetes was 11.6% among Chinese adults[1]. Diabetes is known to be associated with various acute and chronic complications and significantly affects cognitive function[2]. Cognitive dysfunction complicating diabetes has gained much attention in the medical community. Reske-Nielsen et al[3] introduced the concept of “diabetic encephalopathy” in 1966, following autopsies on 16 patients with diabetes concomitant with cognitive decline, in whom the authors observed severe diffuse degeneration of gray and white matter in the brain. Many subsequent epidemiological studies have reported an intrinsic association between diabetes and dementia, particularly Alzheimer’s disease (AD) and vascular dementia (VaD). For example, older age is associated with an increased risk of both diabetes and dementia; the peak age for disease onset is also similar.
in both conditions, and specific genetic predisposition is observed in both diseases. Patients with diabetes are at an increased risk of cognitive dysfunction, age-related cognitive decrements, and dementia[9]. The Rotterdam study reported that the risk of dementia was nearly 2-fold higher in patients with type 2 diabetes (T2DM) [relative risk: 1.9, 95% confidence interval (CI) 1.3–2.8][3]. A meta-analysis performed in China showed that the risk of AD, VaD, and mild cognitive impairment (MCI) was 1.46 (95% CI 1.20–1.77), 2.48 (95% CI 2.08–2.96), and 1.21 (95% CI 1.02–1.45)-fold higher in patients with T2DM than in healthy subjects, respectively[6]. In a longitudinal cohort study (median follow-up of 31.7 years), younger age at diabetes onset was significantly associated with a higher risk of subsequent dementia[7]. Diabetes is a well-recognized risk factor for dementia, and optimal management of diabetes may effectively prevent dementia[9]. The American Diabetes Association (ADA) guidelines (2021) emphasize the importance of awareness regarding diabetes-induced cognitive impairment, which highlights that poor glycemic control is associated with cognitive decline and that chronic diabetes tends to worsen cognitive function[9].

2 DEFINITION AND CLASSIFICATION

Key tips: 1. Cognitive dysfunction in diabetes usually refers to patients with diabetes accompanied by cognitive impairment. 2. Based on disease course or severity, diabetes-related cognitive impairment is categorized into asymptomatic cognitive decline, MCI, and dementia.

2.1 Definition

Diabetes-associated cognitive dysfunction usually refers to diabetes accompanied by impairment of cognitive function[10]. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association defines the following six principal domains of cognitive function: learning and memory, language, executive function, perceptual-motor function, complex attention, and social cognition[11]. Cognitive dysfunction refers to impairment of one or more critical cognitive domains, often accompanied by mental, behavioral, and personality abnormalities at a particular stage of the disease. Cognitive dysfunction mainly includes two stages, MCI and dementia. MCI represents a transitional state between normal aging and dementia. Dementia refers to a clinical syndrome characterized by progressive acquired cognitive decline that interferes with the ability to function independently, such as interference with activities of daily living (ADLs), learning, work-related functions, and social communication[12].

2.2 Classification

Based on disease course or severity, cognitive function deficits are categorized into the following stages: asymptomatic preclinical stage, MCI, and dementia[10]. The asymptomatic preclinical stage involves only minor impairment in a single cognitive domain without significant abnormalities on objective neuropsychological assessment; however, patients show changes in brain pathology, structure, and function. Cognitive impairment in elderly patients with diabetes may represent early-stage dementia. MCI refers to a progressive decline in memory or other cognitive abilities but it does not affect routine activities or fulfill the diagnostic criteria for dementia. Patients with dementia show cognitive impairment of sufficient magnitude to affect their social or occupational functioning, which may be accompanied by psychiatric, behavioral, or personality abnormalities.

Based on various pathogenetic contributors, diabetes-induced dementia is categorized into the following types: (1) cognitive impairment secondary to diabetes-related cerebrovascular injury (mainly VaD), (2) diabetes-induced neurodegeneration (mainly AD).

3 EPIDEMIOLOGY AND PATHOGENESIS

Key tips: 1. The risk of dementia is 2.8-fold higher in patients with T2DM than in those without T2DM. 2. A close association is observed between blood glucose control and cognitive function in patients with diabetes. 3. AD is pathologically characterized by β-amyloid deposition and tau protein hyperphosphorylation; detection of β-amyloid and hyperphosphorylated tau (P-tau) protein in cerebrospinal fluid (CSF) is used for diagnosis of AD.

Per the World Report on Alzheimer’s Disease (2015) statistics, approximately 50 million individuals are affected by dementia worldwide, with one new case reported every 3 s, of which approximately 7%–13% cases are diabetes-related[13]. Epidemiological evidence shows that the risk of dementia is 2.8-fold higher in patients with T2DM than in those without T2DM[14]; up to 20% of patients aged >60 years with T2DM may develop dementia[15].

Cognitive decline in patients with T2DM is insidious in onset and occurs mainly in middle-aged and elderly patients[16]. The rate of cognitive decline in diabetes patients is approximately 50% higher than that in individuals who undergo normal aging. Previous cross-sectional studies have shown that the prevalence of MCI was approximately 20%–30%[17], the incidence of dementia was approximately 17.3%[18], and the risk of AD was approximately 1.5- to 2.5-fold higher in patients with T2DM than in those without diabetes (patients of the same age and sex)[19]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes Study (ACCORD-MIND) showed that each 1% increase in glycosylated hemoglobin A1c
(HbA1c) led to a significant 1.75-point reduction in the digit symbol substitution test score, a 0.20-point reduction in the Mini-Mental Status Examination (MMSE) score, a 0.11-point reduction in the memory score of the Rey auditory verbal learning test, and a >0.75 s delay in the Stroop score[20]. Therefore, a close association is observed between glycemic control and changes in cognitive function in patients with diabetes. The Edinburgh Type 2 Diabetes Study reported that the rate of AD in patients with diabetes was significantly accelerated. The median time from MCI to dementia onset was 5.01 years (95% CI 5.15–6.19) in patients without diabetes and 1.83 years (95% CI 2.44–4.24) in patients with diabetes or prediabetes. Therefore, diabetes or prediabetes was shown to accelerate progression of MCI to dementia by a mean period of 3.18 years[22]. Early detection of MCI and effective interventions are important to prevent and delay the onset of dementia[23].

AD accounts for 50%–70% of all types of dementia; Parkinson’s disease with dementia accounts for approximately 3.6% of all cases of dementia, and VaD is the most common variety of non-degenerative dementia, which accounts for 15%–20% of all cases of dementia[24]. Neuropathological hallmarks of AD include formation of extracellular senile plaques secondary to massive deposition of β-amyloid β (Aβ) between neurons in the cerebral cortex and hippocampus and intracellular neurofibrillary tangles secondary to accumulation of P-tau protein. Reduced β-amyloid 42 (Aβ42) concentrations in the CSF is a well-established biomarker for AD[25]. A longitudinal cohort study performed by Sutphen et al[26] reported that Aβ42 concentrations in CSF may begin to decrease during early middle age and gradually decrease thereafter with increasing amyloid plaque deposition in the brain. Wang et al[27] observed that Aβ42 reduction in CSF was correlated with poor episodic memory and reduced hippocampal volume among cognitively healthy older adults. A meta-analysis performed by Olsson et al[28] reported that CSF concentrations of total tau (T-tau) and P-tau were closely associated with AD and these were significantly higher in patients with AD than in healthy subjects; T-tau and P-tau concentrations in CSF were 2.54-fold (95% CI 2.44–2.64) and 1.88-fold (95% CI 1.79–1.97) higher in patients with AD than in the control group, respectively. Mitochondrial dysfunction also plays an important role in AD progression. Studies have confirmed that the glucose utilization rate in the temporal and parietal lobes of the brain is significantly lower in patients with AD than in healthy subjects of similar age[28]; the brain mitochondria show abnormal morphology, as well as division and distribution, decreased expression of respiratory chain complexes and enzyme activity, decreased adenosine triphosphate production, and increased reactive oxygen species production in patients with AD[29].

