

Mesenchymal Stem Cell-Derived Exosomes: A Novel Approach to Diabetes-Associated Cognitive Impairment

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Abstract: The progression of diabetes frequently results in a myriad of neurological disorders, including ischemic stroke, depression, blood-brain barrier impairment, and cognitive dysfunction. Notably, diabetes-associated cognitive impairment, a prevalent comorbidity during the course of diabetes, progressively affects patients' cognitive abilities and may reciprocally influence diabetes management, thereby severely impacting patients' quality of life. Extracellular vesicles, particularly nanoscale exosomes, have garnered considerable attention in recent years. These exosomes carry and transfer various functional molecules, such as proteins, lipids, and diverse non-coding RNAs, serving as novel regulators and communicators in intercellular interactions. Of particular interest, mesenchymal stem cell-derived exosomes (MSC-Exos) have been reported to traverse the blood-brain barrier and ameliorate intracerebral pathologies. This review elucidates the role of MSC-Exos in diabetes-related cognitive impairment, with a focus on their applications as biomarkers, modulation of neuronal regeneration and synaptic plasticity, anti-inflammatory properties, antioxidative effects, and their involvement in regulating the functionality of β -amyloid proteins during the course of cognitive impairment. The immense therapeutic potential of MSC-Exos in the treatment of diabetes-induced cognitive dysfunction is emphasized.

Keywords: diabetes-associated cognitive impairment, mesenchymal stem cell-derived exosomes, blood-brain barrier, neuronal regeneration, synaptic plasticity

Introduction

Diabetes mellitus is a prevalent metabolic disorder, characterized principally by elevated blood glucose levels surpassing normal thresholds.^{1,2} Over recent decades, there has been a marked upsurge in global diabetes incidence, particularly that of type 2 diabetes mellitus, attributable not solely to lifestyle transformations such as dietary habits, obesity, and physical activity levels,^{2,3} but also to increased life expectancy and population aging. Categorization by etiology delineates diabetes into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), with the latter constituting the most ubiquitous form worldwide, accounting for approximately 90–95% of diabetic individuals.^{4,5} T1DM results from autoimmune-mediated attacks on pancreatic β -cells, culminating in their loss and concomitant insulin secretion defects,^{6,7} whereas T2DM primarily arises from diminished insulin sensitivity in peripheral tissues. T2DM's initial stages are often accompanied by compensatory insulin secretion from pancreatic β -cells, hence its advanced phase typically manifests with concomitant hyperglycemia and hyperinsulinemia.⁸ The onset of T2DM is frequently accompanied by myriad complications, primarily classified into microvascular and macrovascular diseases.^{9,10} Microvascular complications chiefly involve the microvasculature and generally affect organs such as the eyes, kidneys, and the nervous system, encompassing conditions such as diabetic retinopathy, diabetic nephropathy, diabetic peripheral neuropathy, diabetic foot, and diabetic pulmonary arterial hypertension.^{11,12} Macrovascular complications predominantly encompass diabetic cardiovascular diseases and diabetic peripheral vascular alterations, frequently leading to sequelae such as coronary artery disease, myocardial infarction, and arteriosclerosis.^{13,14}

Cognitive impairment and dementia patient populations often exhibit similar demographic trends, which are not coincidental; epidemiological studies have corroborated the association between diabetes and dementia.¹⁵ Furthermore, diabetes is significantly correlated with the onset of mild cognitive impairment, a common early symptom of Alzheimer's disease.^{16,17} Diabetic-related cognitive dysfunction is not a singular disorder, as its manifestations and prognoses tend to vary according to diabetes type and age.^{18,19} Notably, the severity of cognitive impairment engendered by T1DM and T2DM seems to differ. In T1DM, cognitive dysfunction is often influenced by insulin levels, vascular risk factors, and blood glucose levels,²⁰ whereas in T2DM, it is associated with vascular risk factors, diabetes treatment modalities, and disease duration.²¹ Research findings suggest that cognitive impairment and magnetic resonance imaging alterations in T1DM patients are not as pronounced as in age-matched T2DM patients,^{18,22} implying that the pathophysiological differences between T1DM and T2DM exert distinct impacts on the genesis of cognitive impairment in the brain. However, the precise pathogenic mechanisms of T2DM-related brain disorders remain multifactorial, complex, and not entirely understood.²³

Mesenchymal stem cells (MSCs) are a class of multipotent stem cells originating from mesenchymal tissue, possessing self-renewal, multilineage differentiation, and immunomodulatory functions.^{24–26} In addition to directly participating in tissue regeneration and repair, MSCs mediate intercellular communication and signal transduction via the production of extracellular vesicles (EVs).^{27,28} The most crucial constituents of EVs are exosomes, small vesicles formed by the cell membrane, with diameters ranging from 30–150nm.²⁹ MSC-derived exosomes contain various bioactive molecules, including proteins, nucleic acids, and metabolic byproducts, capable of influencing the biological processes of recipient cells through the transfer of these molecules. They possess a wide range of biological functions, such as cell proliferation, migration, angiogenesis, immunomodulation, and repair.^{28,30,31} The application prospects of mesenchymal stem cell exosomes are vast, as they can serve as a novel extracellular matrix-based therapeutic approach for promoting tissue repair and regeneration.²⁹ Furthermore, MSC exosomes can act as an effective drug delivery system, targeting specific biologically functional molecules to particular recipient cells, thereby enabling precision therapy.^{32,33} However, to date, the preparation and purification of mesenchymal stem cell-derived exosomes remain challenging tasks.

