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Review

Novel Insights into the Mechanism and Treatment of Diabetes-Related Brain Complications: Focusing on the Blood-Brain Barrier Impairment

Caiyi Long[1,2#], Yueheng Pu[1,2#], Shunseng Keng[1,2], Jiajing Tao[1,2], Boxun Zhang[1,2*], Rensong Yue[1*]

[1]Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China.
[2]Chengdu University of Traditional Chinese Medicine, Chengdu, China.

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ABSTRACT: Diabetes mellitus often leads to secondary brain disorders, thus increasing the risk of mortality. The blood-brain barrier (BBB) is a peripheral–central defense mechanism that significantly impacts diabetes-related brain complications. Under hyperglycemic conditions, the BBB undergoes pathological structural alterations, leading to increased permeability and transport dysfunction. Clinically, BBB damage induces diabetes-related brain complications such as cognitive impairment, stroke, and depression. Notably, BBB damage can occur before the onset of disease symptoms in the brain and may serve as a predictor of disease progression and prognosis. Hyperglycemia is the main cause of BBB damage and can induce oxidative stress, inflammatory response, Advanced glycation end products (AGEs) accumulation, and high-mobility group box 1 (HMGB1) signaling axis activation. These factors lead to endothelial dysfunction, disruption of tight junction proteins, loss of pericytes, activation of astrocytes and microglia, disruption of the actin cytoskeleton, alterations in the basement membrane, and an increase in matrix metalloproteinases (MMPs). Collectively, these processes contribute to brain injury in patients with diabetes. Lifestyle interventions and hypoglycemic, antihypertensive, and lipid-lowering agents play therapeutic roles in BBB damage and diabetes-related brain complications. However, the role of some drugs in this context is controversial and remains known only at the animal and cellular levels. Several studies have investigated the therapeutic potential of targeted nanomedicines and natural compounds; however, it remains challenging to translate their research findings to clinical practice. In conclusion, this review highlights the clinical evidence, pathological mechanisms, and existing treatment options for BBB damage in patients with diabetes-related brain complications. It also demonstrates the potential of targeted nanomedicines and natural compounds, providing a foundation for future research.

Key words: Blood-brain barrier, diabetes mellitus, cognitive impairment, stroke, depression

1. Introduction

The high prevalence of diabetes mellitus (DM) poses a substantial ongoing global public health challenge, with type 2 diabetes mellitus (T2DM) accounting for approximately 90% of cases [1]. Hyperglycemia in patients with diabetes, along with insulin resistance, chronic inflammation, oxidative stress, genetic factors, and comorbidities (such as hypertension, dyslipidemia, and obesity), contribute to the development and progression of diabetes-related brain complications, particularly cognitive impairment, stroke, and depression, which have recently garnered significant attention [2-4]. A previous meta-analysis indicated that the risk of cognitive impairment, which also encompasses dementia, is 1.25 to 1.91 times greater for patients with DM [5].

***Correspondence should be addressed to:** Dr. Rensong Yue (Email: songrenyue@cdutcm.edu.cn) and Dr. Boxun Zhang (Email: 1243876560@qq.com), Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China. #These authors contribute equally to this work.

Moreover, the prevalence of major depressive disorder (MDD) among patients with DM is reportedly as high as 46.6% [6]. With regard to ischemic stroke and hemorrhagic stroke, the prevalences are 33% and 26%, respectively, among patients with DM [7]; these conditions are twice as common as those in individuals without DM [8]. All these complications may coexist and exacerbate each other [2, 9, 10], not only burdening patients with higher healthcare costs [11] but also leading to a worse prognosis and a higher risk of all-cause mortality [12, 13].

The pathogenesis of these complications is complex and multifactorial. Research has shown that the blood–brain barrier (BBB), a key barrier between the central nervous system and peripheral tissues, also exhibits endocrine functions [14]. BBB damage induced by high glucose levels is closely associated with the development of cognitive impairment [15, 16], stroke [17], and depression [18, 19]. This damage may occur before visible disease symptoms manifest [20]; thus, it could be an early biomarker of diabetes-related brain complications and a crucial target for therapeutic interventions.

In this review, we explored the phenotypic and pathological mechanisms underlying BBB damage caused by diabetes. We review and discuss new evidence regarding BBB damage and its consequences on cognitive impairment, stroke, depression, and other diabetes-related brain complications. In addition, we have identified potential therapeutic interventions, providing valuable directions for future research.

2. Phenotypic alterations of the blood-brain barrier in diabetes: from physiology to pathology

BBB is a highly selective physiological barrier comprising specialized brain microvascular endothelial cells (BMECs) and their junctional complexes (e.g., tight junctions [TJs] and adherens junctions [AJs]), pericytes, astrocyte endfeet, basement membrane, and resting microglia [21-23].

Among these components, BMECs and their junctional complexes constitute a critical element of BBB, meticulously regulating molecular exchange between the blood and brain tissue. Barrier integrity depends on key TJ proteins such as claudin and occludin [24, 25], while zonula occludens proteins (primarily ZO-1 and ZO-2) serve as the principal scaffolding that anchors these transmembrane TJ proteins to the cytoskeleton [26, 27]. TJs control paracellular permeability. Claudin-5, the predominant TJ protein in BBB [28], permits the selective passage of molecules smaller than 800 Da while restricting larger molecules (> 800 Da) from diffusing via the paracellular route [29]. In addition to TJs, endothelial junctional complexes include AJs, which are primarily responsible for the establishment, maturation, and maintenance of endothelial cell–cell adhesion [30, 31].

Pericytes surround BMECs and collaborate with them to sustain the structural stability and functional integrity of BBB through direct intercellular interactions and signaling [32]. Astrocyte endfeet are closely associated with the vascular basement membrane, thus forming an almost continuous barrier that further enhances the protective function of BBB [33]. Furthermore, astrocytes release various growth factors and signaling molecules such as vascular endothelial growth factor (VEGF) and angiotensin-1. These factors play a significant role in regulating BBB permeability, supporting neuronal metabolism and maintaining homeostasis in the central nervous system (CNS) [34-36].

As inherent immune cells within CNS, microglia not only possess phagocytic abilities but also participate in the regulation of inflammatory responses and BBB permeability alterations through cytokine secretion and interactions with other cells [37, 38]. This complex network of cell-cell interactions contributes to efficient screening and precise regulation of blood components by BBB.

In terms of transport mechanisms, the BBB regulates the selective exchange of substances between the blood and brain tissue, primarily via passive diffusion, active efflux, carrier-mediated transport, receptor-mediated transport, and cellular trafficking across BBB. Passive diffusion of molecules across BBB primarily depends on their physicochemical attributes, e.g., molecular weight [39], electric charge [40], and high lipid solubility [41], which facilitate their transcellular passage through the tightly packed endothelial cells. Active efflux removes certain materials from the brain through ABC transporters, e.g., P-glycoproteins (P-GP), breast cancer resistance proteins (BCRPs), and multidrug resistance proteins (MRPs) [42-44]. Carrier-mediated transport sets up a selective influx-efflux system, while glucose transporter proteins and amino acid transporters play vital roles in providing nutritional support to the brain [45, 46]. Receptor-mediated transport identifies and binds macromolecules through specific receptors such as the transferrin receptor, low-density lipoprotein receptor-related protein 1 (LRP1), and the receptor for advanced glycosylation endproducts (RAGE), facilitating their transport across the cell membrane [47-49]. Cellular trafficking involves immune cells invading the brain through BBB to mediate both the central and peripheral immune responses [50]. These transport systems collectively establish a highly regulated transcellular pathway at BBB, facilitating the tight regulation of essential nutrients, metabolic substrates, and signaling molecules, among others, into and out of CNS.

