Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.33306

Research Progress in Diabetic Encephalopathy

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Abstract. Diabetic encephalopathy is mainly characterized by cognitive dysfunction, impaired decision-making ability, and emotional abnormalities. Diabetes-related cognitive dysfunction (DRCD) can affect patients' daily living abilities, induce severe mood swings and personality changes, and lead to the loss of some language, learning, cognitive, and living skills in affected individuals. Clinically, DRCD can be classified based on the severity and pathogenesis of the disease. Multiple factors have been identified as risk factors for DRCD in diabetic patients, including gender, age, genetic background, obesity, hypertension, hyperlipidemia, visual and hearing impairments, olfactory dysfunction, alcoholism, smoking, vascular lesions, abnormal blood glucose levels, and depression. Biomarkers associated with DRCD include the Aβ42/Aβ40 ratio, phosphorylated tau protein at serine 181 (p-tau181), amyloid β-protein 42 (Aβ42), phosphorylated tau protein at threonine 205 (p-tau205), microtubule-binding region tau-243, total tau protein, and glial fibrillary acidic protein (GFAP).Both pharmacological and non-pharmacological interventions have been shown to alleviate symptoms of DRCD and delay the progression of mild cognitive impairment to dementia.

Keywords: Diabetic Encephalopathy, Type 2 Diabetes Mellitus, Diabetes-associated cognitive dysfunction (DACD) , Biomarker

1. Introduction

Diabetic encephalopathy (DE) is a common central nervous system complication of diabetes mellitus, which is mainly characterized by cognitive dysfunction, impaired decision-making ability, and emotional abnormalities [1]. Diabetes-related cognitive dysfunction (DRCD), a key manifestation of DE, can affect patients' daily living abilities, induce severe mood swings, and alter personality [2], and affected individuals may lose some of their language, learning, cognitive, and living skills.

In recent years, with the continuous increase in the global prevalence of diabetes mellitus, the population affected by DE has been expanding [3], which not only imposes a heavy economic burden on patients and their families but also significantly reduces patients' quality of life and may even be life-threatening.

Current studies have confirmed that the occurrence of DE is closely related to various factors, including disorders of glucose and lipid metabolism, insulin resistance, gender, age, genetic background, obesity, hypertension, hyperlipidemia, visual and hearing impairments, olfactory

DOI: 10.54254/2753-8818/2026.33306

dysfunction, alcoholism, smoking, vascular lesions, abnormal blood glucose levels, and depression. The pathogenesis of DE is complex, involving oxidative stress, inflammatory response, blood-brain barrier damage, and other aspects.

Although some progress has been made in the research on DE, many challenges remain in early identification, precise intervention, and effective management. Therefore, in-depth exploration of the pathogenesis of DE and construction of a scientific risk prediction model are of great clinical significance and social value for the early screening, intervention, and improvement of patient prognosis.

This study aims to systematically analyze the related risk factors of DE in elderly patients with type 2 diabetes mellitus, construct a risk prediction model, provide a scientific basis for clinical decision-making, and offer effective support for the prevention and management of DE. Epidemiological survey data show that the incidence of DRCD in diabetic patients is 1.5 - 2 times that in non-diabetic patients [4], and the progression of DRCD to dementia is significantly accelerated.

2. Pathogenesis and risk factors

2.1. Pathogenesis

Diabetes mellitus causes various dysfunctions, with hyperglycemia as the core factor. Long-term hyperglycemia induces persistent chronic inflammation of blood vessels and nerves throughout the body. DRCD is associated with multiple pathogenic factors and a complex pathogenesis. In terms of disease severity, it is divided into two types: mild cognitive impairment (MCI) and dementia. In terms of pathogenesis, multiple factors interact to affect the disease progression of DE, including oxidative stress that damages cell structure and function leading to neurodegeneration, long-term neuroinflammation causing neuronal damage and apoptosis, insulin resistance-mediated cerebral metabolic disorders, cytotoxic effects of long-term hyperglycemia on neurons, and vascular dementia caused by atherosclerosis [5,6].