Different Types of Brain Disorders Caused by Diabetes

In addition to the various microvascular and macrovascular complications mentioned earlier, T2DM is often accompanied by a multitude of brain disorders closely associated with vascular dysfunction.³⁴ T2DM frequently leads to a significant increase in the risk of ischemic and hemorrhagic strokes and is highly correlated with the onset of dementia and depression. In the development of these brain complications, factors such as poor glycemic control, vascular diseases, oxidative stress, genetic predisposition, insulin resistance, and amyloid protein production may all play crucial roles.^{22,35,36}

Ischemic Stroke

Ischemic stroke is a primary cause of morbidity and mortality in patients with T2DM. Studies have shown that endothelial dysfunction and inflammation are highly correlated with the risk, recurrence, and adverse prognosis of stroke.^{37,38} In diabetic patients, insulin resistance, endothelial dysfunction, and inflammation impair stroke recovery, thereby compromising the integrity of cerebral vasculature.³⁹ Large vessel strokes can result in severe neurological deficits and even death due to extensive cerebral infarction caused by embolism, while strokes caused by end-terminal small artery disease lead to “lacunar stroke” infarctions in deep brain structures, often associated with small area brain infarctions, damaging regions such as the lentiform nucleus, internal capsule, thalamus, and pons.⁴⁰ Lacunar strokes may be more common than large vessel strokes in diabetic patients with ischemic stroke,^{41,42} and stroke patients with diabetes have longer hospital stays, worse functional outcomes, and a higher risk of stroke recurrence.^{43–45} Compared to non-diabetic stroke patients, the one-year mortality rate for stroke patients with diabetes is twice as high,^{46,47} and hemoglobin A1c (HbA1c) is significantly associated with stroke prognosis, with a 33% increase in the likelihood of post-stroke death for every 1% increase in HbA1c.⁴⁸ Additionally, the risk of cognitive impairment or dementia caused by lacunar strokes is higher in diabetic patients.^{49,50}

Blood-Brain Barrier Damage

The blood-brain barrier (BBB) is a specialized structural barrier that regulates the exchange between blood and the brain microenvironment, maintaining internal homeostasis.⁵¹ The BBB is located at the interface between blood and brain parenchyma and is composed of tight brain microvascular endothelial cells (BMVECs), pericytes, a single-layered basement membrane, and astrocyte end-feet.^{52,53} Experimental models have reported increased BBB permeability under diabetic conditions,⁵⁴ accompanied by impaired BBB integrity, primarily due to damage and inflammation in brain vascular endothelial cells.⁵⁵ Under high glucose conditions or in the presence of saturated fats and cholesterol, oxidative stress and inflammatory responses in endothelial cells increase,⁵⁶ leading to changes in the expression and function of tight junction proteins and transmembrane proteins within cells, thereby increasing BBB permeability. Additionally, high glucose levels also elevate brain inflammatory cytokines and free radicals, further damaging BBB integrity, and resulting in increased BBB permeability and neuroinflammation in patients with T2DM.⁵⁷ Enhanced magnetic resonance imaging shows that the extent of BBB damage caused by diabetes is also highly age-related and leads to neuronal injury,⁵⁸ suggesting an association between BBB damage and cognitive impairment and dementia. Currently, antioxidants, such as vitamin C, can be used to reduce the harmful effects of glucose,⁵⁹ and anti-inflammatory and lipid-lowering drugs can be used to reduce the BBB damage caused by inflammation and oxidative stress.⁶⁰

Depression

T2DM, depression, and cognitive dysfunction often occur together. Compared with individuals without T2DM, the risk of depression in patients with T2DM is doubled, and the risk of T2DM in patients with depression is increased by 1.5 times.⁶¹ The potential mechanisms of the relationship between T2DM, depression, and cognitive dysfunction are complex and multifactorial. The connections between these diseases may include common risk factors (such as obesity, physical inactivity, and psychosocial stress) and common underlying mechanisms (such as insulin resistance, activation of the hypothalamic-pituitary-adrenal and sympathetic-adrenal systems, and inflammatory factors).

Additionally, the increased blood-brain barrier permeability caused by T2DM⁶² and the reduced cerebral vascular reactivity⁶³ can regulate the emotional regulation of the frontal and subcortical brain regions, which may lead to the development of depression. The neurons in the brains of patients with depression may be damaged due to inflammation and changes in neurotransmitters, affecting cognitive function.⁶⁴ Moreover, research suggests that depression may be associated with microvascular complications of T2DM: in a meta-analysis, the risk of depression was increased in patients with diabetes-related microvascular complications,⁶⁵ but the impact of psychological stress could not be ruled out.

Depression may also cause changes in patients' self-awareness and emotional experience, making it difficult for them to concentrate, pay attention, and remember information. Additionally, patients with depression may experience sleep disorders and fatigue, which can also affect cognitive function.