To date, the exact mechanism underlying cognitive dysfunction in diabetes remains unclear, and insulin resistance is implicated as an essential etiopathogenetic contributor. Insulin acts on the central nervous system to modulate peripheral metabolism, enhance systemic insulin sensitivity, inhibit endogenous glucose production, and regulate cognition. Other hypotheses proposed in this context include structural changes in brain tissue, changes in cerebral blood flow, abnormal metabolism of brain cells, insulin deficiency and impaired insulin signaling pathways, increased inflammatory mediator generation, immune dysregulation, and mitochondrial dysfunction, all of which lead to impaired neural cell structure and function, which eventually affects cognitive function. However, the specific mechanism remains unknown.

4 RISK FACTORS

Key tips: 1. Many risk factors (classified as modifiable and non-modifiable) are involved in the development of cognitive dysfunction in diabetes. 2. Early intervention for management of modifiable risk factors can reduce the risk of cognitive impairment in these patients.

Risk factors for cognitive dysfunction in diabetes are classified into non-modifiable and modifiable types. Non-modifiable risk factors include age, sex, and genetic factors. Modifiable risk factors include cardiovascular and cerebrovascular diseases, blood pressure, lipid profile, T2DM, diet, smoking habits, education level, and physical mental activity[8, 30]. Consistent evidence from observational studies shows that approximately 35% of patients with dementia worldwide are caused by several common modifiable risk factors, primarily diabetes, hypertension, obesity, hearing loss in middle age, lack of exercise, depression and social isolation, smoking habits, and low education levels[31]. Both diabetes and prediabetes are correlated with significant cognitive decline[32]. Clinical and biochemical characteristics of diabetes including chronic hyperglycemia, recurrent hypoglycemia, blood glucose fluctuations, and microvascular complications, as well as diabetic comorbidities including obesity, hypertension, and blood lipid disorders, among others are shown to be associated with cognitive decline.

4.1 Insulin Resistance

Insulin resistance, a characteristic finding in patients with T2DM, is a well-established risk factor for AD[33]. Patients with insulin resistance show poor cognitive function, including orientation, memory,
and attention/calculation ability[34]. Compared with healthy controls, patients with AD show reduced expression and activation of the insulin receptor, insulin-like growth factor 1 and recombinant insulin receptor substrate 1 in the brain[35], as well as decreased insulin levels and binding to insulin receptors in the neocortex[36]. Abnormal Aβ metabolites may lead to glucose intolerance and insulin resistance and promote the development of diabetes[37]. Abnormal insulin metabolism can also affect the synthesis and breakdown of Aβ and accelerate cognitive impairment[38].

4.2 Hyperglycemia

The Adult Changes in Thought, a large-scale retrospective cohort study, observed that higher blood glucose levels in elderly individuals increase the risk of dementia. Higher mean glucose levels within 5 years preceding study enrollment were associated with an increased risk of dementia among participants without diabetes (glucose level 115 mg/dL vs. 100 mg/dL, adjusted hazard ratio for dementia 1.18, 95% CI 1.04–1.33). Higher mean glucose levels were also associated with an increased risk of dementia among participants with diabetes (glucose level 190 mg/dL vs. 160 mg/dL, adjusted hazard ratio 1.40, 95% CI 1.12–1.76)[39]. Hypoxic metabolism secondary to persistent hyperglycemia in patients with T2DM aggravates acidosis and causes hypoxic injury to brain cells and consequent central nervous system injury[40]. Significant accumulation of advanced glycosylation end-products in patients with T2DM leads to nerve cell toxicity via a variety of mechanisms and results in cognitive dysfunction[41]. Chronic hyperglycemia may also promote P-tau protein formation[42]. Studies have shown that hyperglycemia increases aldose reductase activity and activates the sorbitol pathway, which causes intracellular hyperosmolarity and edema, with structural and functional neuronal cell injury, which promotes cognitive dysfunction[43].

4.3 Hypoglycemia

Recurrent hypoglycemia increases the risk of cardiac and cerebrovascular events, stroke, and cardiovascular mortality[44, 45]. Diabetes-induced severe hypoglycemia serves as an important contributor to progressive cognitive impairment. Studies in patients with type 1 diabetes have shown that frequent episodes of severe hypoglycemia were associated with lower cognitive ability, and hypoglycemia is implicated in the development of cognitive decline in children. Hypoglycemic episodes in adults with T2DM were shown to accelerate cognitive decline, which may consequently precipitate severe hypoglycemic episodes[46]. Similarly, studies have shown a significant association between severe hypoglycemia, MCI, and dementia[41, 47]. Therefore, a bidirectional association is observed between hypoglycemia and cognitive dysfunction, which implies that hypoglycemia can increase the risk of dementia, and conversely, cognitive decline may also contribute to a higher risk of hypoglycemia. The possible pathophysiological mechanisms underlying this finding include injury to hippocampal neurons, inflammatory processes, coagulation defects, endothelial cell abnormalities, and synaptic dysfunction during hypoglycemic episodes[41].

4.4 Microangiopathy

Blood glucose control in patients with diabetes is closely associated with microvascular complications that may lead to diabetic neuropathy, diabetic retinopathy (DR), and/or diabetic nephropathy. Crosby-Nwaobi et al[48] observed a 3-fold higher risk of cognitive impairment in patients with DR than in those without DR; notably, impairment was prominent in the cognitive domains of verbal learning and recent memory. DR reflects cerebral microvascular injury to some extent, and aggravation of DR is associated with more severe cognitive decline, which suggests that cerebral microvascular disease plays a key role in promotion of the aging cognitive decline in patients with T2DM[49]. Evidence-based studies have confirmed that cognitive dysfunction is positively correlated with renal microangiopathy in patients with T2DM with concurrent diabetic nephropathy[40]. However, clinical evidence is limited, and further studies are needed to provide deeper insight in this regard.

4.5 Cerebral Macroangiopathy

Cerebral arteriosclerosis, an important complication of diabetes, may present with cerebral hemodynamic changes, chronic cerebral ischemia, hypoxia, and energy metabolism disorders, which can cause cognitive dysfunction. Comprehensive neuropsychological evaluation using carotid-femoral pulse wave velocity in patients with T2DM showed that attention and/or executive function and processing speed were significantly poor in patients with T2DM[50].