2.2. Risk factors

The risk factors for DRCD in DE can be divided into 2 categories: controllable factors and uncontrollable factors. Understanding these factors can help implement more targeted prevention and management of DE. Uncontrollable factors include 3 types: gender, age, and genetics. Aging is one of the most significant risk factors for DRCD, among which males have a higher incidence risk than females. A family history of cognitive dysfunction due to genetic factors increases an individual's susceptibility to DRCD. Controllable factors include obesity, hypertension, hyperlipidemia, visual and hearing impairments, olfactory dysfunction, alcoholism, smoking, vascular lesions, abnormal blood glucose, depression, lack of physical exercise, and many other factors. See Table 1 for details.

Table 1. Risk factors for dysfunction in diabetic encephalopathy

	Risk factors		
Uncontrollable Factors	Gender	Age	Genetic Factors

DOI: 10.54254/2753-8818/2026.33306

Table 1. (continued)

Controllable Factors	Obesity	Hypertension	Hyperlipidemia
	Visual Impairment	Hearing Impairment	Olfactory Dysfunction
	Alcoholism	Smoking	Vascular Lesions
	Abnormal Blood Glucose	Depression	Lack of Physical Exercise
	Introverted Personality	Low Social Activities	Low Educational Level

A glycated hemoglobin (HbA1c) level greater than 7.5% indicates poor blood glucose control [7], which can increase the risk of DRCD by 2-fold. The incidence of DRCD in diabetic patients with diabetic retinopathy is 2.4 times that in patients without retinopathy, and the progression of DRCD is significantly accelerated when proliferative diabetic retinopathy occurs [8]. For patients with visceral obesity, each 0.27 kg increase in visceral fat is associated with a 0.7-year acceleration in cognitive aging [9-10]. Hypertension is strongly associated with cognitive impairment, and elevated diastolic blood pressure has a significant negative correlation with cognitive function [11,12]. When cholesterol levels exceed 5.2 mmol/L, there is a significant negative correlation with cognitive function [13]. In addition, low-frequency social activities, accumulation of negative emotions, low educational level, and introverted personality are also associated with DRCD.

3. Screening and evaluation of cognitive dysfunction in diabetic encephalopathy

The screening, evaluation, and diagnosis of DRCD mainly rely on laboratory tests [14,15], imaging examinations [16], genetic tests, risk model prediction, neuropsychological assessment scales [17], and other methods to detect early DE and achieve accurate diagnosis.

Table 2. Screening and evaluation of cognitive dysfunction in diabetic encephalopathy

Screening and Evaluation Methods	Common Approaches	Introduction
Laboratory Tests	Cerebrospinal Fluid (CSF) Test	Aβ42/Aβ40; p-tau181; Aβ42; p-tau205; microtubule-binding region tau-243; total tau protein;
	Plasma Test	Glial fibrillary acidic protein (GFAP);
Imaging Examinations	MRI	Safe; non-invasive; provides high resolution for soft tissue contrast; It is suitable for brain imaging and is often used for brain atrophy and brain injury.
	fMRI	Detect blood oxygen level-dependent signals, reflect brain oxygen saturation, blood flow, local glucose metabolism changes, and indirectly reflect neuronal changes.
	PET	Accurate detection of β amyloid and tau protein entanglement can effectively distinguish between cognitive dysfunction in type 2 diabetes and Alzheimer's disease.
Genetic testing	Precocious Elderly 1	The core catalytic subunit of the γ-secretase complex
	Precocious Elderly 2	Participate in the processing of amyloid precursor protein APP and directly affect the production of Aβ
	Amyloid precursor protein	β-amyloid is a precursor to Aβ, and Aβ abnormal aggregation is a core marker of the pathological features of Alzheimer's disease

DOI: 10.54254/2753-8818/2026.33306

Table 2. (continued)

Risk model prediction	Age	It is one of the most important and irreversible risk factors for cognitive dysfunction.
	Educational Attainment	Significantly negative correlation
	DR Dementia Scale	-
	P-tau181	Abnormally phosphorylated tau proteins self-aggregate to form paired helical filament PHFs, which eventually form neuronal fiber tangled NFTs, leading to neuronal death.
Neuropsychological assessment scale	Mini-Form Mental State Examination Scale	-
	Montreal Cognitive Function Assessment Scale	-
	CDR	-
	ADAS-cog	-
	Activity of Daily Living (ADL)	-
	Cognitive Function Screening Scale (CASI)	-
	Neuropsychiatric Inventory (NPI)	-
	Hamilton Rating Scale for Depression (HAMD)	
	Hamilton Rating Scale for Anxiety (HAMA)	

4. Treatment of diabetic encephalopathy

DRCD is a major public health problem, and there is currently no clear treatment strategy. Due to its complexity and the lack of clear therapeutic methods, the current mainstream treatment is to relieve symptoms. Through lifestyle interventions targeting disease risk factors, drug therapy, and other means, the progression from cognitive dysfunction to dementia can be delayed. The promotion of universal health care knowledge should also be strengthened.