Cognitive Impairments Caused by T2DM

In adults with T2DM, cognitive deficits can be broadly classified into three distinct stages based on severity: diabetes-related cognitive decline, mild cognitive impairment, and dementia²³ (Table 1). The first stage typically involves subtle changes in cognitive function and cognitive discomfort without affecting daily activities or diabetes self-management. The second stage, mild cognitive impairment, is characterized by a significant decline in cognitive function but not severe enough to be considered dementia. At this stage, patients may struggle with self-management tasks such as medication management, blood glucose monitoring, and dietary planning. In the third stage, dementia caused by T2DM affects patients' daily life and independence. Dementia may involve multiple cognitive domains, including memory, communication, attention, reasoning, judgment, and visual-spatial skills.^{18,66}

The etiology of T2DM-associated cognitive dysfunction is likely multifactorial, with insulin resistance, inflammation, oxidative stress, gut microbiota dysregulation, metal ion imbalance, and lymphocyte dysfunction potentially contributing to cognitive impairment.³⁴ Dementia has also been linked to transcriptional and proteomic alterations in diabetes. The prevalence of cognitive impairment in T2DM patients is significantly increased,²² with a higher incidence of dementia associated with T2DM as the duration of illness and age increase.⁶⁶ Concomitant research demonstrates a significant positive correlation between cognitive

Table 1 Symptoms and Incidence of Diabetes-Related Cognitive Impairment

Types of Cognitive Impairments	Symptom	Incidence Rate in Non-Diabetic Patients	Incidence Rate in Non-Diabetic Patients
Diabetes-related cognitive decline	Memory loss, slower cognitive processing	/	/
Mild cognitive impairment	Memory problems, difficulty with complex tasks	15.6%	17.4%
Dementia	Severe memory loss, confusion, difficulty with daily tasks	6.1%	8.4%

Note: Data from these studies.^{66,67}

impairment and the incidence of dementia in T2DM patients, with both HbA1c levels and diabetes duration serving as salient factors.⁶⁷

Despite the connection with other diabetes complications, there is currently no definitive evidence that the increased risk of cognitive impairment can be solely attributed to elevated blood sugar levels.²³ Reduced cerebral vascular reactivity and resting cerebral blood flow changes are associated with worse cognitive test scores.⁴⁰ In dementia caused by diabetes, multiple disease manifestations are present, including the accumulation of amyloid and tau proteins in the brain, leading to neuronal loss and vascular brain injury.⁶⁸ T2DM has serious adverse effects on the cardiovascular system, increasing the risk of stroke and small vessel disease in the brain.⁶⁹

Managing cognitive dysfunction in diabetes patients is crucial as there is a bidirectional relationship between cognition and diabetes management, with cognitive dysfunction adversely affecting diabetes management and poor diabetes management increasing the risk of cognitive dysfunction.⁷⁰ Current therapies, such as anti-diabetic medications, weight loss surgery, lifestyle interventions, and anti-oxidant and anti-inflammatory compounds, may improve cognitive function in T2DM patients. Patients with T2DM-related cognitive impairment often present with older age and frailty, characterized by weight loss, fatigue, reduced muscle mass and strength, and decreased mobility.^{71,72} As a result, older individuals with diabetes are more likely to exhibit depression, chronic pain, and medication intolerance.^{73,74} Identifying these issues is critical for developing personalized management plans, requiring early clinical diagnosis and screening, combined with appropriate treatment approaches and psychological assessments.⁷⁵

Mesenchymal Stem Cell-Derived Exosomes

MSCs are a type of adult stem cell found in various tissues, first discovered in bone marrow in the 1960s. MSCs, derived from bone marrow, umbilical cord, adipose tissue, placenta, and other tissues, have self-renewal and multilineage differentiation capabilities, enabling them to differentiate into various adult cell types, such as osteocytes, adipocytes, and chondrocytes.⁷⁶ Furthermore, MSCs possess anti-inflammatory, immunomodulatory, and tissue repair functions.⁷⁷ MSCs have a wide range of sources and can release a series of biologically active molecules and cytokines through exosomes, facilitating intercellular signaling and regulation.⁷⁸

Exosomes are nanoscale, double-membrane structures containing proteins, lipids, RNA, metabolites, growth factors, and cytokines that act as multifunctional transporters between cells.²⁹ Exosomes and microvesicles typically carry specific markers such as tetraspanins (CD9, CD63, and CD81), HSP70, MHC, and TSG101.⁷⁹ Research has shown that all cells can secrete exosomes under normal physiological conditions and pathological processes,²⁹ and exosomes can participate in various diseases, promoting communication as paracrine mediators. Due to the transport properties of exosomes, functional cargoes can be delivered to target cells, making them suitable drug delivery carriers.^{80,81} Simultaneously, compared to other commonly used drug delivery carriers (eg, liposomes), bioengineered exosomes have advantages such as inherent targeting ability, low immunogenicity, high modification flexibility, and biological barrier permeability.⁸²

Mesenchymal Stem Cell Exosome Biogenesis

Mesenchymal stem cell exosomes (MSC-Exos) secretion can be divided into three key stages: initiation, intermediate formation, and release stages.⁸³