4.6 Miscellaneous Factors

Patients with T2DM and concomitant hypertension showed greater cognitive changes than normotensive patients with diabetes[51]. Additionally, a study that investigated elderly patients with diabetes over 6 years observed that low levels of high-density lipoprotein cholesterol and an increase in diastolic blood pressure were significantly associated with cognitive decline based on logistic analysis[52]. Therefore, optimal control of metabolic disorders in diabetes is important to maintain cognitive function and delay cognitive decline. The cognitive status in patients with T2DM is correlated with serum homocysteine levels, and homocysteine is an independent risk factor for MCI[53]. Depression is also a critical factor in the self-management of dementia and diabetes prevention and serves as an independent risk factor for age-induced cognitive impairment in patients with diabetes[54].

Greater awareness and early evaluation and
prevention/control of the aforementioned risk factors, as well as further investigation to identify newer diagnostic targets are important to delay or avoid the onset of cognitive decline in patients with diabetes, to reduce the risk of long-term dementia and improve patients’ quality of life.

4.7 Screening

Comprehensive evaluation of the medical, functional, psychological, and social environment of older adults with diabetes is necessary to determine treatment targets and establish diabetes self-management regimens. Specifically, these measures include: (1) Annual neuropsychological assessment to screen for early identification of MCI or dementia in adults aged ≥65 years. Elderly patients with diabetes should be carefully screened and monitored for cognitive dysfunction, particularly in cases of suspected dementia; simple neuropsychological assessment tools to screen for cognitive impairment include the MMSE and Montreal Cognitive Assessment (MoCA) tests. (2) Cognitive impairment screening should be considered in patients with significantly clinical decline secondary to difficulties with self-care activities (for example, insulin dose calculation errors, and difficulties with carbohydrate counting, among others)\[55\]. Studies have shown that glucagon-like peptide 1 receptor agonist (GLP-1 RA) therapy improved cognitive and olfactory abnormalities in patients with diabetes diagnosed with obesity. However\[56\], olfactory dysfunction is not currently classified as a component of neuropathy. Olfactory dysfunction may potentially be a useful predictor of the risk of cognitive dysfunction in diabetes.

Recommendation 1: Early screening for MCI or dementia (using the MMSE and MoCA) is recommended for adults aged ≥65 years at the initial visit and, if appropriate, annually. Patients screened for cognitive impairment should undergo appropriate diagnostic evaluation\[55\]. Screening for cognitive impairment should be considered in patients with significant clinical decline secondary to difficulties with self-care activities (for example, insulin dose calculation errors, or difficulties with carbohydrate counting among other such issues).

5 DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Key tips: 1. Neuropsychological assessment is currently considered the gold standard for cognitive impairment evaluation. 2. Imaging is a prerequisite for cognitive impairment assessment. 3. Functional imaging is useful for early evaluation of AD. 4. CSF biomarker evaluation is a standard method for diagnosis of cognitive dysfunction. Blood AD biomarker tests are promising tools; however, these are not recommended as routine tests to evaluate cognitive dysfunction. 5. CSF biomarker evaluation is a standard method for diagnosis of cognitive dysfunction. Blood AD biomarker tests are promising tools; however, these are not recommended as routine tests to evaluate cognitive dysfunction.

Cognitive dysfunction is multifactorial. Based on the etiopathogenesis, AD and VaD are the two main types of diabetes-induced dementia. Prognosis and management of patients with cognitive dysfunction depend on the severity and disease stage. Accurate diagnosis and differential diagnosis of cognitive dysfunction in diabetes are clinically important, and it is necessary to determine the severity and stage of this condition. Characteristics of diabetes-related cognitive dysfunction can be analyzed using neuropsychological behavioral assessments, imaging, and laboratory tests.

Although epidemiological evidence suggests an increased risk of dementia and MCI in patients with diabetes, the causal association remains debatable\[10\]. In contrast to other well-known end-organ complications of diabetes, there is lack of clear evidence to conclusively establish the association between glycemic control and the risk of cognitive impairment\[57\]. Cognitive impairment is attributable to multifactorial etiologies in most patients, and inter-individual variability is evident in clinical practice\[10\]. Diabetes-induced cognitive impairment is invariably indistinguishable from cognitive impairment comorbid with diabetes.

The assessment of cognitive dysfunction in patients with diabetes includes detailed history taking and physical examination. Monitoring at 1- to 2-year intervals and brief neuropsychological testing

![Flow chart for the diagnosis of cognitive dysfunction in patients with diabetes](#)

**Fig. 1** Flow chart for the diagnosis of cognitive dysfunction in patients with diabetes

**Risk factors for cognitive dysfunction:**
(1) self-reported or informant-reported concerns about cognitive function;
(2) one or more unexplained falls;
(3) history of recurrent hypoglycemia;
(4) difficulty with diabetes self-management (including errors in self-administration of drugs);
(5) symptoms of depression, stress, or both

- **Targeted assessment, detailed medical history and examination, brief cognitive testing (e.g., MMSE)**
  - Scores suggesting a high probability of cognitive dysfunction
  - Scores suggesting a low probability of cognitive impairment
  - Excluding other causes, particularly endocrine and metabolic dysfunction
  - Monitoring every 1–2 years
  - Referred to a specialist for neuropsychological evaluation, laboratory evaluation, and imaging to enable diagnosis of minor and major neurocognitive disorders, and underlying causes

**MMSE:** mini-mental state examination
are recommended in those with a low and high risk, respectively. Neurology consultation and further neuropsychological evaluation, supplemented with laboratory and imaging evaluation for diagnostic confirmation are warranted in patients with a high risk of cognitive dysfunction. It is however necessary to rule out and treat common reversible conditions associated with cognitive dysfunction, including delirium, adverse drug reactions, metabolic or endocrine abnormalities, sleep disorders, and depression[15]. Figure 1 shows the diagnostic process.

5.1 Neuropsychological Assessment

For clinical judgment of the overall cognitive function and objective memory ability in the diagnostic criteria, the scale is usually used to assess the degree of impairment. Neuropsychological assessment is currently recommended as the primary tool to diagnose cognitive impairment. The following tools are commonly used in clinical practice.

(1) The MMSE focuses on screening for overall cognitive function (time and place orientation, calculation, memory, language ability, attention, and visuospatial ability). It includes 30 questions with a total score of 30 points. The MMSE is administered over 5–10 min. This preliminary screening tool for dementia is widely used in clinical and community investigations as a short and sensitive screening test with a wide range of practicalities; however, the test scores are affected by the patient’s education level[58].

(2) The MoCA, an assessment tool, is used for rapid screening for MCI. It includes 11 items distributed in eight cognitive domains including attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, calculation, and orientation. The MoCA is administered over approximately 10 min. Similar to the MMSE, the MoCA score is affected by patients’ education level[59].

(3) The clinical dementia rating (CDR) scale is used to clinically stage the severity of cognitive function and social life function impairment in patients with dementia. The CDR scale is based on a semi-structured interview with the patient and an appropriate informant and rates impairment in each of six cognitive categories including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care on a five-point scale in which none, questionable, mild, moderate, and severe dementia are described as a continuous, dynamic process. Each category contains 5–15 questions, with a total score of 3.0, and the test is administered over 10 min. Typically, CDR score 0 indicates no dementia, and CDR scores 0.5, 1.0, 2.0, or 3.0, indicate very mild (MCI), mild, moderate, or severe dementia, respectively[60]. The cognitive impairment scoring criteria for the CDR scale are also affected by the patient’s education level.