4.1. Non-pharmacological interventions

4.1.1. Acupuncture therapy

Acupuncture can be used as an adjuvant treatment to improve cognitive dysfunction, especially for vascular cognitive dysfunction and mild cognitive impairment, but it cannot replace drug therapy. After neurologists or endocrinologists rule out cognitive dysfunction and dementia caused by other reasons, acupoint selection can be formulated based on the patient's overall condition. Different

DOI: 10.54254/2753-8818/2026.33306

syndromes such as kidney essence deficiency and phlegm-stasis blocking the orifices are distinguished to select acupoints for treatment. Commonly used acupoints include Baihui (GV20), Sishencong (EX-HN1), Shenting (GV24), Fengchi (GB20), and Zusanli (ST36). Feng et al. [18] selected Benshen (GB13), Baihui (GV20), Shaofu (HT8), Taichong (LR3), Zusanli (ST36), Fengchi (GB20), Taixi (KI3), Xuehai (SP10), Renzhong (GV26), Juegu (GB39), and Dazhui (GV14). After deqi was achieved, the electroacupuncture parameters were 80-100 Hz, 2-4 mA, 30 minutes per session, twice a day, 10 days per course, and continuous treatment for 5 courses was required. It was found that acupuncture therapy had a significant therapeutic effect on mild cognitive impairment in the elderly. Zhu et al. [19] found that the Du meridian regulating and spirit soothing acupuncture therapy could significantly reduce the levels of serum high-sensitivity C-reactive protein (hs-CRP) and IL-6 in the body, and improve amnestic mild cognitive impairment.

4.1.2. Lifestyle interventions

Adhering to a healthy lifestyle, such as quitting smoking, abstaining from alcohol, regular diet, and regular exercise, can significantly improve cognitive dysfunction and reduce its incidence risk. Combined with the Mediterranean diet, increase the intake of brain-beneficial foods such as green leafy vegetables, fish, whole grains, nuts, and berries, and reduce the consumption of red meat, butter, and excessive sugars. Perform >150 minutes of moderate-intensity aerobic physical exercise per week, such as brisk walking, jogging, and swimming. Sufficient and high-quality sleep is an effective intervention to delay cognitive decline and cognitive dysfunction.

4.1.3. Family and social support

Diabetes mellitus is a chronic underlying disease that requires lifelong medication for patients, and various complications may occur with the progression of the disease, causing severe interference to patients and their families [20]. Patients may have poor blood glucose control, poor compliance, and cognitive impairment or dysfunction with the disease course. Therefore, effective family and social support to assist patients in self-management, such as timely and in-place medication reminders, inclusion of high-quality drug medical insurance, and development of intelligent software, can build a more comprehensive diabetes management model and improve long-term prognosis [21,22].

4.2. Pharmacological interventions

At present, there is no unified treatment standard for the drug treatment of DRCD. Studies have found that hypoglycemic drugs with low hypoglycemia risk and neuroprotective effects have potential benefits in improving cognitive dysfunction. The dosage of drugs should be reasonably adjusted according to the health status, complications, liver function, glomerular filtration rate, and other conditions of elderly diabetic patients to reduce the incidence of adverse events. For elderly diabetic patients, individualized stratified management of blood glucose control targets should be carried out with reference to their physical health status and cognitive function [23]. See Table 3 for stratified management of blood glucose control targets under different health statuses.

Table 3. For stratified management of blood glucose control targets under different health statuses

-	Health Status Good	Health Status Moderate	Health Status Poor
Fasting Blood Glucose (mmol/L)	4.4-7.2	5.0-8.3	5.6-10.0
Pre-sleep Blood Glucose (mmol/L)	4.4-10.0	5.6-10.0	6.1-11.1

DOI: 10.54254/2753-8818/2026.33306

Table 3. (continued)

HbA1c (%)	<7.0-7.5	<8.0	-

4.2.1. Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

SGLT2i are a new type of oral hypoglycemic drugs that lower blood glucose by excreting excess glucose from the urine. In addition to lowering blood glucose, SGLT2i also have clear protective effects on cardio-renal-cerebral complications. Related drugs include empagliflozin, dapagliflozin, and henggliflozin [24]. Common adverse reactions of SGLT2i include urinary and reproductive system infections, dehydration caused by hypovolemia, dizziness, and symptomatic hypotension. During medication, attention should be paid to personal hygiene and adequate water intake.