Extracellular

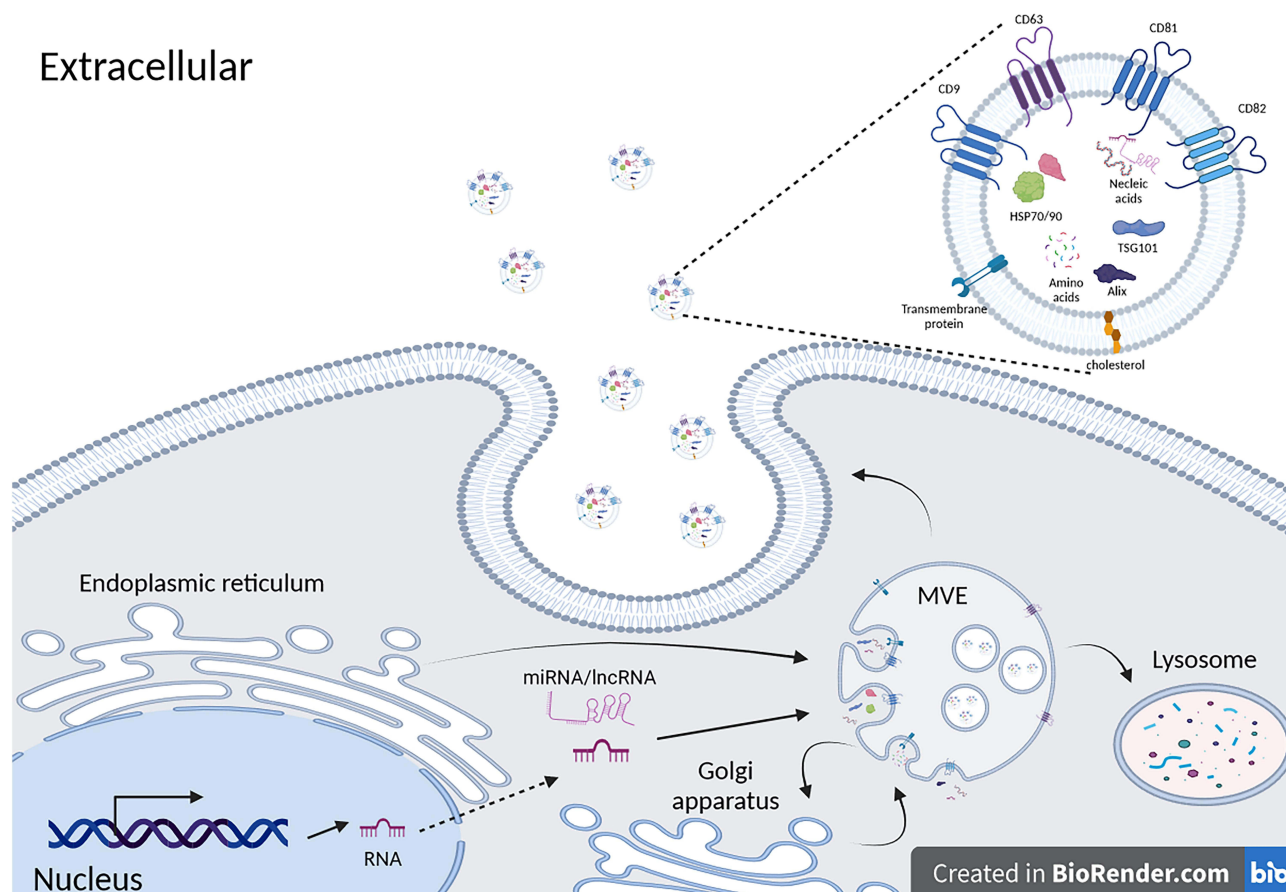


Figure 1 After stimulated by external signal series, MSCs activate multiple signaling pathways and activate the synthesis of various proteins and non-coding RNAs through signaling. Several exosome-associated proteins such as TSG101, Alix, CD63, etc., become enriched in MVEs and participate in the packaging of exosomal cargo. With the assistance of ESCRT, ILVs are formed within MVEs. Simultaneously, MVEs may undergo material exchange with the Golgi apparatus and undergo partial degradation within lysosomes. The remaining MVEs then fuse with the plasma membrane, releasing exosomes into the extracellular space. Exosomes released in this manner often have molecular markers such as CD9, CD63, CD81, CD82 on their surface (created with BioRender.com).

In the initiation stage, MSCs receive various stimuli, including inflammation, stress, and injury, to obtain initiating signals. These stimuli can be conveyed to MSCs through multiple pathways, such as membrane receptor activation and cytokine induction.⁸⁴ Once MSCs receive the stimulus signals, the signals are transmitted to the interior of the cell through signaling pathways, activating multiple proteins and signaling pathways. These proteins include exosome-associated proteins (such as TSG101, Alix, CD63, etc.) and other proteins and signaling pathways involved in exosome formation. Exosome-associated proteins are essential components of exosome formation. These proteins can be enriched on multivesicular endosomes (MVEs) and participate in the packaging of biomolecules within the cell.⁸⁵ With the help of the endosomal sorting complex required for transport (ESCRT) and key proteins involved in exosome formation, intraluminal vesicles (ILVs) are formed within MVEs through secondary invagination of the plasma membrane. TSG101 is a common exosome-associated protein that participates in the assembly and disassembly of ESCRT (endosomal sorting complexes required for transport) complexes, promoting exosome formation.^{86,87} Alix, CD63, and tetraspanins CD81, CD82, and CD9 are also widely considered key proteins involved in exosome formation.^{88–90} Finally, although some MVEs are degraded through fusion with autophagosomes or lysosomes,^{91,92} another portion of MVEs fuses with the plasma membrane to release the ILVs contained within through exocytosis, which ultimately form exosomes. These exosomes are released outside MSCs and bind to molecules on the target cells through their surface molecules, realizing signal transmission (Figure 1).