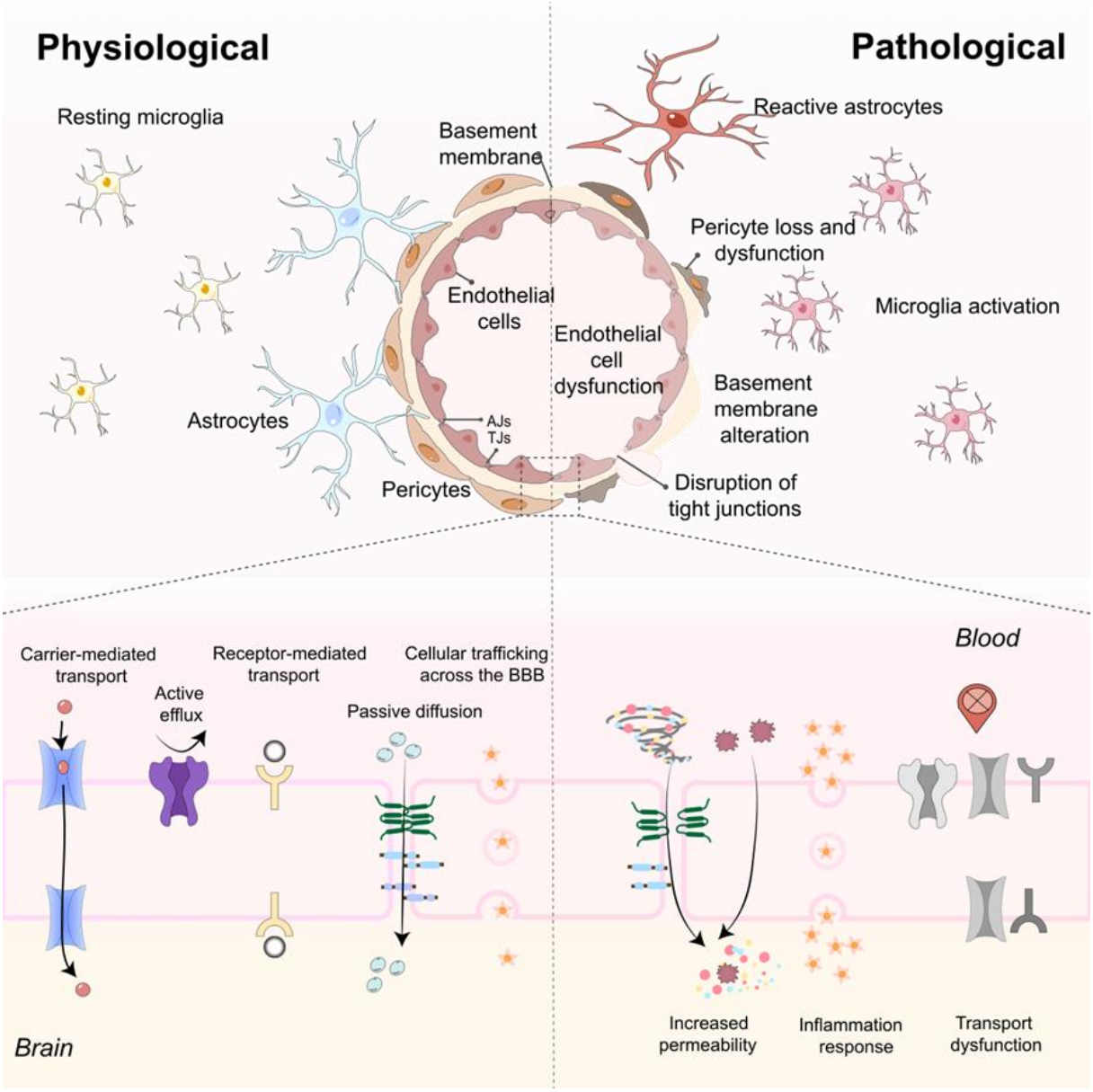

Figure 1. Phenotypic changes in blood–brain barrier damage. The left side of the figure shows the principal structural components and transport pathways of the blood–brain barrier under physiological conditions. The right side depicts the structural disruption and functional impairment of the blood–brain barrier under pathological conditions.

In the pathological state of diabetes, structural and functional impairments occur in vascular cells and glial cells of BBB; these include (a) disruption of endothelial cells and their TJs [51-58], (b) dysfunction and loss of pericytes [53, 54, 59, 60], (c) activation of microglia [59], (d) activation and crinkling of astrocytes [60], (e) damage to vascular structures [61-64], and (f) thickening of the basement membrane [65]. These morphological changes disrupt BBB integrity, leading to dysfunction characterized by increased permeability and transport deficiencies. In clinical studies, increased BBB permeability manifests as an increased cerebrospinal fluid (CSF)/serum albumin quotient (QAlb) [66-69], altered expression of proteins such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and VEGF [68, 69], and altered brain imaging findings [70, 71]. In animal and cellular experiments, this is shown as loss of TJs; leakage of the immunoglobulin G (IgG) index [72]; enhanced permeability of albumin [64, 65], inulin [51], and [14C] sucrose [51]; and upregulation of fluorescein (FL) [73]. BBB transport dysfunction mainly involves abnormal levels of transport proteins, such as P-GP, BCRP, and glucose transporter type 1 and 4 (GLUT1 and GLUT4), as well as impaired cation transport. The main structures and functions are shown in Figure 1.

3. BBB damage affects diabetes-related brain complications: clinical evidence

3.1 Cognitive impairment

Patients with diabetes exhibit increased BBB permeability, and this increase may contribute to further clinical deterioration in individuals with cognitive impairment [66, 67]. Evidence indicates that these patients show increased BBB permeability compared with that in individuals without diabetes, as shown by elevated Qalb values and high levels of ICAM-1, VCAM-1, and VEGF [66-70, 74]. In imaging studies, patients with T2DM have also demonstrated increased gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) enhancement [71] and elevated K^{trans} values [75]. Cerebral blood flow (CBF) is similarly linked to BBB permeability; clinical data indicate that every 2.2-mL/min/100 g decrease in CBF corresponds to a 0.7% increase in BBB leakage [76]. In addition, research has focused on the association between cognitive impairment and altered cerebral hemodynamics in T2DM [77]. A case report indicated a link between cognitive impairment and cerebral microangiopathy in patients with acute diabetes [78], while a cohort study revealed a 42% increase in the risk of dementia in individuals with diabetic retinopathy [79].

BBB damage promotes the progression of diabetic cognitive impairment (DCI). A cohort study found that the risk of DCI progression increased by 8% with every 10% increase in log-Qalb levels [66]. Another 17-month cohort study demonstrated that elevated QAlb serves as a significant predictor of DCI progression [67]. An 8-12-year cohort study by Mielke et al. found that elderly patients with T2DM showing overweight or obesity had higher plasma neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) levels, which are linked to later cognitive decline and a greater risk of cognitive impairment [80]. Therefore, it is crucial to recognize that impaired BBB permeability can precede cognitive decline. However, one study has also shown that increased BBB permeability does not correlate with cognitive function, likely because cognitive decline typically emerges as a late-stage biomarker, and the relationship between BBB permeability and cognitive decline may take time to develop [70].