(4) The Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-cog) mainly assesses episodic memory and consists of 12 items, including memory, orientation, language, use, and attention, among other items, which measure the severity of cognitive symptoms and therapeutic changes in AD. This scale contains 12 questions and is commonly used for evaluation of drug efficacy in mild-to-moderate AD (usually 4 points of improvement are used as the judging criteria for significant drug efficacy in clinical practice). However, this scale is unsuitable for patients with very mild and very severe disease and cannot be used for diagnosis and differential diagnosis.

(5) The auditory word memory test is an independent test that reflects auditory episodic memory. It is simpler and relatively shorter than the Wechsler Adult Intelligence Scale and includes three immediate free recalls, delayed free recalls, cue recalls, and recognition. This test is a commonly used screening tool for memory loss in MCI research in China and overseas.

(6) The ADL scale consists of a physical self-care scale and instrumental activities of daily living scale and is mainly used to evaluate patients’ ADLs. This test uses a short-range self-rating scale, which is user-friendly, remains unaffected by age, sex, economic status, and other factors. Therefore, it has a wide range of applications and is suitable for individuals across various occupations, cultural classes, and age groups, or patients with multiple types of mental illnesses. The ADL scale includes 14 items classified into the Physical Self-Care Scale (includes six items, specifically, using the toilet, eating, dressing, combing, walking, and bathing) and the Instrumental Activities of Daily Living Scale, which includes eight items, such as calling, shopping, preparing meals, doing housework, washing, using transportation, self-administration of medication, and self-care economy. The results are analyzed based on the total, sub-scale, and single-item scores. A total score <16 indicates a completely normal evaluation result, and scores ≥16 indicate varying degrees of functional decline. Score 1 in the single-item tests indicates normal function and scores 2–4 indicate reduced function. Scores ≥3 in ≥two items or a total score ≥22 indicate obvious dysfunction.

(7) The Cognitive Abilities Screening Instrument (CASI) is a set of cognitive function scales used for screening of dementia that are developed from the MMSE. The MMSE scores can be obtained simultaneously, although the CASI is superior to the MMSE because it can determine the severity of AD and enables differential diagnosis of different types of dementia. The CASI test quantitatively evaluates attention, remote memory, new memory, mental arithmetic, calculation, verbal fluency, language ability, composition ability, and conceptual judgment within 15 to 20 min. The CASI is a well-established
dementia screening tool, but its utility as a screening tool for large sample sizes in the community remains unknown. Currently, the CASI cutoff score remains unclear and varies across individuals depending on education levels. Notably, the CASI-Chinese version 2.0 is a cognitive function screening scale specifically developed for the Chinese population. It is suitable for use among individuals with low levels of education (usually the elderly Chinese population has a relatively low education level). Zhou et al. concluded that the sensitivity of this scale for detection of MCI and mild AD was 70.6% and 82.7%, respectively, with 73.9% specificity. However, the CASI is considered overly simplistic and may show false-negative results in individuals with college-level and higher education. Overall, the CASI is considered an auxiliary tool for detection of MCI and can effectively assess severity of cognitive impairment in patients with AD.

Presently, attention should be paid to the application of the aforementioned scales: (1) Testing should be performed in a quiet environment to reduce interference. The individual who administers the test should speak clearly and slowly and encourage an active response from the patient; (2) The scale used should only focus on a particular aspect or several aspects of dementia; (3) The cognitive assessment results need to be interpreted considering the patient’s educational level, as well as background and lifestyle, which cannot replace the clinician’s thinking and judgment; (4) The individual who administers the test should be adequately trained and use the scale in an objective manner.

**Recommendation 2:** The MMSE is recommended for screening of dementia.

**Recommendation 3:** The MoCA is recommended for screening of MCI.

**Recommendation 4:** The ADAS-cog is recommended for evaluation of drug efficacy in mild-to-moderate AD, the CDR for staging and follow-up of dementia severity, and the ADL scale for assessment of patients’ ADLs.

### 5.2 Imaging Evaluation

Brain imaging changes associated with cognitive function in patients with diabetes mainly include changes in the brain parenchyma and cerebral vessels, remodeling of fibrous connections, changes in the degree of activation of brain regions, and changes in brain metabolism. Imaging is a prerequisite to assess cognitive impairment.

#### 5.2.1 Magnetic Resonance Imaging

Cranial magnetic resonance imaging (MRI) is useful to establish the etiology of cognitive dysfunction. T1-weighted structural MRI scans evaluated in 811 patients from the AD neuroimaging project database showed that the area under the receiver operating characteristic curve of T1-weighted MRI scans was 96.95% for diagnosis of AD, which indicates good diagnostic accuracy of three-dimensional T1-weighted images for AD. Coronal T1-weighted images may be a feasible alternative in patients in whom three-dimensional T1-weighted images are unavailable. Atrophy of the medial temporal lobe (reduced size of the hippocampus, entorhinal cortex, and amygdala) can be visualized using MRI. Diffusion-weighted imaging (DWI) and enhanced T1-weighted images are useful for diagnosis and differentiation of inflammation and tumor-induced dementia. For example, DWI shows new infarcts in patients with VaD.

Changes in parenchymal and cerebrovascular tissues: (1) Change in brain volume: Brain volume changes may be detected in prediabetes, with reduced local gray matter in type 1 diabetes and extensive predominantly periventricular brain atrophy in T2DM. (2) White matter hyperintensities: Ischemic demyelinating changes in the white matter (which is associated with attention, and executive function, among other such functions) accelerate cognitive decline. White matter hyperintensities were slightly more prevalent in patients with diabetes, although heterogeneity was observed across studies that reported this finding. (3) Cerebral infarcts: The risk of cerebral infarction was 1.3- to 2.2-fold higher in patients with T2DM, particularly in elderly patients with frequent lacunar infarction. (4) Small vessel disease: Compared with controls, patients with diabetes showed increased rates of localized ischemia or microhemorrhage in the brain microvasculature.

Functional changes: (1) Diffusion tensor imaging indicates that fiber functional connectivity is associated with reduced speed of information transmission. (2) Functional MRI reflects activation or inhibition of brain nerve cells in various regions. Despite heterogeneity across studies, patients with diabetes showed extensively reduced brain activity.

#### 5.2.2 Functional imaging

Patients with AD show changes in regional cerebral blood flow and metabolic activity in the early stages and structural changes in the later stages. Functional imaging is useful for early diagnosis of AD. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are mainly used to diagnose lesions that are difficult to differentiate using structural imaging and improve the specificity of clinical diagnosis and structural imaging. Although SPECT and PET are based on similar principles, they differ with regard to instrumentation and radiochemistry, and PET shows higher sensitivity owing to its higher resolution.