Isolation and Purification of Mesenchymal Stem Cell-Derived Exosomes

Exosomal surfaces comprise an array of distinctive biomolecules, including membrane proteins and glycoproteins, which bestow diverse specificities upon exosomes. The release mechanisms of exosomes may encompass techniques such as

Table 2 Comparison of Exosome Isolation Methods

Separation Method	Mechanism	Advantages	Disadvantages
Ultrafiltration	Density	Easy, gold standard	Time-consuming (>4h), low yield
Differential Centrifugation	Densities and sizes	High yield, well-established	Requires equipment, time-consuming
Density Gradient Centrifugation	Density	High purity, separates sizes	Requires equipment, complex procedure
Immunoaffinity Chromatography	Binding affinity	High specificity, high purity	Expensive, antibody-dependent
Size Exclusion Chromatography	Size	No reagent required, preserves exosome integrity	Lower yield, slower process
Polymer Precipitation	Solubility	Simple, high yield	Lower purity, potential co-precipitation
Microfluidics	Flow dynamics	Rapid, high specificity	Requires special equipment, complex setup

differential centrifugation, ultrafiltration, density gradient centrifugation, and immunoaffinity chromatography.⁹³ These methodologies hinge on the analysis and differentiation of the physicochemical properties of exosomes, including size, density, charge, and surface specificity (Table 2).

Ultrafiltration, a technique for separating and enriching small molecules utilizing filter membranes, employs membranes with specific pore sizes to filter out macromolecules such as proteins and cell debris, while extracellular exosomes can permeate the membrane pores for concentration and separation.⁹⁴ However, this approach may result in exosome loss and diminished purity.⁹⁵

Differential centrifugation, a technique for separating extracellular exosomes from other cellular components (eg, cell debris, large particles) by modulating centrifugation speed,⁹⁶ achieves separation as distinct cellular components settle in different locations due to their disparate densities and sizes. Nevertheless, this method may lead to mechanical damage, exosome membrane distortion, protein aggregation, lipoprotein contamination, and low purity.⁹⁷

Density gradient centrifugation separates cellular components of varying densities using layered solutions of different densities to create a gradient. During centrifugation, extracellular exosomes sediment and are separated within the corresponding density gradient layer. Analogous to differential centrifugation, density gradient centrifugation may also inflict mechanical damage on exosomes.⁹⁵

Immunoaffinity chromatography, a technique leveraging the affinity between specific antibodies and their corresponding antigens for the separation and enrichment of target substances, enables the isolation of extracellular exosomes by employing specific antibodies to recognize and capture surface proteins on exosomes, followed by elution and purification steps to obtain pure exosomes.^{98,99} However, this method may also cause exosome damage.

Additionally, size exclusion chromatography, polymer precipitation, and microfluidics^{100,101} may be employed for high-purity preparations, albeit at higher costs or with limited applicability to small samples.

MSC-Exos in Diabetes-Associated Cognitive Impairment

The exosomes in the brain have been demonstrated to participate in normal biological processes, encompassing but not limited to, cellular communication, transcriptional regulation, neurogenesis, neuronal plasticity, and immune responses.^{102,103} Studies reveal that exosomes derived from bone marrow mesenchymal stem cells (BMSCs) are capable of ameliorating diabetes-induced cognitive dysfunction, amyloid-beta (A β) plaques, A β deposition area, A β 1-42, A β degradation-associated factors (insulin-degrading enzyme and neprilysin), and levels of pro-inflammatory cytokines.¹⁰⁴ Notably, the relatively constant contents within MSC-derived exosomes, such as miRNA and cytokines, play a pivotal role.

Exosomes as Biomarker

In neurodegenerative diseases, certain molecules within MSC-derived exosomes have been identified as potential biomarkers. Particularly, specific microRNAs (miRNAs) and proteins hold significant value in the onset, progression, and diagnosis of these diseases. In neurodegenerative diseases, particular miRNAs have been found to be enriched in MSC-derived exosomes, and numerous miRNAs have been discovered to possess diagnostic capabilities for cerebral or neurodegenerative diseases, such as miR-133b, miR-9,¹⁰⁵ miR-134,¹⁰⁵ miR-34a,^{106,107} and miR-125b.¹⁰⁸ These miRNAs exhibit significant alterations in cerebrospinal fluid and serum in Alzheimer's disease (AD) and are highly associated with mesenchymal stem cell origin.^{109–111} These RNAs exhibit not only significant quantitative differences but also potentially regulate neuronal development, differentiation, apoptosis, and inflammatory response.

Additionally, significant alterations in cargo protein levels may occur in exosomes isolated from the blood and cerebrospinal fluid of AD patients, including remarkable increases in key proteins such as soluble A β 1-42, A β oligomers, and different site-phosphorylated Tau.^{112–114} These proteins can be detected years before the clinical diagnosis of AD¹¹⁵ and are closely related to blood glucose levels,¹¹⁶ offering the possibility of using exosomes as a diagnostic method for AD. It is noteworthy that the content of neurotrophic factors (eg, brain-derived neurotrophic factor, BDNF) and anti-inflammatory factors (eg, interleukin-10, IL-10) in MSC-derived exosomes also changes during the progression of neurodegenerative diseases, accompanied by alterations in inflammation levels. Recent studies have shown that the levels of mitochondrial proteins NDUF53 and SDHB within plasma exosomes decrease significantly with the onset of diabetes-induced cognitive impairment.¹¹⁷ With advancements in technology, employing high-throughput sequencing and Olink¹¹⁸ for quantitative analysis of various miRNAs and proteins may provide precise prevention and treatment for neurodegenerative diseases caused by diabetes.