3.2 Stroke

The incidence of stroke is higher for patients with DM than for individuals without diabetes, often leading to poor prognoses in the former [81-83]. BBB damage is a significant feature of early brain injury following stroke [84-86]. This is primarily indicated through brain imaging parenchymal enhancement (PE) signals, K^{trans}, blood-retinal barrier (BRB) dysfunction, and relevant biocirculatory markers. A study examining BBB damage on the basis of PE in T1-weighted imaging with a 5-minute delay after contrast injection revealed that patients with diabetes showing varying PE increases experienced adverse stroke outcomes [87]. Kawamura et al. found that patients with T2DM who had silent cerebral infarcts showed higher levels of soluble ICAM-1 (sICAM-1), soluble E-selectin, and soluble VCAM-1 than did those without infarcts, and that patients with a baseline sICAM-1 level of >260 μg/L had a higher risk of stroke [88]. Moreover, an 8-year cohort study reported that patients with T2DM and cerebral infarction had significantly elevated sICAM-1 levels, and that sICAM-1 was an independent risk factor for stroke in these patients [89]. Another study showed a negative correlation between brain-derived neurotrophic factor and hyperglycemia, along with elevated endothelial progenitor cell counts, in post-stroke patients with diabetes [90]. BRB is functionally and structurally similar to BBB and may reflect BBB integrity. A 10-year clinical study indicated that patients with DM and BRB dysfunction tended to experience stroke more quickly [91].

BBB permeability assessment also helps predict the prognosis of patients with clinical stroke. Research has shown that evaluation of BBB permeability using perfusion computed tomography can predict the risk of symptomatic hemorrhagic transformation and malignant edema in patients with ischemic stroke [92].

3.3 Depression

DM and depression often co-occur because of shared underlying pathological mechanisms, e.g., inflammation, metabolic dysfunction, oxidative stress, and insulin resistance [93]. A meta-analysis indicated a 40% prevalence of comorbid depression in patients with DM [94]. Depression is associated with a nearly 1.5-fold increased risk of death in patients with DM [95], greatly impacting their quality of life.

Clinical findings have shown that patients with depression often have increased BBB permeability and transport dysfunction [96-98]. Biomarkers such as Qalb [96], S100B protein [99], sICAM-1 [100], VEGF [101], and proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) [102] were found to be elevated in patients with MDD. A human genetics study suggested a notable association between altered P-GP and MDD, indicating a potential relationship between BBB transport dysfunction and MDD progression [103]. Some studies have explored the relationship between diabetes, depression, and BBB function. Insulin resistance and related inflammatory pathways can lead to BBB

leakage, thereby exacerbating depression [104, 105]. In patients with T1DM, higher serum sICAM-1 levels correlate with worse depressive symptoms [100]. In patients with T2DM, depressive symptoms measured using serial Patient Health Questionnaire-9 scores positively correlate with VEGF levels [101]. Similarly, a meta-analysis suggested that depression in patients with diabetes is associated with an increased risk of macrovascular and microvascular complications [106]. Another cross-sectional study found that retinal vascular calibers were significantly wider in patients with T2DM showing depression than in patients with diabetes without depression and healthy controls, suggesting early microvascular changes in patients with DM showing depression [107].

Diabetes-related brain complications often occur simultaneously or sequentially [108-110]. Diabetes is an independent predictor of poor cognitive recovery following stroke [111]. In addition, poorer glycemic control [109], long duration of diabetes [112], and high levels of glycosylated hemoglobin [112] are risk factors for cognitive impairment following stroke in patients with T2DM. Cognitive impairment is also associated with an increased risk of stroke in patients with diabetes [113]. Depression is an independent risk factor for cognitive impairment [114]. A study of 5,263 individuals showed that patients with diabetes showing depression had a subjective decline in cognitive abilities [110]. These findings suggest that BBB damage underlies diabetes-associated brain complications, forming a self-perpetuating loop that accelerates disease progression.

3.4 Other brain diseases

BBB damage in diabetic patients may also contribute to the development of other neurological disorders such as epilepsy [115] and tuberculous meningitis [116]. However, only preclinical animal studies have been reported on conditions such as Parkinson's disease and anxiety [117, 118], and further clinical evidence is needed for confirmation.

A case report described a patient with nonketotic hyperglycemia (NKH) who exhibited intermittent jerky movements of the left arm and blurred vision in the left visual field of both eyes following intravenous gadolinium injection, which showed a tiny overlying area of interstitial CSF enhancement around the right parietal lobe. The findings from this case suggested that seizures in patients with NKH result from hyperglycemia-induced BBB damage [115]. Navasardyan et al. suggested that diabetes leads to diminished BBB integrity and increased permeability, which allows the infiltration of harmful and infectious pathogens (e.g., *Mycobacterium tuberculosis*) and induces conjugate meningitis [116].

Table 1. Summary of studies on blood-brain barrier (BBB) impairment-related markers and brain complications in diabetic patients.

Author and year	Type of Research	Follow-up time (year)	sample size	BBB damage-related markers	Detailed description
Cognitive impairment					
Albert Puig-Pijoan2024 [66]	CC	3	334	Log-Qalb	With every 10% increase in log-Qalb levels, the risk of DCI progression increased by 8%
Xiaorui Tian2024 [67]	CC	1.4	295	Qalb	Patients with AD exhibited the highest levels of QAlb compared to patients with MCI and SCD. After a mean follow-up of 17 months, 117 patients (51.31%) were identified with progression of cognitive decline, and QAlb was a significant predictor of DCI progression.
Shorena Janelidze2017 [69]	CC	5.7	1015	Qalb	BBB permeability is increased in major dementia diseases. Elevated Qalb levels are associated with high concentrations of ICAM-1, VCAM-1, and VEGF in the cerebrospinal fluid.
Jinghuan Gan2023 [68]	CS	/	95	Qalb	Ratios of Aβ1-42/Aβ1-40 or t-tau/Aβ1-42 mediate the association between Qalb and GHb
Michelle M Mielke2025 [80]	CC	8-12	758	Plasma GFAP and NfL	In an elderly cohort of T2DM patients with overweight or obesity, higher plasma NfL and GFAP levels were associated with cognitive decline and an increased likelihood of cognitive impairment 8–12 years later.
J M Starr 2003 [71]	CS	/	20	Gd-DTPA enhancement	The signal intensity curves indicated a greater increase in brain signal intensity in the diabetic group compared to controls within the first 15 minutes following Gd-DTPA administration.