**SPECT**: The relative cerebral perfusion volume can be evaluated based on measurement of uptake of lipophilic tracers such as 99mTc-hexamethyl propyleneamine oxime or N-isopropyl-p-iodoamphetamine in brain tissue. A clinical trial
reported that a positive SPECT scan increased the likelihood of detection of AD to 92%, whereas a negative SPECT scan reduced the likelihood of detection to 70%. SPECT examination can improve diagnostic accuracy in cases of suspected AD, with a likelihood of 84% with a positive SPECT and 52% with a negative SPECT scan\[^{65}\].

**PET:** (1) Glucose metabolism imaging: 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) is currently the most common tracer used to detect glucose metabolism in the human body. The accuracy of FDG in differentiating healthy individuals from those with AD was 93%, with a sensitivity of 96% and specificity of 90%\[^{66}\]. Clinical combination with PET imaging can improve diagnostic accuracy. FDG-PET imaging is more sensitive and specific than SPECT and can detect decreased metabolism in the hippocampus, amygdala, and temporoparietal cortex. (2) Aβ-PET and tau-PET imaging: Aβ amyloid imaging tracers include 11C-labeled and 18F-labeled agents; both can specifically bind to Aβ plaques. Increased retention of Aβ PET tracers can detect abnormal Aβ protein deposition in the hippocampus, amygdala, and cortex, which can accurately distinguish between AD and frontotemporal dementia, although the association with dementia severity remains weak. However, P-tau observed on tau-PET imaging is initially confined to the medial temporal lobe and gradually spreads to the neocortex with disease progression, which matches atrophy of brain tissue\[^{67}\].

**Recommendation 5:** MRI is a routine imaging modality used for the diagnosis and differential diagnosis of dementia. Follow-up MRI is useful to evaluate prognosis of patients with dementia\[^{68}\]. Functional imaging is not routinely used as a diagnostic test for dementia; however, SPECT and PET may be selected in specific patients with a high index of clinical suspicion to improve diagnostic accuracy.

### 5.3 Laboratory Investigations

#### 5.3.1 Cerebrospinal Fluid

CSF examination is a standard method used for diagnosis of cognitive dysfunction. Accurate diagnosis of AD involves estimation of at least four CSF biomarkers [Aβ42, the amyloid 42/40 ratio (Aβ42/Aβ40), T-tau, and phosphorylated site 181 on tau protein (P-tau181)]\[^{68}\] in combination with other evaluation (medical history, neuropsychological assessment, and routine imaging to rule out secondary causes). Patients with sporadic AD show significantly reduced levels of Aβ42 in the CSF\[^{69}\]. The mean specificity of CSF Aβ42 was 64% and the sensitivity was 81% for diagnosis of AD in patients with MCI\[^{70}\]. The CSF Aβ42/Aβ40 ratio can reflect pathological changes in AD more significantly than the decrease in Aβ42 levels\[^{71}\]. The sensitivity of the CSF Aβ42/Aβ40 ratio for diagnosis of AD ranges between 64% and 88%, with specificity between 70% and 78%\[^{70}\].

The increase in CSF tau reflects changes in axonal degeneration and neurofibrillary tangles in patients with AD, following release of tau protein into the CSF\[^{72}\]. The T-tau in CSF was shown to significantly increase by approximately 300% in patients with AD, with sensitivity and specificity of 80%–90%\[^{73}\], 74]. T-tau reflects overall cortical axonal damage and may also be detected in patients with stroke and brain trauma. Compared with T-tau, increased levels of CSF P-tau reflect pathophysiological changes in AD and specifically suggest formation of neurofibrillary tangles. P-tau181 is useful to distinguish between AD and VaD and depression\[^{75}\]. CSF P-tau levels are significantly higher in patients with AD-induced MCI during the initial stage; therefore, P-tau can be used as an early marker of this type of disease\[^{76}\]. Compared with healthy controls, patients with T2DM show significantly increased levels of CSF P-tau\[^{77}\].

#### 5.3.2 Blood Tests

Recent studies have reported the efficacy of plasma biomarkers as diagnostic predictors of AD, and these appear to be promising tools for rapid diagnosis of AD.

**Plasma P-tau181:** It has been shown that plasma P-tau181 levels are significantly positively correlated with both P-tau181 and tau-PET in CSF. During 8-year follow-up, Janelidze et al\[^{78}\] observed that the plasma P-tau181 level could predict AD progression among cognitively unimpaired participants and among those with MCI. Notably, the risk of progression to AD was higher in those with high baseline plasma P-tau181 levels. In a large-scale study that included four different cohorts (a discovery cohort, two validation cohorts, and a primary care cohort), Karikari et al\[^{79}\] observed that P-tau181 levels showed high differential diagnostic ability in distinguishing AD from other neurodegenerative diseases, including among Aβ-negative young adults (area under the curve: 99.40%), cognitively unimpaired elderly individuals (area under the curve: fluctuated between 90.21% and 98.24% across different cohorts), among other groups with neurodegenerative diseases, such as frontotemporal dementia (area under the curve: fluctuated between 82.76% and 100.00% across different cohorts), and among those with vascular dementia (area under the curve: 92.13%).

**Plasma P-tau217:** In a large-scale study that included 1402 patients distributed across three different cohorts, Palmqvist et al\[^{80}\] observed that P-tau217 showed good diagnostic and differential diagnostic efficacy for AD. In cohort 1 (mean age of 83.5 years, approximately 38% women), P-tau217 showed an area under the curve of 0.89 (95% CI 0.81–0.97) and significantly higher accuracy than plasma P-tau181 and neurofilament light chain (area under the curve: 0.50–0.72) in distinguishing AD from non-AD. In cohort 2
(mean age of 69.1 years, approximately 51% women), P-tau217 showed significantly higher accuracy than plasma P-tau181, neurofilament light chain, and MRI measurements and was not inferior to tau-PET, CSF P-tau217, and CSF P-tau181 in distinguishing AD from other neurodegenerative diseases (area under the curve: 0.96; 95% CI: 0.93–0.98). In cohort 3 (mean age of 35.8 years, approximately 57% women), plasma P-tau217 levels were significantly greater in presenilin 1 mutation carriers than in non-carriers and could predict MCI onset 20 years prior to estimated onset among mutation carriers.

Plasma neuronal-derived exosomes (NDE): A two-stage multicenter study confirmed that NDE is highly consistent with AD core marker (Aβ42, T-tau, and P-tau181) levels in CSF and shows high potency in distinguishing between AD, MCI, and healthy controls[83].

5.3.3 Genetic testing In addition to age, the genetic blueprint is the most evident risk factor for AD; presenilin 1 (PSEN1), presenilin 2 (PSEN2), and the amyloid protein precursor (APP) genes are implicated in familial AD. Screening for the relevant causative genes is important to improve the detection rate in patients with dementia or presenile dementia with a known family history[68].

5.4 Diagnosis and Differential Diagnosis Currently, the following international guidelines are available for the diagnosis of AD: the 1984 National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) guideline, the 2011 National Institute on Aging-Alzheimer Association (NIA-AA) guideline, and the 2014 International Working Group (IWG) guideline.