It should be noted that although these molecules hold potential as biomarkers in neurodegenerative disease research, they are still in the early stages. For the clinical analysis of exosomal content as biomarkers, extensive research is required to verify their specificity, sensitivity, and reliability.

Promoting Neuronal Regeneration and Synaptic Plasticity

Cognitive impairments and histological abnormalities similar to those observed with mesenchymal stem cell injections have been found to be reversed. Fluorescently labeled exosomes demonstrated that the injected exosomes were internalized into astrocytes and neurons, subsequently reversing the dysfunction.¹¹⁹ MSC-derived exosomes mediated the transfer of miR-133b to astrocytes and neurons, regulating ras homolog gene family member A,¹¹⁹ and potentially possessing the ability to activate the PI3K/Akt signaling pathway,¹²⁰ which is beneficial for neural sprouting remodeling and functional recovery. At the same time, miR-132 from MSC-derived exosomes in cognitively impaired mice can target the regulation of GTPase-activating protein RASA1 and increase the phosphorylation of Ras, Akt, and GSK-3 β , improving neuronal and synaptic activation.^{121–123} Additionally, various miRNAs, such as miR-21, which are specifically highly expressed in MSC-derived exosomes, may improve synaptic transmission and plasticity by suppressing inflammation and immunity, but their function and mechanism are currently unclear.¹²⁴ Recent research has shown that miR-21-5p and miR-486-5p have the highest expression levels in MSC-derived exosomes, and miR-21-5p has been proven to directly target EphA4 and CDKN2C, while miR-486-5p can inhibit FoxO1 in neural stem cells, thereby promoting hippocampal neural stem cell proliferation and neurogenesis in diabetes-induced cognitive impairments.¹²⁵

Moreover, Bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos) contain various growth factors and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF).¹²⁶ BDNF can activate multiple signaling pathways, such as PI3K/Akt, MAPK/ERK, and PLC γ , by binding to its specific receptor TrkB,^{126–128} while NGF binds to its receptors TrkA and p75NTR, activating signaling pathways like PI3K/Akt, MAPK/ERK, and JAK/STAT.^{129,130} The activation of these signaling pathways promotes the proliferation, differentiation, and migration of neural stem cells, thereby improving diabetes-induced cognitive impairments through the promotion of neuronal regeneration.¹³⁰

Anti-Inflammatory Effects

In obesity and T2DM, as well as in elderly and dementia patients, disruptions in brain insulin action can be observed, often accompanied by the occurrence of inflammation, leading to further deterioration of cognitive impairments.^{131,132}

Astrocytes, microglia, and neurons play crucial roles in maintaining tissue homeostasis and promoting inflammatory responses through the secretion of cytokines.¹³³ Exosomal miRNAs regulate inflammatory responses by targeting the expression of various signaling pathways and immune molecules, thus counteracting inflammation.¹³⁴ BMSC-Exos have been found to have application value in treating diabetes-related cognitive impairments, mainly through the anti-inflammatory effects based on exosomal miRNA content. Intravenous injection of BMSC-Exos can reduce the expression of pro-inflammatory mediators TNF- α , IL- β , and IL-6 in the cortex and hippocampus, but changes in anti-inflammatory factors IL-10 and IL-13 are not obvious.¹³⁵ However, intracerebroventricular injection of BMSC-Exos can better improve exosomal efficacy, accompanied by significant reductions in BACE, A β 1-42, and p-Tau protein expression levels, and significant elevations in BDNF expression levels. This greatly reduces the brain inflammatory response caused by diabetic cognitive impairments,¹²⁶ which may depend on the non-coding RNA content of the exosomes and brain-derived neurotrophic factor (bDNF).

In STZ-induced diabetic rats, an enriched environment can improve the levels of miR-146a in BMSC-Exos, thereby targeting the expression of IRAK1, NF- κ B, and TNF- α in astrocytes of diabetic rats and exerting anti-inflammatory effects, inhibiting the onset of diabetes-induced cognitive impairments.¹³⁶ After the occurrence of diabetic cognitive impairments, exosomes secreted by BMSC enter the cerebrospinal fluid and regulate astrocytes through the exosomal content miR-146a, modulating IRAK1 and NFAT5 and reducing NF- κ B signaling pathway levels,¹³⁷ thereby reducing the proportion of microglia polarizing towards the M1 type and lowering inflammation levels.^{110,138} However, contradictorily, research has shown that the common MSC-Exos content miR-21-5p seems to promote the polarization of microglia towards the M1 type and is the main source of miR-21-5p in microglia,^{139,140} but at the same time, miR-21-5p may exert anti-inflammatory effects in other brain tissues,¹⁴¹ for example, intracerebroventricular injection of miR-21-5 significantly inhibits neural defects in rats, repairs cognitive impairments, reduces blood-brain barrier (BBB) permeability, and suppresses the occurrence and apoptosis of neuronal inflammation,¹⁴² which may be due to miR-21-5p affecting the PTEN/Akt pathway in the frontal cortex and hippocampal neurons.¹⁴³ Therefore, further investigation into the tissue- and specificity-dependent effects of miRNAs in MSC-Exos contents is still needed.