Ying-Chen Chen2022 [75]	CS		37	K^{trans}	T2DM patients show significantly increased K^{trans}, especially in the CSVD subgroup with a high dementia prevalence
Salwa S Hosny 2019 [74]	CS	/	90	sVCAM-1	Elderly T2DM patients with MCI exhibit significantly higher sVCAM-1 levels compared to T2DM patients without cognitive impairment and healthy controls.
Betul Sumbul-Sekerci2025 [121]	CS	/	183	sVCAM-1	VCAM-1 levels were significantly lower in patients with T2DM compared to the control group and the prediabetes group.
Stroke					
Junxia Niu2025 [122]	CS		94	K^{trans}	In patients with ischemic stroke, those with diabetes exhibited significantly higher K^{trans} values compared to non-diabetic patients, along with elevated enhancement ratio measured from 3D-SPACE T1-weighted imaging.
Xinfeng Yu2016 [87]	CS	/	62	PE	Patients with both diabetes and stroke exhibited significantly increased PE.
Yonatan Serlin2016 [91]	CC	10	2982	Retinal microvascular lesions assessed by fluorescein angiography	The incidence of stroke, epilepsy, and mental disorders is higher in patients with proliferative diabetic retinopathy compared to those with non-proliferative diabetic retinopathy.
Takahiko Kawamura2006 [88]	CC	3	179	sICAM-1, sE-selectin and sVCAM-1	At baseline, patients with diabetes and asymptomatic cerebral infarction showed higher levels of sICAM-1, sE-selectin, and sVCAM-1 compared to those without infarction. Additionally, T2DM patients with baseline sICAM-1 levels >260 μg/L had an increased risk of developing stroke.
Akio Kanai2008 [89]	CC	8	179	sICAM-1	Patients with T2DM and cerebral infarction show significantly elevated sICAM-1 levels.
Depression					
Thanh Tan Nguyen2010 [107]	CS		82	Retinal vascular caliber measured from digital photographs	Compared with healthy controls and patients with T2DM alone, those with T2DM and comorbid major depression show more pronounced retinal arteriolar dilation.
Malgorzata Gorska-Ciebiada2015 [123]	CS	/	219	sICAM-1, sVCAM-1, and sE-selectin	In elderly diabetic patients, those with both MCI and depressive symptoms exhibit significantly higher levels of sICAM-1, sVCAM-1, and sE-selectin compared to controls.
Jean-Pierre S. Laake2014 [101]	CS		1790	VEGF	depressive symptoms measured by the continuous PHQ-9 score are positively correlated with VEGF levels.
Vera Novak2011 [124]	CS		147	sVCAM and sICAM	Patients with diabetes exhibit greater vascular reactivity, more cortical atrophy, and depression. sVCAM and sICAM are associated with increased vascular contraction, reduced vasodilation, and increased cortical atrophy in the frontal, temporal, and parietal lobes.
Christian Herder2017 [100]	CS		434	sICAM-1	sICAM-1 is positively correlated with depressive symptoms in patients with T1DM.

CC: cohort studies, CS: Cross-sectional studies, CR: case reports, Qalb: cerebrospinal fluid (CSF)/serum albumin quotient, ICAM-1: intercellular cell adhesion molecule-1, VCAM-1: vascular cell adhesion molecule-1, VEGF: Vascular endothelial growth factor, Gd: Gadolinium, MCI: Mild cognitive impairment, SCD: Subjective cognitive decline, AD: Alzheimer's disease, MRI: Magnetic Resonance Imaging, GHb: Glycosylated hemoglobin or glycated hemoglobin, PE: parenchymal enhancement, PDR: proliferative diabetic retinopathy.

Although animal experiments have shown significant BBB damage (e.g., pericyte loss, increased pathological neovascularization, microglial activation, and IgG leakage) in diabetic mice with Parkinson's disease, there is no clinical evidence linking BBB dysfunction to Parkinson's disease [117]. Further clinical studies are needed to explore the impact of BBB damage in patients with diabetes-related brain complications. Evidence suggests that anxiety is a diabetes-related brain complication [119]. In addition, preclinical evidence has indicated that anxiety is associated with BBB damage in female rats [120]. However, no clinical studies have confirmed the association between BBB damage and anxiety in patients with diabetes, highlighting the need for further clinical investigations.

3.5 Mini conclusion

The aforementioned clinical evidence indicates that the key role of BBB damage in diabetes-related brain complications has been widely recognized. BBB permeability is strongly correlated with DM-related cognitive impairment and can predict disease risk and progression [66]. In addition, BBB damage not only exacerbates early brain injury after stroke but also significantly increases the incidence of stroke and poor prognosis in patients with diabetes [87]. Finally, in patients with diabetes showing depression, BBB leakage induced by inflammation and insulin resistance is also reflected by serum biomarker levels (such as sICAM-1, S100B, and VEGF) [101, 123], and it interacts with the risk of cognitive impairment, stroke, and other diabetes-related brain disorders.

However, some controversial issues require further investigation. First, although various methods are available for BBB evaluation, including the measurement of biochemical biomarkers (such as QAlb and S100B) and imaging (Gd-DTPA enhancement, K^{trans} values, and perfusion CT findings), differences in sensitivity among these techniques may lead to discrepancies in research conclusions. Therefore, establishment of a unified multimodal assessment system and standardized evaluation criteria to improve the reproducibility of conclusions requires further consideration. Second, although some longitudinal studies have confirmed research conclusions, many cross-sectional studies have been conducted, and some of them have been unable to establish a causal relationship between BBB damage and related diseases and may have errors in their findings. BBB damage is typically an early pathological change [75] and apparent biological phenotypes of the disease may gradually emerge in its later stages [125]. Therefore, there may be a temporal difference between BBB damage and the onset of clear biological phenotypes, and further longitudinal studies with more precise designs are required to establish a clearer cause-and-effect relationship.

4. Pathological mechanisms of BBB damage in diabetic-related brain diseases

Hyperglycemia represents the primary insult to BBB. A number of phenotypic studies have demonstrated that hyperglycemia leads to increased BBB permeability [126-128] and impaired transport function [129-131]. Both of these effects appear to worsen over time [65]. These manifestations of BBB damage are primarily driven by a range of molecular mechanisms induced by hyperglycemia, particularly inflammation, oxidative stress, AGE accumulation, and high-mobility group box 1 (HMGB1) activation. These processes act synergistically to compromise BBB damage and contribute to the development of diabetes-related brain complications.

4.1 Oxidative stress

Hyperglycemic conditions can induce oxidative stress, to which the BBB is highly sensitive [132]. During hyperglycemia, glucose influx disrupts cellular energy metabolism and contributes to mitochondrial dysfunction. This disruption triggers an increase in the production of reactive oxygen species (ROS). Increased ROS further impair glucose metabolism, resulting in a vicious cycle [133, 134]. Finally, increased oxidative stress decreases the functionality of BECs [135], disrupts TJs [136], causes pericyte loss [54], and damages the actin cytoskeleton [137]. Collectively, these changes compromise BBB integrity leading to increased permeability and brain injury.

Animal studies have shown that when diabetes lasts for 3 weeks, significant oxidative stress occurs, as evidenced by reduced glutathione levels and higher levels of 3-nitrotyrosine, 4-hydroxy -2-trans-nominal, and superoxide dismutase (SOD) [138]. Meanwhile, inhibition of mitochondrial carbonic anhydrase in diabetic mice alleviates oxidative stress in the brain [138, 139], rescues pericyte loss, and reduces BBB permeability [140]. In in vitro studies, hyperglycemia promoted oxidative stress by increasing ROS levels in endothelial cells and activating SOD and catalase [135, 141, 142]. Although low hydrogen peroxide (H_2O_2) concentrations promote BEC proliferation, migration, and tube formation, higher concentrations (H_2O_2>100 μM) increase BEC permeability and reduce TJ localization [136]. The actin cytoskeleton undergoes alterations due to stress fiber contraction, resulting in gaps between endothelial cells. Oxidative stress affects the actin cytoskeleton, contributing to a significant increase in stress fiber formation and the loss of claudin-5, thus increasing BBB permeability [137]. Simultaneously, pericytes under HG have increased ROS and mitochondrial superoxide production, causing ATP depletion and decreased contractility, which leads to pericyte dysfunction and diminished coverage [54].

4.2 Inflammatory response

Hyperglycemia has been shown to induce both systemic and localized inflammatory responses, which play a critical role in disrupting the integrity of the BBB [143]. Animal studies have confirmed that both type 1 and type 2 diabetic mice exhibit elevated inflammatory factors in the brain tissue, contributing to memory impairment through BBB damage [59]. Another study showed that, in

a diabetic insulin-resistant mouse model, BBB dysfunction and neuroinflammation in the cortex and hippocampus occurred as early as 4 weeks after high-fat, high-fructose feeding, whereas cognitive impairment only became evident after 24 weeks [20]. This suggests that BBB dysfunction related to inflammation may precede overt neurodegeneration and cognitive impairment [20]. In cellular experiments, hyperglycemic conditions prompted BECs to release inflammatory factors, e.g., TNFα, IL-6, MMP-2, and MMP-9, which in turn induced BEC damage and BBB breakdown [141, 144].