The NINCDS-ADRDA guideline is based on the following diagnostic criteria[82]: (1) clinical symptoms of dementia verified by neuropsychological tests such as the MMSE, Blessed Dementia Scale, or other similar tools; (2) ≥two cognitive deficits; (3) progressive decline in memory and other cognitive functions; (4) no disturbance of consciousness; (5) symptom onset between ages 40 and 90 years (mainly after 65 years); (6) no other physical or brain diseases that may contribute to progressive decline in memory and cognition.

Compared with the NINCDS-ADRDA guideline, the NIA-AA guideline adds imaging evidence and abnormal CSF biomarkers as diagnostic criteria as follows[85]: (1) AD is considered a multidimensional disease process including MCI, that progresses along a continuum; AD is categorized into preclinical AD, AD-induced MCI, and AD-induced dementia, (2) in accordance with the clinical core criteria for AD-induced dementia, etiological diagnosis is based on measurement of biomarkers to improve diagnostic accuracy, (3) positive results on any of the following tests: medial temporal atrophy (reduced volume of hippocampus, entorhinal cortex, and amygdala) on MRI, abnormal CSF biomarkers (decreased Aβ42 levels, a reduced Aβ42/Aβ40 ratio, or increased P-tau levels), PET-specific molecular imaging (FDG-PET shows decreased metabolism in the hippocampus, amygdala, and temporoparietal cortex; the Pittsburgh compound B-PET shows abnormal Aβ protein deposition in the hippocampus, amygdala, and cortex), and autosomal dominant mutations in AD confirmed in immediate family members.

The IWG guideline differs from the NIA-AA guideline in that the diagnosis of AD is further simplified. AD is diagnosed based on a combination of the clinical phenotype (typical/atypical) of AD and pathophysiological biomarkers consistent with AD pathology as follows[86]: (1) For specific clinical phenotypes, early significant episodic memory impairment includes both of the following criteria: (i) gradual progressive change in memory impairment for >6 months reported by patients or informants, (ii) objective evidence of hippocampal amnestic syndrome. (2) Evidence of pathological changes in AD including one of the following features: (i) decreased CSF Aβ42 and increased T-tau or P-tau levels, (ii) increased retention of Aβ-PET tracers, (iii) autosomal dominant mutations in genes associated with AD (PSEN1, PSEN2, or APP genes). Typical AD can be diagnosed by meeting i and ii.

Clinical diagnosis of AD may be based on the criteria proposed by the NINCDS-ADRDA in 1984 or the NIA-AA in 2011[85]. Diagnosis of AD may be based on the 2011 version of the NIA-AA or the 2014 version of the IWG-2 in patients in whom molecular imaging and CSF-based detection of AD are conditional[85].

Clinicians should consider depression in the differential diagnosis because depression can also present with cognitive dysfunction, and may occasionally be associated with dementia. Therefore, the differential diagnosis requires close attention. Hypothyroidism, hypovitaminosis, anemia, and renal or hepatic insufficiency may also lead to cognitive dysfunction; therefore, it is necessary to re-assess cognitive function following symptomatic treatment and symptom improvement in patients with these disorders.

Recommendation 6: Measurement of CSF T-tau, P-tau181, and Aβ is feasible in patients with diabetes who show a high index of clinical suspicion for AD, following neuropsychological assessment. Although blood AD biomarkers have shown promise for clinical application, they are not widely accepted or approved to date; therefore, estimation of blood biomarkers is not recommended for routine evaluation of dementia and cognitive dysfunction.
6 TREATMENT AND PREVENTION

Key tips: 1. Maintenance of a healthy lifestyle reduces the risk of cognitive dysfunction in patients with diabetes. 2. A blood glucose target of serum HbA1c <7.0%–7.5% is feasible in elderly patients in good health with few chronic diseases and good cognitive function; however, the blood glucose target should be fixed at a higher level (serum HbA1c <8.0%–8.5%) in patients with multiple chronic diseases and cognitive dysfunction. 3. The effects of hypoglycemic agents on cognitive function depend on the type of agent used. Metformin and GLP-1 RAs potentially improve cognitive function, whereas the effects of sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase 4 inhibitors (DPP-4i), and sodium-glucose co-transporter 2 inhibitors (SGLT2i) on cognitive function are unknown. 4. The specific treatment for patients with diabetes-related cognitive impairment is similar to that used for non-diabetes-related cognitive impairment. Physicians should consider the patient’s diabetic status and not focus exclusively on treatment of cognitive dysfunction when prescribing medications for AD. 5. Early detection of cognitive dysfunction is important in diabetes care. Treatment of patients with cognitive impairment should focus on simple medication regimens, with emphasis on supportive care, and clinicians should adopt a holistic approach to patient care.

Cognitive dysfunction is an important contributor to death and disability in the elderly population, and the risk of cognitive impairment is significantly high in patients with diabetes. The high disability rate secondary to cognitive dysfunction, loss of the ability to live independently in the later stages of the disease, and complete dependence on others result in a heavy economic and care burden on society and families. Early detection of risk factors and prompt intervention for cognitive impairment, optimal blood glucose control, administration of the appropriate hypoglycemic drugs, and conventional treatment of cognitive impairment are currently the main therapeutic strategies against cognitive impairment in diabetes.

6.1 Lifestyle Interventions

Diet control and exercise may improve neuronal plasticity in brain regions associated with cognitive function in patients with diabetes-related cognitive deficits. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Cognitive Impairment in the Elderly reported that the risk of cognitive decline and memory difficulties was lower in elderly individuals who received various co-interventions such as a healthy diet, exercise, training memory ability, and management of cardiovascular risk factors than in elderly individuals who did not receive such interventions. Simultaneously, greater engagement in mental activity (for example, playing cards, reading, learning new skills, and acquiring knowledge, among other such activities) increases cognitive reserve and can reduce the risk of AD. Compared with a low-fat diet, a diet rich in olive oil or nuts was shown to improve cognitive performance. Therefore, expert panels recommend a Mediterranean diet rich in fruits and vegetables, olive oil, nuts, legumes, and coarse grains with ingestion of fish twice a week for patients with early cognitive difficulties. Regular physical activity in middle-aged individuals can reduce the risk of dementia and AD. A meta-analysis showed that high- and moderate-intensity physical activity could reduce the risk of cognitive decline by 38% and 35%, respectively. A meta-analysis of 16 prospective studies showed that active physical activity reduced the overall risk of dementia and AD by 28% and 45%, respectively. Even low-intensity physical activity, such as walking, has shown protective benefit against AD and cognitive decline. Epidemiological data show that impaired systemic circadian rhythms in adults serve as an important risk factor for development of AD. A holistic approach using combinations of measures such as exposure to morning light, forced activity during the day, and fixed sleep duration establishes normal diurnal patterns, and this approach has shown encouraging results in patients with AD and warrants further investigation.

Recommendation 7: Lifestyle interventions such as diet control, exercise, greater engagement in mental activity, consumption of a Mediterranean diet rich in olive oil, vegetables, fruits, fish, seafood, and beans and maintenance of a good circadian clock rhythm reduce the risk of AD in patients with diabetes.