Antioxidant Effects

In diabetic patients, elevated blood glucose levels precipitate an escalation of oxidative stress, thereby exacerbating neuronal injury and adversely affecting neuronal function and synapse formation. Although there are relatively few reports on the regulatory role of extracellular vesicles in oxidative stress pertaining to cerebral diseases, it has been demonstrated that exosomes derived from BMSCs can ameliorate cognitive impairment in streptozotocin (STZ)-induced diabetic mice by reducing oxidative stress levels in damaged neurons and astrocytes.¹¹⁹ Furthermore, BMSC-Exos miR-132-3p and miR-126 are postulated to mitigate oxidative stress-induced injury to cerebral endothelial cells by activating the PI3K/Akt/eNOS signaling pathway, inhibiting the production of reactive oxygen species (ROS) in cerebral blood vessels, and attenuating endothelial cell apoptosis,^{123,144} thereby potentially playing a significant role in diabetes-induced cognitive impairment. Bone marrow-derived miR-146a can suppress the inflammatory response, thereby markedly improving neuronal function and reducing apoptosis and degenerative neurons. Concurrently, exosomes enriched with miR-146a-5p can attenuate oxidative stress associated with the PI3K/Akt/mTOR pathway, thereby reducing neuronal apoptosis.¹³⁷ Additionally, a study indicates that although the aforementioned literature elucidates the potential mechanisms underlying the regulation of oxidative stress in cognitive impairment by exosomes derived from MSCs and the critical roles played by various miRNAs in cerebral oxidative stress,^{145,146} further evidence is required to establish the direct link between MSC-Exos and oxidative stress in neurons and microglial cells.

Reducing Beta-Amyloid Protein

Beta-amyloid protein (A β) is a polypeptide generated through the cleavage of large precursor protein molecules (Amyloid Precursor Protein, APP) by β - and γ -secretases.^{147,148} Prolonged hyperglycemia in diabetic patients may promote aberrant A β protein aggregation via multiple factors,¹⁴⁹ and diabetes may impair the insulin signaling pathway, consequently affecting APP metabolism.¹⁵⁰ This could lead to an increase in non-physiological APP cleavage, subsequently elevating A β production, adversely impacting neurons, synaptic function, microvasculature, astrocytes and microglia.¹⁵¹ A β can induce neuronal

apoptosis, synaptic dysfunction, microvascular damage, and inflammatory responses,^{150,152} culminating in impaired brain function and manifesting as memory and cognitive decline in diabetic patients.

Exosomes' role in modulating A β protein has been frequently reported. Adipose MSC-Exos can reduce A β deposition, inhibiting mouse neuronal cell apoptosis.¹⁵³ Exosomal miR-29b can mitigate A β pathogenic effects by targeting β -secretase 1 BACE1 and BIM, effectively improving spatial learning and memory capabilities in Alzheimer's disease model mice.¹⁵⁴ Recent studies reveal that BMSC-Exos can reduce Amyloid Precursor Protein (APP) density,¹⁵⁵ alleviate β -amyloid protein1-42 (A β 1-42) induced cognitive impairments, augment neurogenesis and myelin regeneration in the subventricular zone,¹⁵⁵ and enhance mouse learning capabilities.¹⁵⁶ Additional research demonstrates that stem cell exosomes, delivered through intravenous injection, can cross the blood-brain barrier, reduce hippocampal A β aggregation and neuronal loss, and restore Alzheimer's disease-related calcium oscillations, dendritic spine alterations, action potential abnormalities, or hippocampal mitochondrial changes.¹⁵⁷ Various exosomal components may play a role, including miR-16, miR-107, and miR-124, which can reduce A β by targeting BACE1,¹⁵⁸⁻¹⁶¹ although further evidence is needed to confirm whether this regulation occurs in cortical and hippocampal regions via BMSC-Exos.

Furthermore, MSC-Exos can enhance microglial uptake and degradation of A β ; annexin V deficiency results in impaired exosome uptake accompanied by reduced A β uptake. Although comprehensive understanding of exosomes was lacking at the time, this study demonstrated the involvement of MSC-Exos in modulating microglial uptake and clearance of A β .¹⁶² Subsequent studies confirmed hippocampal A β levels, amyloid deposition, and A β -mediated synaptic toxicity are associated with brain-derived exosomes, and glycosphingolipids (GSLs) within exosomes can serve as potent A β -clearing agents.^{163,164} Additionally, *in vivo* studies revealed exosomes can bind and isolate small A β oligomers (trimers, tetramers) and mitigate the impact of A β on synaptic plasticity.¹⁶⁵ Contrarily, some research has shown exosomes may promote amyloid formation, and blocking exosome formation can ameliorate cognitive impairments in mice,^{166,167} potentially attributable to exosomes' varying origins.¹⁶⁸

Limitations and Future Remark

While the use of MSC-EVs for the treatment of diabetic cognitive impairment currently faces challenges such as unclear mechanisms, unknown long-term effects, limited preparation methods, and undetermined frequency of use. Therefore, more extensive clinical trials are needed to verify these findings and establish a comprehensive database for safety and efficacy. Moreover, by analyzing the surface markers and contents of MSC-EVs from different cellular origins, and with advancements in biotechnology, we can obtain functionally uniform MSC-EVs through *in vitro* culture, separation, and purification. Personalized adjustments can then be made based on the patient's clinical phenotype and metabolic characteristics to achieve optimal therapeutic outcomes.