Inflammation damages BBB through several mechanisms: (a) activation of BECs involved in BBB formation and downregulation of TJs (claudin-5, occludin, ZO-1) expression [145, 146], (b) upregulated expression of inflammation-related factors and adhesion molecules (VCAM-1, ICAM-1, MMPs, and pronflammatory cytokines) [141, 145, 147], (c) an increase in reactive astrocytes [148], (d) damage to the basement membrane [149], and (e) a significant decline in P-GP efflux activity [150].

4.3 Advanced glycation end-products (AGEs) accumulation

Chronic hyperglycemia leads to the generation of AGEs and upregulation of their associated receptor (RAGE). This constitutes a mechanistic link between diabetes and its associated brain complications [151]. Clinical studies have shown that individuals with both T2DM and Alzheimer's disease exhibit significantly elevated levels of AGEs in the brain [152]. Recent studies have confirmed the effects of AGEs on BBB, e.g., TJ disruption, pericyte dysfunction, MMP upregulation, and pathological changes in the basement membrane [153]. AGEs can downregulate claudin-5 expression in BECs by upregulating tumor growth factor beta-1 (TGF-β1) [154]. Furthermore, under hyperglycemic conditions and elevated AGE levels, ICAM and VCAM expressions were increased in BECs; this enhanced leukocyte adhesion and migration to BMECs monolayers. Downregulation of integrin α1, PDGF-R1β, and Cx-43 in pericytes, suggesting cellular dysfunction, has also been observed [53]. The accumulation of AGEs also increases fibronectin levels in pericytes [155] and upregulates MMP-2 [155] and MMP-9 [156] activities in rats, driving pathological changes in the basement membrane. The AGE-RAGE axis is one of the pathogenic pathways in diabetic brain injury. Through interaction with RAGE, AGEs can induce BBB damage by activating neuroinflammation [157].

4.4 HMGB1 signaling axis activation

The activation of the HMGB1 signaling axis under hyperglycemic conditions is another important contributor to BBB damage. HMGB1, a nuclear DNA-binding protein, is elevated in patients and mice with diabetes [158, 159]. Overactivation of HMGB1 can mediate downstream signaling pathways and interact with RAGE, TLR4, NLRP3, NMDAR, and other molecules, affecting the BBB by promoting neuroinflammation [160], disrupting TJs [161], inducing oxidative stress [162], and leading to endothelial barrier injury [163]. These responses eventually increase BBB permeability, causing various diabetes-related brain complications such as stroke and cognitive impairment.

Thus, HMGB1 is a potential therapeutic target for diabetes-related brain complications. Suppression of HMGB1-related signaling can inhibit amyloid beta (Aβ) accumulation in the hippocampus and improve BBB permeability in aging mice, leading to the restoration of cognitive functions [164]. Additionally, HMGB1 inhibition modulates microglia-mediated neuro-inflammation and improves BBB integrity, thereby preventing cerebral ischemic injury [165]. One study found a significant positive correlation between elevated clinical serum HMGB1 levels and depression severity [166]. In a depressed C57BL/6 mouse model, depression-associated spontaneous behavior was alleviated by inhibiting the colonic HMGB1-RAGE-TLR4 signaling axis [167]. Nevertheless, till date, there has been no direct evidence linking HMGB1 to depression via BBB damage.

4.5 Mini conclusion

Based on the discussed pathological mechanisms, hyperglycemia is the primary driving factor for BBB damage in diabetes-related brain complications. Oxidative stress, inflammation, AGEs accumulation, and HMGB1 signaling activation synergistically contribute to BBB damage. These processes promote TJ protein degradation, dysfunction of transport proteins, alterations in the basement membrane structure, activation of reactive astrocytes, loss of pericytes, and dysfunction of endothelial cells. Ultimately, these pathological responses lead to significantly increased BBB permeability, BBB dysfunction, and various brain complications, including cognitive impairment, stroke, and depression. In these studies, the pathological mechanisms did not occur in isolation but amplified each other through multiple positive feedback loops, collectively exacerbating BBB damage. This highlights the need for multitarget combination therapies based on BBB damage.