6.2 Antidiabetic Therapy

6.2.1 Establishment of Blood Glucose Control Levels

Poor glycemic control increases the hospitalization frequency in patients with diabetes-related cognitive impairment, particularly in those with impaired executive function. However, strict glycemic control may increase the risk of hypoglycemia. The ACCORD-MIND study showed that intensive glucose management did not benefit cognitive decline after a 40-month intervention. Other studies, such as the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation study also support this conclusion. Therefore, intensive hypoglycemic therapy is not recommended for patients with cognitive impairment, and an individualized therapeutic regimen is preferred. Clinical self-management ability and treatment compliance should be evaluated, blood glucose control goals should be appropriately relaxed, insulin levels should be dynamically monitored, and appropriate drug intervention to screen and manage hypoglycemic events and avoid aggravation of cognitive impairment is
essential in elderly patients with cognitive dysfunction. Individualized screening for diabetic complications is useful in elderly patients. According to the ADA diagnostic and therapeutic criteria for diabetes, the blood glucose control target should be fixed at lower levels (serum HbA1c <7.0%–7.5%) for elderly patients with good health status, few chronic diseases, and good cognitive function; however, a more relaxed blood glucose control target (serum HbA1c <8.0%–8.5%) is feasible for patients with multiple chronic diseases and cognitive dysfunction[9].

6.2.2 Antidiabetic Drugs Antidiabetic agents improve hyperglycemia, insulin resistance, cellular metabolism, and counteract tissue inflammation and oxidative stress associated with insulin-resistant states. These agents may also positively affect cellular metabolism in the brain and improve cognitive performance. Studies have shown that inhaled insulin can increase the insulin concentration in the CSF and consequently improve cognitive status; metformin and GLP-1 RA may improve cognitive function and reduce the risk of dementia; sulfonylureas, TZDs, DPP-4i, and SGLT2i may have a protective effect on cognitive function. However, evidence from clinical studies is insufficient, and further studies are needed to validate these findings. Therefore, under appropriate conditions, glycemic management in patients with diabetes and cognitive impairment should be prioritized using the aforementioned drugs, along with close monitoring of changes in cognitive function.

*Sulfonylureas:* There is lack of clarity regarding the role of sulfonylureas in treatment of cognitive dysfunction. In a prospective cohort study, the combination of metformin and sulfonylureas reduced the risk of dementia by 35% during 8-year follow-up[100]. However, the results of a population-based study suggest that long-term use of sulfonylureas does not affect the overall risk of AD[101]. Future studies are essential to elucidate the benefits of sulfonylureas in the treatment of cognitive dysfunction and the molecular mechanisms underlying these effects.

*Metformin:* Metformin has neuroprotective effects on cognitive function, although the exact mechanism remains unclear. A clinical study that included patients aged ≥50 years reported that compared with no drug therapy, metformin significantly reduced the risk of dementia; the hazard ratios for dementia during period 1 (<27.0 months), period 2 (27.0–58.1 months), and period 3 (>58.1 months) using cumulative metformin treatment were 0.975, 0.554, and 0.286, respectively[102]. In a randomized double-blind study on elderly patients with T2DM, combination treatment using metformin + glibenclamide or rosiglitazone showed significant improvement in working memory[103]. A recent meta-analysis that investigated the role of peroxisome proliferator-activated receptor agonists in patients with AD showed that pioglitazone administration in patients with T2DM and concomitant mild AD showed that compared with the control group, 6-month treatment with pioglitazone (15–30 mg) improved cognition and parietal cerebral blood flow[104]. A randomized double-blind trial that investigated elderly patients with T2DM reported that metformin therapy combined with rosiglitazone showed significant improvement in working memory[105]. Another population-based case-control study showed that usually, long-term TZD use was not associated with the risk of AD[106]. Reportedly, compared with other treatment groups, 40-month treatment with TZDs was associated with significant cognitive impairment[107].

*GLP-1RA:* Pancreaticaglobin-1 can cross the blood-brain barrier, and the pancreaticaglobin-1 receptor, which is expressed in the central nervous system areas closely associated with cognition, including the hippocampus, prefrontal cortex, hypothalamus, and amygdala, shows neuroprotective effects. A 26-week, randomized, double-blind placebo-controlled study in Danish patients (mean age of approximately 66 years), showed that compared with the placebo group, liraglutide improved glucose metabolism and cognitive function in patients with MCI and AD[108]. The 5.4-year, randomized, double-blind placebo-controlled Researching Cardiovascular Events With a Weekly INcretin in Diabetes trial, which included participants of mean age >50 years confirmed that long-term treatment with dulaglutide may reduce cognitive impairment in patients with T2DM[110]. GLP-1RAs are potentially promising agents for treatment of cognitive dysfunction.

*DPP-4i:* The association between DPP-4i and diabetes-induced cognitive dysfunction has been investigated only in animal models. No relevant human clinical studies are available in the literature.

*SGLT2i:* Recent studies in a mouse model of T2DM have reported that glycemic control using empagliflozin significantly improves cognitive decline[112]; however, evidence remains limited. No clinical trials have used this drug for treatment of AD.

*Nasal insulin therapy:* Currently, there is no drug deficiency secondary to metformin use[104]. The role of metformin in the treatment of cognitive dysfunction remains controversial; however, most clinical trials suggest that metformin may potentially be useful for treatment of cognitive dysfunction in T2DM.

*TZDs:* Studies have reported inconclusive results regarding the effectiveness of TZDs in patients with diabetes and cognitive dysfunction. A pilot study of pioglitazone administration in patients with T2DM and concomitant mild AD showed that compared with the control group, 6-month treatment with pioglitazone (15–30 mg) improved cognition and parietal cerebral blood flow[104].
or related research in China. Clinical evidence suggests that short-term insulin therapy has a protective effect in patients with AD. Adults with AD and a hyperinsulinemic state without hyperglycemia show improved memory, which suggests that this hormone enhances memory. However, systemic insulin injection increases the risk of hypoglycemia. To overcome this limitation, a few studies have investigated the effects of intranasal insulin injection, which was shown to increase intracranial insulin levels. A small-scale, randomized, placebo-controlled study showed that intranasal insulin injection (20 U administered twice daily) over 21 days in patients with early AD or amnestic MCI resulted in better language memory compared with controls. Intranasal insulin improved cognitive function at lower doses in patients with mild AD/MCI and negative apolipoprotein E-4 expression. A controlled study in older adults (mean age of 74 years) with AD/MCI showed positive effects in those who received nasal insulin (20 or 40 U). Comprehensive evaluation showed a significantly positive effect on memory in patients with AD and MCI, who received nasally administered insulin detemir[101]. However, another 12-month clinical trial reported no cognitive or functional benefit of intranasal insulin therapy in patients with AD or MCI, who received 40 U of intranasal insulin therapy[113].

6.2.3 Drug Treatment of Dementia and Alzheimer’s Disease

Currently, no effective therapy is known to alleviate disease progression in standard AD. Existing strategies provide symptomatic but limited clinical benefit[114]. No clinical trial has investigated drugs to treat dementia in patients with diabetes and concomitant cognitive impairment. Acetylcholinesterase inhibitors (ChEIs) have shown consistent benefit across all stages of dementia; memantine has a small overall benefit in cognition, and its administration is limited to moderate-to-severe stages of AD. Combination therapy using ChEIs and memantine may show additional efficacy. Limited evidence is available regarding the effectiveness of vitamin E supplementation and medical foods, and their administration is guided by cost and availability of these substances, as well as patient safety. Interventions that target the amyloid cascade hypothesis of AD have not shown therapeutic effectiveness; therefore, development of novel AD therapies remains challenging[114].