Conclusion

Diabetes-associated cognitive impairment is a prevalent comorbidity in elderly diabetic patients, exhibiting a bidirectional relationship with diabetes. This association often impacts patients' quality of life, disease prognosis, and increases the risk of other neurological disorders. Although pharmacological interventions controlling blood glucose levels and modulating cerebral chemical messenger concentrations may alleviate the severity of cognitive impairment, these measures typically fail to reverse or halt neuronal and synaptic damage.

MSCs are a heterogeneous population of stromal stem cells that can be isolated from various adult tissues. These cells possess the capacity to suppress the release of pro-inflammatory cytokines and promote the survival of damaged cells. Recent studies have demonstrated that MSC-Exos contain an array of bioactive substances, including cytokines and growth factors, signaling lipids, mRNAs, and regulatory miRNAs, which modulate cellular metabolism *in vivo*. In comparison to MSC therapy, exosome therapy avoids immune rejection, reduces the risk of tumor formation, and is more readily obtainable, rendering it a safer, more convenient, and efficacious treatment approach.

MSC-Exos, nanoscale extracellular vesicles, have been extensively reported to traverse the blood-brain barrier and exert regulatory effects on the intracerebral milieu. This article summarizes the positive influence of MSC-Exos on neuronal and synaptic regeneration in diabetes-related cognitive impairment and highlights their anti-inflammatory, antioxidative, and amyloid-beta clearance properties, thereby mitigating the generation of detrimental factors in diabetes-associated cognitive impairment (Figure 2). However, due to the complexity of exosomal components, further in-depth investigation is warranted to

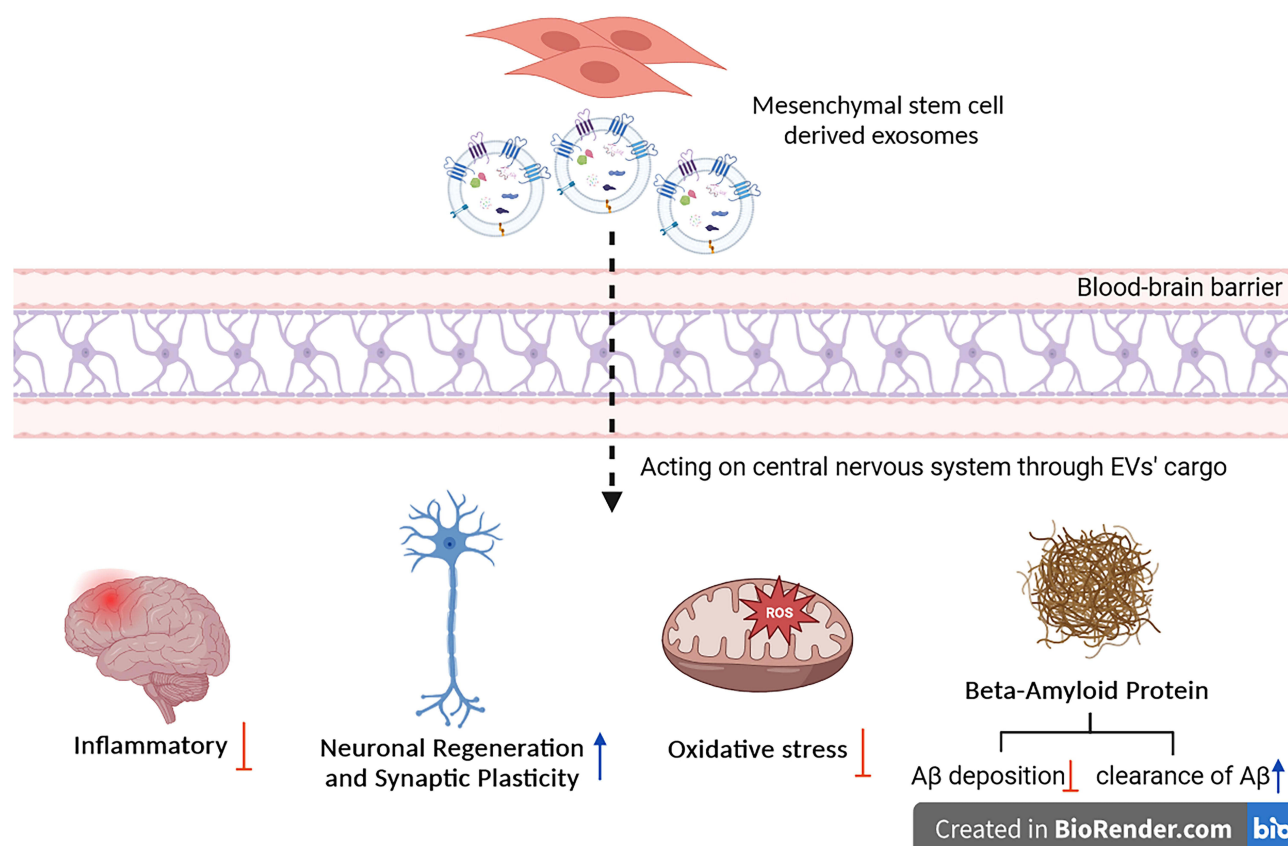


Figure 2 Overview of the beneficial effects of mesenchymal stem cell-derived exosomes on diabetes-associated cognitive impairment (created with BioRender.com).

elucidate their precise effects on neurological disorders. Nevertheless, based on MSC-Exos isolation techniques, the current application of exosome therapy for diabetes-induced cognitive impairment presents novel research directions and potential clinical applications.

Data Sharing Statement

The current study was based on the results of relevant published studies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared that they have no competing interests in this work.

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