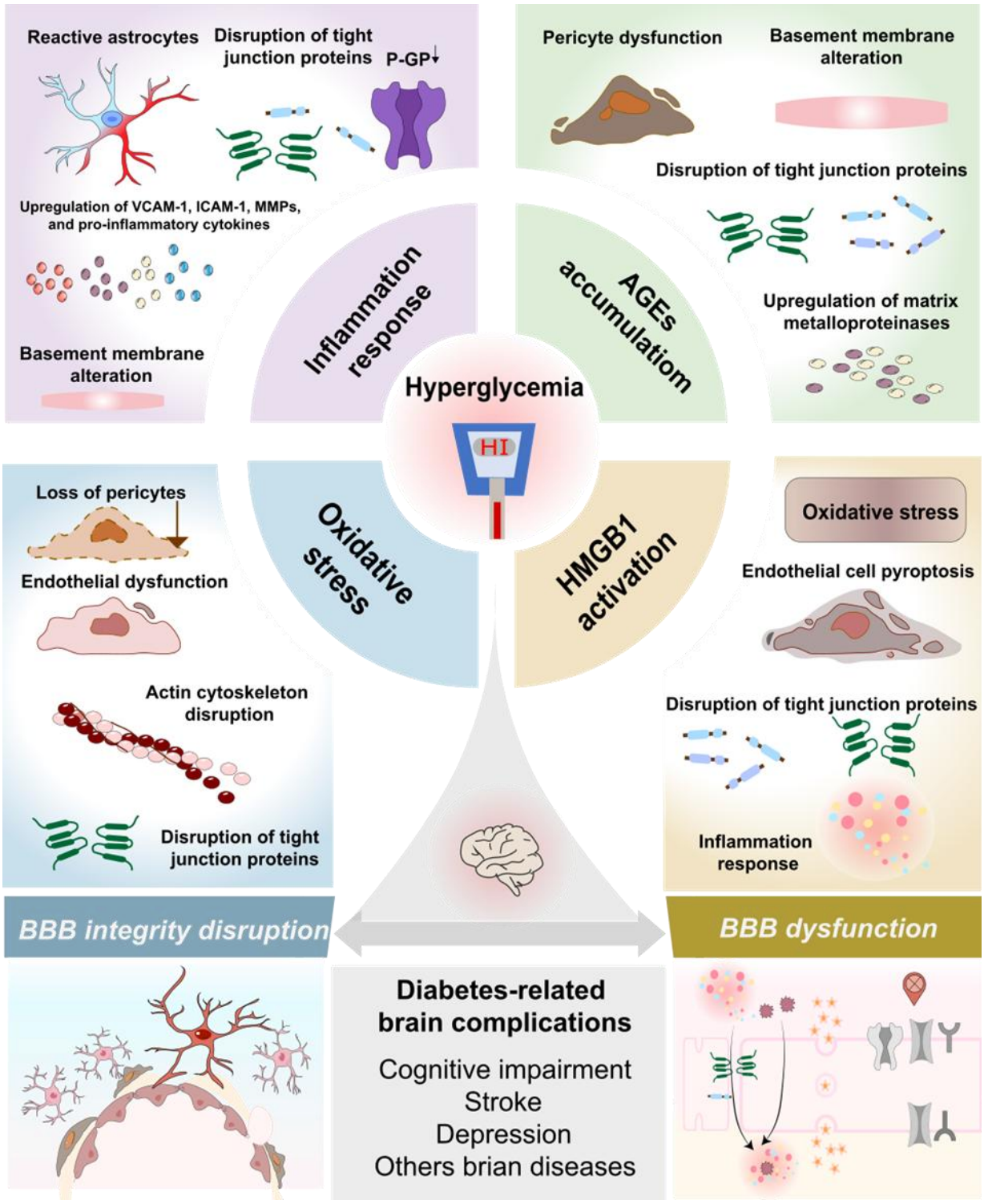

Figure 2. Pathological mechanisms underlying blood–brain barrier (BBB) disruption in diabetes-related brain complications. Hyperglycemia and pathological factors such as inflammation, oxidative stress, accumulation of advanced glycation end products (AGEs), and activation of the high-mobility group box 1 (HMGB1) signaling axis collectively contribute to structural damage and functional disruption of BBB, ultimately leading to diabetes-associated brain complications. P-GP: P-glycoproteins, AGEs: advanced glycosylation end products, HMGB1: the high mobility group protein 1, VCAM-1: vascular cell adhesion molecule-1, ICAM-1: intercellular adhesion molecule-1, MMPs: matrix metalloproteinases, BBB: blood-brain barrier

5. Interventions to repair BBB damage in diabetic-related brain complications

BBB damage is a common phenotypic feature and a potential therapeutic target in diabetes-related brain complications. Lifestyle improvements and medications can be effective and exert a combined therapeutic effect.

5.1 Lifestyle interventions

The impairment of BBB integrity and permeability can be partially reversed by physical activity and a healthy diet. A study showed that aerobic exercise can improve the oxidant–antioxidant imbalance in subjects with obesity and reduce the levels of serum S100β and neuron-specific enolase (NSE), findings suggesting an improvement in BBB [168]. Animal experiments showed that claudin-5 expression was upregulated in the striatum of diabetic rats after exercise, while synaptic plasticity was restored in the prefrontal cortex, leading to improved short-term memory [169, 170]. Similarly, running exercises alleviated depressive symptoms in mice by activating the AMPK-NF-κB/STAT3 signaling pathway, which can maintain the balance between M1 and M2 microglia and alleviate neuroinflammation [171]. Lu et al. found that swimming protected BBB integrity, reduced neuroinflammation, and preserved cognitive function in diabetic rats by downregulating fibrinogen levels and astrocyte activation [172]. Research has also found a positive effect of exercise on BBB integrity and brain edema in post-stroke rats [173].

Dietary patterns strongly correlate with DM. Several clinical studies have found that an inflammatory diet is independently associated with an increased risk of T2DM and may also elevate the mortality risk in patients with diabetes [174-176]. A Mediterranean diet can improve fasting blood glucose levels, HbA1c levels, and insulin sensitivity in patients with T2DM [177]. Similarly, a low-carbohydrate diet can promote weight loss; reduce blood glucose, IL-1Ra, and IL-6 levels; and improve the inflammatory status in patients with T2DM [178]. After 12 weeks of intermittent fasting, mice fed a high-fat diet showed memory recovery, coinciding with increased claudin-5 and ZO-1 expression and reduced extravascular albumin leakage; these findings suggested that intermittent fasting reduces BBB leakage [179]. Similarly, meta-analyses have highlighted that physical activity and dietary changes are beneficial for alleviating cognitive dysfunction [180-183], stroke [184, 185], and depression [186, 187] in patients with DM.

5.2 Clinical medications

5.2.1 Hypoglycemic agents

Many studies have reported the beneficial effects of hypoglycemic agents on diabetes-related brain complications; these were also found to improve BBB permeability and transport function. However, the results of some of these studies remain controversial.

Meta-analyses have suggested that metformin benefits patients with DM who show cognitive impairment [188] and stroke [189], but not those who show depression [190]. However, in a recent cohort study of 89,711 individuals with DM, metformin was found to reduce the risk of anxiety and depression [191]. Metformin reduces neuroinflammation and gliosis while enhancing BBB permeability and transport function, mainly by (a) protecting endothelial cells from emergency stimuli and infiltration of inflammatory factors [192-195], (b) increasing expression of ZO-1 and occludin to maintain BBB integrity [196], (c) inhibiting cortical microglia activation and decreasing proinflammatory factors [197], (d) improving pericyte coverage [198], and (e) suppressing the RAGE signaling pathway and upregulating LRP1 [199].

Dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA) also protect CNS by increasing the active form of GLP-1 [200, 201]. GLP-1RA is expressed in cognitively relevant CNS regions, e.g. the hippocampus, prefrontal cortex, and hypothalamus. Thus, elevated GLP-1RA levels play a vital role in restoration of BBB integrity and maintenance of permeability [202-204]. The DPP-4 inhibitor rosiglitazone reduces the pathological vasculature and increases pericyte density, thus restoring BBB integrity and reversing T2DM-induced BBB leakage [205]. Meta-analyses reported positive effects of GLP1-RA on cognitive impairment [206], stroke [207, 208], and depression [209]. As for DPP-4 inhibitors, although it may benefit cognitive function [210], their use in cases of stroke [211, 212] and depression [213, 214] remains controversial.

Meta-analyses have indicated that sodium-glucose transporter-2 (SGLT2) inhibitors (SGLT2is) diminished the risk of brain diseases such as dementia [206], stroke [215], and depression [214] in patients with diabetes and may be more efficient than other hypoglycemic agents. SGLT2 is present in the brain parenchyma and BBB [216], where it interacts with SGLT-2i, thereby offering neuroprotective effects [217, 218]. Animal experiments demonstrated that canagliflozin downregulates VEGF-A and upregulates ZO-1 in diabetic mice, significantly reducing pathological cerebral neovascularization and restoring BBB permeability [219].

Thiazolidinediones enhance BBB permeability and transport functions. An in vitro study confirmed that pioglitazone reduces BBB permeability of sodium fluorescein and ICAM-1 expression [220]. Furthermore,

pioglitazone and rosiglitazone were found to upregulate LRP1 expression and recover Aβ uptake [221, 222]. With regard to clinical settings, meta-analyses have suggested that thiazolidinediones reduce the risk of dementia [223], depression [190], and stroke [224] among patients with DM.

However, the efficacy of sulphonylureas in diabetes-related brain complications remains controversial. Some meta-analyses have revealed that sulfonylureas increase the risk of dementia in patients with diabetes [206], and that the risk is significantly higher than that with other hypoglycemic agents [225]. However, another study found no significant effect of sulfonylureas on the increased risk of stroke [226]. A retrospective study suggested that sulfonylureas may be neuroprotective and alleviate adverse neurological outcomes in patients with diabetes showing aneurysmal subarachnoid hemorrhage [227]. Variations in study criteria and literature volume may explain these discrepancies. Additionally, induced hypoglycemia may be a key reason for its contribution to CNS diseases [206]. Animal experiments revealed that glimepiride protects BBB by restoring pericyte coverage and reducing microglial activation [205]. Glibenclamide was also found to prevent cognitive impairment and depression in mice [228]. Possible mechanisms include inhibition of NLRP3 inflammasome activation in BMECs, boosting of ZO-1 expression, and a decrease in inflammatory cytokine levels, resulting in preserved BBB integrity and permeability [229].