ChEIs: ChEIs increase acetylcholine content in the synaptic cleft and these drugs (mainly donepezil, rivastigmine, galantamine, and huperzine) are currently the first-line therapeutic agents for mild-to-moderate AD. Donepezil, rivastigmine, and galantamine have shown proven efficacy in improvement of cognitive function, global impression, and ADLs in patients with mild-to-moderate AD[115–117]. Several studies have shown that donepezil and rivastigmine are also effective in patients with moderate-to-severe AD. Large-scale randomized controlled trials have reported that galantamine significantly improves cognition, overall function, ADLs, and behavior in patients with VaD[118]. ChEIs are usually well tolerated, although some patients may experience adverse reactions such as diarrhea, nausea, vomiting, loss of appetite, and vertigo. Diarrhea is the most common adverse effect of donepezil[119], and rivastigmine is known to cause vomiting, with dizziness being the least common adverse reaction. Galantamine is known to cause decreased appetite, with vertigo being the least common adverse effect[119, 120]. A clear dose-response association is observed in patients who receive ChEIs. The efficacy increases in a dose-dependent manner; however, adverse reactions are also likely to occur. A meta-analysis of 10 clinical trials reported that among patients with mild-to-moderate AD, the ADAS-Cog improved more significantly in the patient group that received donepezil at a dose of 10 mg/day than in the group that received 5 mg/day. Another multicenter, randomized, double-blind controlled study across 219 international clinical centers observed that donepezil administered at a dose of 23 mg/day could improve overall cognitive function, particularly language and visuospatial functions, in patients with significantly severe AD. Treatment-emergent adverse events such as nausea, vomiting, and dizziness were reported in 73.7% of patients in the group that received 23 mg/day donepezil and in 63.7% of patients in the group that received 10 mg/day[120]. Switching the route of administration to rivastigmine as transdermal patches and donepezil as disintegrating tablets was associated with better medication compliance and minimized adverse drug reactions to varying degrees in patients with AD[121]. Therefore, ChEIs are useful for treatment of patients with a definite diagnosis of AD or VaD. A different class of ChEIs or a patch may be considered based on the patient’s condition and degree of adverse reactions in patients in whom a particular ChEI is ineffective or not tolerated owing to adverse reactions. Strict monitoring is important for possible adverse reactions during treatment. A dose-response relationship is observed in patients who receive ChEIs, and patients with moderate-to-severe AD can be administered high-dose ChEIs, although gradual titration with a low initial dose is advisable with close attention to possible adverse reactions[55].

Memantine: Memantine hydrochloride, a first-line drug against AD, is the first drug approved by the Food and Drug Administration for the treatment of moderate-to-severe dementia. Three large, randomized, double-blind placebo-controlled trials have confirmed that memantine (20 mg/day) improves cognitive function, ADLs, global ability, and psychobehavioral
symptoms in patients with moderate-to-severe AD[122]. Memantine selectively improves key cognitive domain functions, such as language, memory, orientation, behavior, and visuospatial ability in patients with moderate-to-severe AD[123]. A meta-analysis of 12 studies showed that memantine improved cognitive performance and physician global impression scores in patients with AD[124]. Another meta-analysis of 6 multicenter, randomized, double-blind placebo-controlled studies (6-month duration) suggested that standard doses of memantine (20 mg/day) improved ADLs in patients with moderate-to-severe AD[125]. A meta-analysis based on cohort study data also showed that memantine administration (10–20 mg/day) for 24 weeks significantly attenuated disease progression from moderate-to-severe AD and effectively prevented and even treated the decline in comprehension and cognitive function[126]. Therefore, memantine or memantine combined with donepezil and rivastigmine is useful to treat patients with a definite diagnosis of moderate-to-severe AD or VaD, and the combination of ChEIs and memantine is specifically recommended for patients with severe AD, with significant psychobehavioral symptoms. The benefits of treatment and possible adverse effects should be fully discussed with the patient or the informant[85].

Traditional Chinese medicine and other therapeutic drugs: Ginkgo biloba, brain protein hydrolysate, oxiracetam or piracetam may be selected as synergistic adjuvant therapy for AD, following a clear explanation regarding the therapeutic benefits and possible risks of these agents[85].

In conclusion, no specific treatment regimen is currently available for patients with diabetes and concomitant MCI or dementia, and treatment in such cases is similar to that administered in patients with MCI or dementia alone. Treatment of patients with cognitive dysfunction should successfully control risk factors (diabetes, hypertension, and stroke among others), non-drug treatment (physical exercise, lifestyle and behavioral intervention, cognitive training), etiological treatment with drugs (folic acid, and vitamin B12 supplementation among other strategies), and symptomatic treatment with drugs (ChEI, ergot alkaloids, and glutamate receptor antagonists). Currently, no drug is recommended by the Food and Drug Administration for treatment of MCI, and the efficacy of drugs available for treatment of cognitive dysfunction needs further confirmation. It is particularly important to actively prevent or delay the onset and progression of dementia. Cognitive impairment in patients with diabetes shows gradual progression; therefore, most patients show favorable prognosis, particularly those aged <60 years. It is necessary to emphasize the importance of monitoring cognitive health of elderly individuals in clinical practice and create greater awareness and provide extensive education for effective primary and secondary prevention.

**Recommendation 8:** A blood glucose control target of serum HbA1c <7.0%–7.5% is feasible in elderly individuals in good health with few chronic diseases and good cognitive function. However, greater relaxation in the blood glucose control target (serum HbA1c <8.0%–8.5%) is required in patients with multiple chronic diseases and cognitive dysfunction[9].

Specific treatment of patients with diabetes and concomitant cognitive impairment is similar to that rendered to patients with non-diabetes-related cognitive dysfunction. Although conventional AD therapeutics may show negligible clinical benefit, their safety has been evaluated. Physicians should consider the patient’s general condition and not merely focus on treatment of AD alone in patients who receive these agents[15].

Antidiabetic drugs that contribute to cognitive improvement, such as metformin (with vitamin B12 supplementation if necessary) and GLP-1 RA [daily administration (liraglutide) or weekly administration (dulaglutide)] should be selected in patients with diabetes and cognitive impairment. The role of other hypoglycemic drugs in cognitive impairment remains unclear, and further investigations are warranted.

Despite the lack of effective therapies to prevent or treat cognitive decline, early detection of cognitive dysfunction is important for optimal diabetes care. Treatment of patients with cognitive impairment should fundamentally focus on simplification of medication regimens, timely supportive care, and adoption of a holistic therapeutic approach[9].

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**Conflict of Interest Statement**

On behalf of all authors, the corresponding author states...
that there is no conflict of interest.

Author Xue-feng YU is a member of the Editorial Board for Current Medical Science. The paper was handled by the other editor and has undergone rigorous peer review process. Author Xue-feng YU was not involved in the journal’s review of, or decision related to, this manuscript.

Appendix

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