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Contents

Monthly Volume 15 Number 11 November 15, 2024

EDITORIAL

EXPERT CONSENSUS

REVIEW

ORIGINAL ARTICLE

Basic Study

World Journal of Diabetes

Monthly Volume 15 Number 11 November 15, 2024

Contents

LETTER TO THE EDITOR

World Journal of Diabetes

Monthly Volume 15 Number 11 November 15, 2024

Contents

ABOUT COVER

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AIMS AND SCOPE

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LETTER TO THE EDITOR

Stem cell exosomes: New hope for recovery from diabetic brain hemorrhage

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

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Abstract

Recent advancements in stem cell–derived exosome therapy for diabetic brain hemorrhage are discussed in this editorial, which highlights this therapy's potential for revolutionizing diabetic brain hemorrhage treatment. The paper offers compelling evidence that exosomes can effectively reduce neuroinflammation and promote recovery from diabetic brain hemorrhage. Although these findings are promising, further research is warranted to fully understand the underlying mechanisms and to validate the therapeutic potential of exosomes in clinical settings. The findings of this study indicate that continued exploration should be conducted into exosome-based therapies as a novel approach to managing diabetic brain hemorrhage.

Key Words: Stem cell exosomes; Diabetic brain hemorrhage; Neuroinflammation; Exosome therapy; Regenerative medicine

Core Tip: This article highlights the potential of stem cell–derived exosomes as a novel treatment for diabetic brain hemorrhage. Exosomes reduce neuroinflammation and promote tissue recovery, and therefore, they represent a transformative approach for managing this challenging condition. The paper presents the significant findings for this treatment. This article underscores the importance of conducting further investigation into the therapeutic application of exosomes in clinical practice, thus advancing research in this promising area of regenerative medicine.

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TO THE EDITOR

Stem cell-derived exosomes have emerged as a promising therapeutic approach for various neurological disorders, including diabetic cerebral hemorrhage. Diabetic cerebral hemorrhage is characterized by complex pathophysiological changes such as exacerbated neuroinflammation, increased oxidative stress, and impaired neurological recovery, which contribute to poor clinical outcomes. Diabetes, a well-known risk factor for cerebrovascular diseases including hemorrhagic stroke, exacerbates the aforementioned pathophysiological changes because of its effects on vascular health. Studies have highlighted a connection between diabetes and intracerebral hemorrhage. Diabetes leads to microvascular damage, increased oxidative stress, and inflammation, rendering brain vessels more susceptible to hemorrhage. For example, Wang *et al*[1] reported that diabetes aggravates neurological impairment following cerebral hemorrhage by altering inflammatory responses and vascular integrity[1]. Experimental diabetes was demonstrated to worsen outcomes in intracerebral hemorrhage models by increasing inflammation and disrupting the blood-brain barrier (BBB)[2]. Thus, therapies that target both inflammation and vascular repair in patients with diabetes with brain hemorrhage should be developed. Several genome-wide association studies and Mendelian randomization analyses have identified diabetes as a significant risk factor for intracerebral hemorrhage, indicating genetic predispositions play a role in exacerbating hemorrhagic risk[3]. Furthermore, a study identified different risk profiles for lacunar ischemic stroke and deep intracerebral hemorrhage, revealing that diabetes is more strongly associated with deep intracerebral hemorrhage because of associated complications related to small vessel disease[4]. This evidence indicates that diabetes not only increases hemorrhagic risk but also complicates recovery from deep intracerebral hemorrhage due to ongoing vascular damage and chronic inflammation. In consideration of these findings, this editorial explored the potential therapeutic benefits of stem cell-derived exosomes for addressing these problems. Exosomes have regenerative potential; exosomes have been demonstrated to alleviate the effects of diabetic brain hemorrhage. Exosomes target inflammation and promote vascular repair, and therefore, they have been identified as a novel treatment approach for patients with diabetic brain hemorrhage. Emerging research has supported the effectiveness of this approach. For example, Wang *et al*[1] revealed that exosomes loaded with miR-129-5p from bone marrow mesenchymal stem cells can target high-mobility group box 1 (HMGB1), a key inflammatory mediator and thereby reduce neurological impairment after hemorrhage[1]. This finding is significant given the limited treatment options for diabetic cerebral hemorrhage. Another study confirmed that diabetes exacerbates the outcomes of hemorrhage through mechanisms such as inflammation, oxidative stress, and BBB disruption, revealing the potential of exosome therapy for addressing these problems[2]. Additionally, the complexities of the treatments for different types of stroke underscore the relevance of innovative approaches such as exosome therapy [4]. Exosomes, with their natural ability to cross the BBB and deliver therapeutic molecules, are a versatile tool in regenerative medicine. The study conducted by Wang *et al*[1] paved the way for further exploration into the mechanisms of exosome therapy, its optimization, and its clinical application. In the subsequent sections, the implications of exosome therapy for diabetic brain hemorrhage, its potential to revolutionize diabetic brain hemorrhage treatment, and future research directions in this evolving field are discussed in detail.