Insulin treatment improves the diabetes-impaired BBB in a dose-dependent manner, both in terms of barrier and transporter functions. Insulin treatment reduces the monolayer permeability of hCMEC/D3 cells to IgG, increases brain transepithelial electrical resistance, and elevates the levels of the transporter protein ABCB1 [230]. In diabetic rats, insulin may increase occludin, claudin-5, and ZO-1 levels in BBB while enhancing P-GP levels through the ROS/AGE/RAGE/NF-κB signaling pathway, leading to reduced BBB permeability and restored transport function [231, 232]. Different routes of administration have varying clinical effects. A recent meta-analysis showed that insulin injections have no significant effect on the risk of dementia in patients with diabetes [223], likely because of hypoglycemic risk factors [206]. Another meta-analysis proposed the use of intranasal insulin (INI) to improve cognitive function, especially in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) [233]. Compared with traditional multiple daily insulin injections, insulin pump usage reportedly decreased the incidence and mortality rate of severe cardiovascular diseases, such as coronary heart disease and stroke, in patients with diabetes [234]. A meta-analysis also showed that although insulin injections improve diabetes-related distress, they do not affect depression and anxiety [235].

5.2.2 Antihypertensive agents

Clinical studies have shown that intensive blood pressure control can reduce the risk of cognitive impairment [236] and stroke [237] in patients with DM.

Table 2. Effect of different interventions on blood-brain barrier damage and comorbidities in diabetes mellitus.

Interventions	BBB-related indicators	Diabetic comorbidities		
		Cognitive impairment	Stroke	Depression
Lifestyle factors				
Exercise	Claudin-5↑ [169]	A meta-analysis including 12 trials found a beneficial effect [180].	A meta-analysis including 43 trials found a beneficial effect [184].	A meta-analysis including 17 trials found a beneficial effect [186].
Diet	Claudin-5 and ZO-1↑, extravasated albumin ↓ [179]	Meta-analyses have shown beneficial effects of dietary interventions in both diabetes [181] and cognitive impairment [182, 183], but no studies related to comorbidities.	A meta-analysis including 41 trials found a beneficial effect [185].	A meta-analysis including 13 trials found a beneficial effect [187].
Hypoglycemic agents				
Metformin	LRP1↑[199]	A meta-analysis including 28 trials found a beneficial effect [247].	A meta-analysis including 21 trials found a beneficial effect, but not in combination with other hypoglycemic agents [189].	A meta-analysis that included five trials found no significant effect [190]. However, the latest cohort study, which included 89,711 patients, found a beneficial effect of metformin [191].

GLP-1RA	Occludin and AQP4⬆, EB, MMP-2 and MMP-9⬇[203, 204]	A meta-analysis including 5 trials found no beneficial effect[248]. However, a beneficial effect was found in the latest network meta-analysis including 27 trials [206].	Two meta-analyses both found beneficial effects [207, 208].	A meta-analysis including 5 trials found a beneficial effect [209].
DPP-4 inhibitors	IgG and albumin⬇[205]	A meta-analysis including 10 trials found a beneficial effect [210].	Meta-analysis suggested no significant effect [211, 212].	A case-control study suggested a beneficial effect [213], but another cohort study suggested it was not significant [214].
SGLT-2i	VEGF-A and EB⬇, ZO-1⬆[219]	A network meta-analysis including 27 trials found a beneficial effect [206].	A meta-analysis including 12 trials found a beneficial effect [215].	A cohort study suggested a beneficial effect [214].
Thiazolidinedione drugs	LRP1⬆, Fluorescein sodium⬇, Increased Aβ efflux from the BBB and decreased Aβ influx [220-222]	A network meta-analysis including 27 trials found a beneficial effect [206].	A meta-analysis including 3 trials found a beneficial effect [224].	A meta-analysis including 19 trials found a beneficial effect [190].
Sulfonylureas	Pericyte coverage⬆, microglia activation , IgG， and albumin ⬇[205]	A network meta-analysis including 27 studies found an increased risk of dementia [206].	A meta-analysis including 108 trials suggested a significantly higher risk than other hypoglycaemic agents [225]. Another meta-analysis that included 47 trials suggested no significant effect [226].	A randomized trial suggested no significant effect [249].
Insulin	Occludin⬆, claudin-5⬆, ZO-1⬆, P-GP⬆, Rho123⬇， IgG⬇, and TEER⬆[230-232]	A meta-analysis of 27 trials suggested no significant effect [223], and a meta-analysis including 29 trials suggested a beneficial effect of intranasal insulin [233].	An observational study including 18,168 patients with type 1 diabetes suggested a beneficial effect of insulin pumps [234].	A meta-analysis including 9 trials suggested a reduction in diabetes-related pain, but no significant effect on depression [235].
Antihypertensive agents				
Telmisartan	ZO-1, occludin, claudin-3, claudin-5, and VE-Cadherin⬆, MMP-2 and MMP-9⬇[238]	A cohort study of 65,511 patients suggested a beneficial effect [250].	A retrospective study of 54,186 patients suggested a beneficial effect [251].	No relevant clinical studies.
Candesartan	EB⬇, TEER⬆[239, 240]	No relevant clinical studies.	No relevant clinical studies.	No relevant clinical studies.
Nifedipine	EB⬇[241]	No relevant clinical studies.	No relevant clinical studies.	No relevant clinical studies.
Lipid-lowering agents				
Probucol	IgG⬇， occludin-1⬆[15]	No relevant clinical studies.	No relevant clinical studies	No relevant clinical studies.
Statin	250-, 70-, and 40-kDa dextrans volume of distribution⬇, Annexin A1, claudin-3, and VE-cadherin⬆[242, 243]	A meta-analysis including 15 trials showed a beneficial effect [244].	A meta-analysis including 9 trials showed a beneficial effect [245].	A meta-analysis including 90 trials suggested a non-significant effect [246].

ZO-1: zonula occludens-1, LRP1: lipoprotein receptor-related protein 1, VEGF-A: vascular endothelial growth factor-A, MMP-2: matrix metalloproteinase-2, MMP-9: matrix metalloproteinase-9, EB: Evans blue extravasation, TEER: transepithelial electrical resistance, P-GP: P-glycoproteins, Rho123: rhodamine 123, IgG: immunoglobulin G

Some studies have supported the potential benefits of renin-angiotensin-aldosterone system inhibitors and calcium channel blockers in the treatment of diabetes-associated depression; however, there are no relevant clinical studies till date. The efficacy of antihypertensive agents against BBB damage in diabetes has also been investigated in animal studies. Telmisartan can alleviate BBB damage to improve diabetes-induced cognitive impairment via the activation of peroxisome proliferator-activated receptor γ [238]. A study showed that candesartan significantly reduced BBB permeability and lowered lipid peroxide levels [239], consistent with the

findings of another study [240]. A study also showed that nifedipine significantly reduced Evans blue extravasation, indicating improved BBB permeability [241].

5.2.3 Lipid-lowering agents

Probucol tablets exhibit both lipid-lowering and anti-lipid peroxidation effects. Research indicated that probucol tablets not only improved insulin resistance and peripheral inflammation in diabetic mice but also prevented IgG efflux in BBB and upregulated occludin-1 expression in BECs, driving a reduction in cognitive impairment [15]. Research on statins has highlighted that rosuvastatin and simvastatin decrease the distribution volumes of dextrans in diabetic rats, suggesting restoration of BBB permeability [242]. Another study of diabetic rats confirmed that rosuvastatin upregulates biomarkers of BBB integrity such as annexin A1, claudin-3, and VE-cadherin, restoring cognitive function [243]. Meta-analyses of clinical studies have indicated that statins may slow cognitive decline [244] and lower the stroke risk [245], while showing no association with increased depression risk [246], among patients with DM.