4.2.2. Metformin

The main function of metformin is to control blood glucose, and it has potential protective effects on cognitive dysfunction, but it is not a drug specifically used to treat cognitive dysfunction. Metformin controls blood glucose levels by improving insulin resistance and reducing hepatic glucose production. Research data show that metformin benefits the brain through multiple pathways such as reducing neuroinflammation, decreasing oxidative stress, and improving cerebral blood flow, has a potential protective mechanism against DRCD, and reduces the risk of dementia [25].

4.2.3. GLP-1RA glucagon-like peptide-1 peceptor agonists (GLP-1RA)

GLP-1RA are a class of injectable hypoglycemic drugs that lower blood glucose by simulating intestinal hormones, while significantly reducing weight and protecting the heart and kidneys. GLP-1RA only works when blood glucose is high, intelligently promoting insulin secretion, inhibiting glucagon, and delaying gastric emptying. It acts on the central nervous system to reduce appetite and increase satiety. Large cohort analyses have shown that it can reduce the risk of myocardial infarction and stroke, and improve cognitive function [26]. It can significantly reduce proteinuria in patients with diabetic nephropathy complications and delay the progression of kidney disease.

4.2.4. Thiazolidinediones (TZD) and dipeptidyl peptidase 4 inhibitors (DPP-4i)

TZD drugs have a protective effect on dementia. Large cohort analysis data show that pioglitazone can reduce the risk of dementia in patients with type 2 diabetes and stroke. Common adverse reactions include edema, weight gain, and increased risk of heart failure and fractures. DPP-4i drugs such as linagliptin have a neutral effect on DRCD; sitagliptin has been shown to improve cognitive scores in Alzheimer's disease patients compared with metformin; vildagliptin has been shown to improve some cognitive dysfunctions in clinical data.

4.2.5. Intranasal insulin and sulfonylureas

Intranasal insulin may enhance immune function by inhibiting the inflammatory response in the central nervous system to achieve cognitive protection. Research data show that patients receiving intranasal insulin treatment have reduced IL-6 levels, increased eosinophil chemokine levels, increased CSF interferon-γ levels, and better performance in the ADAS-cog test. Sulfonylurea drugs are often used in combination with metformin, which can reduce the risk of dementia by 35%, but

DOI: 10.54254/2753-8818/2026.33306

the adverse reaction is hypoglycemia, which has side effects on neurological function after occurrence.

4.2.6. Others

Other drugs that are helpful for DRCD and dementia are described in the following. Acetylcholinesterase inhibitors are used to treat mild to moderate Alzheimer's disease, such as galantamine, rivastigmine, and donepezil. Glutamate receptor antagonists are used to treat moderate to severe Alzheimer's disease; for example, memantine (20 mg/d) can improve daily living ability, cognitive function, and neurobehavioral symptoms, and is contraindicated in patients with liver damage. Lecanemab can reduce amyloid plaques, improve and restore cognition, and produce clinical benefits, and Phase 3 clinical trials have been completed. Gantenerumab has been shown to improve the quality of life and cognitive function in patients with Alzheimer's disease. Traditional Chinese medicines such as Qinggong Shoutao Pills [27] and Tianzhi Granules are effective in improving cognition; Ginkgo biloba extract EGb761 can delay the progression of cognitive dysfunction to dementia.

5. Conclusion

Active and healthy lifestyle interventions can delay memory decline and are key strategies for preventing cognitive dysfunction [28]. Therefore, promoting a good and healthy lifestyle is one of the core and feasible means for the prevention, intervention, and management of DRCD [29]. Medical institutions need to formulate individualized treatment plans for patients, taking into account patient compliance, economic status, and feasibility, and guide medication use. At present, there is no unified treatment standard for DRCD. With more in-depth studies, data have shown that some hypoglycemic drugs have a significant positive correlation with the therapeutic effect of improving cognitive dysfunction [30].

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