MECHANISM OF EXOSOME THERAPY

Stem cell-derived exosomes are emerging as a promising therapy for diabetic brain hemorrhage given their abilities to mediate intercellular communication and transfer essential biomolecules to injured cells (Table 1). These nanosized vesicles with abundant proteins, lipids, and nucleic acids play crucial roles in cellular modulation. In diabetic cerebral hemorrhage, exosomes significantly influence neuroinflammation and neural regeneration, thereby offering protection against further neuronal damage. One of the primary mechanisms through which exosomes exert their therapeutic effects is targeting and modulating the inflammatory response. In diabetic brain hemorrhage, inflammation is a major contributor to secondary brain injury. Wang *et al*[1] demonstrated that exosomes loaded with miR-129-5p effectively targeted and downregulated HMGB1 expression, thereby reducing neuroinflammation, which is crucial for mitigating neuronal damage and promoting recovery in patients with diabetic brain hemorrhage[1]. In addition to having anti-inflammatory effects, exosomes promote neural regeneration through the transfer of beneficial biomolecules, such as microRNAs, to damaged brain cells. This transfer aids in the repair of injured neural tissues by enhancing cell prolif-

Table 1 Key mechanisms of action of stem cell–derived exosomes for neurological recovery post–diabetic cerebral hemorrhage

Mechanism of action	Description	Ref.
miR-129-5p modulation	Bone marrow–derived mesenchymal stem cell–derived exosomes deliver miR-129-5p, which targets and downregulates HMGB1. This leads to reduced neuroinflammation and improved neurological outcomes	Wang *et al*[1], 2024
Attenuation of oxidative stress	Exosomes reduce oxidative stress by modulating the expression of antioxidant enzymes and by reducing the production of reactive oxygen species, thereby protecting neurons from damage	Gómez-de Frutos *et al*[2], 2024
Promotion of neurogenesis	Stem cell–derived exosomes promote neurogenesis by delivering growth factors and microRNAs that support the proliferation and differentiation of neural progenitor cells in the damaged brain	Cheng *et al*[4], 2024
Inhibition of apoptosis	Exosomes carry antiapoptotic signals, such as miRNAs and proteins, which inhibit the activation of apoptotic pathways in neurons, reducing cell death in the affected brain regions	Larsson *et al*[3], 2024
Reduction of blood–brain barrier disruption	Bone marrow–derived mesenchymal stem cell–derived exosomes strengthen the blood–brain barrier by enhancing tight junction protein expression and reducing vascular permeability, thus preventing further brain injury post-hemorrhage	Lv *et al*[5], 2024
Modulation of immune response	Exosomes modulate the immune response by altering the activity of microglia and macrophages, reducing the production of proinflammatory cytokines, and promoting a neuroprotective environment	Southerland *et al*[6], 2024
Enhancement of angiogenesis	Bone marrow–derived mesenchymal stem cell–derived exosomes promote angiogenesis by delivering proangiogenic factors such as VEGF, which support the formation of new blood vessels and improve blood supply to the injured brain tissue	Wang *et al*[1], 2024
Regulation of autophagy	Exosomes influence autophagy processes in neurons and glial cells, contributing to the clearance of damaged proteins and organelles and supporting cellular homeostasis and survival	Wang *et al*[1], 2024
miRNA-mediated gene expression modulation	Through the delivery of various miRNAs, exosomes modulate the expression of genes involved in inflammation, cell survival, and repair processes, facilitating recovery from brain injury	Gómez-de Frutos *et al*[2], 2024
Neuroprotection through anti-inflammatory effects	Bone marrow–derived mesenchymal stem cell–derived exosomes reduce the expression of proinflammatory genes and increase anti-inflammatory cytokines, protecting neural tissue from secondary damage post-hemorrhage	Cheng *et al*[4], 2024

The table presents the key mechanisms through which stem cell–derived exosomes contribute to neurological recovery following diabetic cerebral hemorrhage. These exosomes modulate various molecular pathways, including the regulation of miR-129-5p, oxidative stress reduction, neurogenesis promotion, apoptosis inhibition, and immune response modulation. They also play a crucial role in strengthening the blood–brain barrier, enhancing angiogenesis, and regulating autophagy, thereby offering a multifaceted therapeutic approach to mitigating brain injury and promoting recovery. HMGB1: High-mobility group box 1; VEGF: Vascular endothelial growth factor.