5.3 Preclinical therapeutic approaches

5.3.1 Targeted nanomedicines in diabetes-related brain complications

Targeted nanomedicines represent a treatment modality that utilizes nanoparticles as drug carriers for delivery. Research has increasingly explored these therapeutics in conditions associated with BBB damage, with the aim of mitigating BBB inflammatory responses and enhancing drug delivery across BBB to improve pharmacokinetics and intracerebral drug concentrations. Recent research indicated that in mice with ischemic stroke, lipid nanocarriers that target VCAM significantly enhanced drug localization within the compromised BBB region, leading to a 62% reduction in the volume of cerebral infarcts compared to that with non-targeted controls [252]. Anti-VCAM/liposomes also specifically target the inflamed brain, binding to endothelial cells, reducing BBB permeability, and attenuating TNF-α-induced brain edema [253]. Other studies have focused on creating nanoparticle delivery systems to transport medications across BBB. This strategy aims to increase the intracerebral concentrations of therapeutic agents and enhance their efficacy. For instance, a nanoparticle platform using small interfering RNA (siRNA) can triple drug concentrations in mice with traumatic brain injuries [247]. Another example is a nanoparticle-targeting ginsenoside, Rg1, capable of penetrating the BBB effectively and reducing the cerebral infarction volume [254]. Quercetin-conjugated superparamagnetic iron oxide nanoparticles show significant efficacy against diabetes-related cognitive impairment; however, their specific mechanisms remain unexplored [255].

5.3.2 Other agents

Some potential treatments, e.g., natural compounds and antioxidants, focus on the effects of BBB damage in DM. Allen et al. found that hyperglycemia may impair BBB integrity through oxidative stress, and different antioxidants such as NAD(P)H oxidase inhibitors, vitamin C, free radical scavengers, antioxidant enzymes, and different SOD mimetics can alleviate oxidative stress and lower hyperglycemia to restore BBB integrity [135]. Another study also found that antioxidant polyphenols can reduce high glucose-mediated cerebral infarct volume and hemorrhagic transformation, mainly by weakening redox reactions, lowering ROS levels, and inhibiting NOX activation to protect cerebral endothelial cells [256]. Sesamol, a natural antioxidant, upregulates TJ expression in BBB and reduces barrier permeability in diabetic rats [257]. T The major lignan (SDG) in flaxseed is a natural compound with anti-inflammatory properties. Studies have confirmed that SDG reduces leukocyte adhesion and migration across BBB, downregulates VCAM-1 expression, and restores BBB permeability [258]. Lauric acid, a naturally occurring fatty acid, has also been shown to reduce infarct volume and brain edema in post-stroke diabetic mice by reducing BEC death and stabilizing BBB barrier functions [259]. Likewise, several inhibitors have shown protective effects on BBB in patients with diabetes; these include the RAGE-specific inhibitor FPS-ZM1 [260], the NLRP3 inhibitor MCC950 [261], the HDAC3 inhibitor RGFP966 [262], and the NF-κB inhibitor pyrrolidine dithiocarbamate [263].

Although many studies have demonstrated a relationship between the gut–brain axis, diabetes, and its associated brain complications [264], conclusions regarding the effects of prebiotics and probiotics remain inconsistent. One study found that fructo-oligosaccharide (FOS) treatment increased the abundance of *Bifidobacterium* in the gut of db/db mice and improved neuroinflammation and BBB integrity; however, it failed to alleviate anxiety-like behavior and spatial memory deficits [265]. In contrast, Morshedi et al. reported that supplementation with inulin, *Lactobacillus plantarum*, or a combination of both improved depressive and anxiety-like behaviors in diabetic rats [266]. Similarly, Hosseinifard et al. found that supplementation with *L. plantarum* and inulin modulated the composition of the gut microbiota, leading to reduced GFAP and glial cell-line derived neurotrophic factor (GDNF) levels in the amygdala [267]. This reduction was associated with an

improvement in anxiety-like behavior in diabetic rats. However, no significant effects were observed in the prefrontal cortex. Further research is needed to determine whether prebiotics and probiotics influence diabetes-related brain complications through BBB regulation.

5.4 Mini conclusion

BBB damage is a potential therapeutic target in diabetes-related brain complications such as cognitive impairment, stroke, and depression. Lifestyle interventions, various clinical medications, and emerging nanocarrier drug delivery systems can repair diabetes-induced BBB damage by varying degrees, thereby lowering the risk of such complications. However, some aspects deserve further discussion. First, although some studies have evaluated the role of hypoglycemic agents in improving BBB integrity and reducing diabetes-related brain complications, the results remain controversial, particularly for DPP-4 inhibitors [210-214], sulfonylureas[206, 225, 226, 249], and insulin[223, 233-235]. This suggests the need to focus on differences between basic research and clinical practice as well as the impact of potential adverse side effects on the human body. We also found differences in the effects of various insulin formulations (e.g., INI improves cognitive function in patients with diabetes) [223, 233]; therefore, methods to optimize the use of different forms deserve further study. Second, preclinical studies highlight the advantages of rigorous blood pressure and lipid control for managing diabetes-related brain complications [238, 243]; however, clinical evidence remains limited and requires further examination. Third, nanocarrier-based drug delivery systems are being increasingly studied as emerging strategies for improving BBB integrity [252, 253]. However, further research is needed to confirm the safety of these treatments and elucidate their specific mechanisms, which will help promote their clinical translation.

6. Final conclusion and prospects

Diabetes-related brain complications such as cognitive impairment, stroke, and depression often occur simultaneously or sequentially. Their complex pathological mechanisms and the use of multiple medications pose significant challenges in clinical management. Although some studies have focused on changes in the structure and function of BBB in cases of diabetes with cognitive impairment [268] and stroke [17], elated clinical evidence and interventions remain unclear. This paper provides a review of the structure and function of BBB and analyzes the mechanisms by which pathological factors such as hyperglycemia, oxidative stress, inflammation, AGEs, and HMGB1 contribute to BBB damage. It also summarizes the evidence generated by clinical and animal studies on lifestyle and pharmacological interventions for repairing BBB and reducing brain complications. We found that BBB permeability markers such as Gd-DTPA enhancement and QAlb and S100β levels are significantly associated with cognitive decline, stroke outcomes, and depressive symptoms. However, current assessment methods are not standardized, and most intervention studies are based on small sample sizes or short-term durations. Larger-scale, more rigorously designed clinical trials are urgently required for further validation.

Future research should focus on the following directions: integration of heterogeneous data such as magnetic resonance imaging and other imaging data with biological markers through machine learning models can improve diagnostic sensitivity and specificity. Additionally, focusing on subclinical features before disease onset to predict high-risk patients before the appearance of symptoms enables early intervention. Implementation of personalized screening for high-risk diabetic populations and testing of preventive interventions (e.g., INI and microbiome modulation) can help maintain BBB integrity before significant neurodegeneration occurs. For patients with BBB damage and diabetes-related brain complications, treatment precision needs to be enhanced by selection of glucose-lowering and antihypertensive medications that are more favorable for BBB repair, in conjunction with lifestyle interventions. Finally, preclinical drugs targeting BBB, such as nanomedicines and inhibitors, require further research for evaluation of their safety and ability to cross BBB.

Data availability

No datasets were generated or analyzed during the current study.

Declaration of Interest Statement

The authors have no conflicts of interest.

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Authors' contributions

All authors have read and agreed to the publication of the final manuscript. Caiyi Long: writing-original draft, writing-review & editing, investigation, data curation, conceptualization, visualization. Yueheng Pu: writing-original draft, investigation, data curation. Shunseng Keng: writing-review & editing. Jiajing Tao: writing-review & editing. Boxun Zhang: writing-review & editing, conceptualization, visualization, supervision. Rensong Yue: writing-review & editing, conceptualization, visualization, supervision.

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