eration, differentiation, and survival. The anti-inflammatory and neuroprotective properties of exosomes are particularly beneficial in diabetic brain hemorrhage; in diabetic brain hemorrhage, chronic hyperglycemia exacerbates oxidative stress and inflammatory processes, leading to more severe neurological outcomes[2]. Exosomes exert protective effects against oxidative stress, which is increased in diabetic conditions and has potential to further damage neuronal cells and impede recovery. Because it addresses both the immediate effects of hemorrhage and the long-term detrimental effects of diabetes, exosome therapy is a comprehensive treatment approach[4]. The regenerative potential of stem cell-derived exosomes is supported by their abilities to modulate inflammation, promote neurogenesis, and enhance angiogenesis. Exosomes are rich in bioactive molecules, including mRNAs, microRNAs, and proteins, which influence key cellular processes. Wang *et al*[1] demonstrated that exosomes derived from bone marrow mesenchymal stem cells and loaded with miR-129-5p significantly attenuated neurological impairments by targeting HMGB1 in a diabetic cerebral hemorrhage model[1]. This modulation of HMGB1 by exosomes not only reduced inflammation but also promoted tissue repair and functional recovery. Moreover, research on the impact of experimental diabetes on intracerebral hemorrhage has highlighted that mesenchymal stem cell-derived exosomes can counteract diabetes-induced damage by enhancing angiogenesis, which is essential for delivering nutrients and oxygen to injured areas of the brain[2]. This angiogenic effect of exosomes, combined with their ability to promote neurogenesis, underscores their potential to facilitate brain tissue regeneration. Moreover, research has explored how sodium/glucose cotransporter 1 (SGLT1) and SGLT2 inhibition modulates circulating metabolites and their impact on cerebral small vessel disease, which is closely linked to brain hemorrhage[5]. Although the study focused on pharmacological interventions, it indicated that targeting metabolic pathways - a capability of exosomes - can be beneficial for treating hemorrhagic brain injuries. Additionally, exosomes may alleviate small vessel disease, which is often exacerbated by diabetes and can lead to deep intracerebral hemorrhage [4]. The ability of exosomes to cross the BBB and deliver therapeutic molecules directly to the injury site renders this therapy valuable for treating conditions such as brain hemorrhage, where targeted delivery is crucial. In summary, the

regenerative potential of stem cell-derived exosomes for brain hemorrhage is supported by their ability to modulate inflammation, promote neurogenesis, and enhance angiogenesis. Exosomes can carry a diverse array of bioactive molecules that can aid in repairing and regenerating damaged brain tissue, particularly in diabetic patients at high risk of hemorrhagic events. These findings provide compelling evidence indicating that exosome therapy is a promising approach for improving clinical outcomes in patients with diabetic brain hemorrhage.

EVIDENCE OF EFFICACY

Research, including preclinical studies, has been obtained robust evidence supporting the efficacy of exosome therapy for diabetic brain hemorrhage. Studies have demonstrated that stem cell-derived exosomes significantly improved neurological function and markedly reduced brain damage in diabetic models following hemorrhagic events. One notable finding is that exosomes reduce neuroinflammatory markers, which is crucial given the role of inflammation in exacerbating brain injury (Table 2). Wang *et al*[1] highlighted the therapeutic potential of exosomes loaded with miR-129-5p for cerebral hemorrhage; these exosomes were discovered to target and downregulate HMGB1, thereby attenuating neuroinflammation and subsequent neurological impairment[1]. In addition to mitigating inflammation, exosomes have been demonstrated to enhance neurogenesis, the process by which new neurons are generated. This is relevant in diabetic brain hemorrhage, where the regeneration of damaged brain tissue is critical for functional recovery. Current evidence indicates that exosomes not only promote the survival and proliferation of neural progenitor cells but also stimulate the differentiation of these cells into functional neurons. This neurogenic effect contributes to the improvements that were observed in neurological outcomes in preclinical models[2]. Furthermore, a study obtained the key finding of a reduction of oxidative stress markers in diabetic brain hemorrhage models treated with exosome therapy. Oxidative stress is a major contributor to neuronal death and tissue damage in hemorrhagic stroke, particularly in the diabetic brain, which is more susceptible to oxidative stress. By reducing oxidative stress, exosome therapy exerts neuroprotective effects that support brain recovery and reduce the extent of injury[4]. The cumulative evidence from these preclinical studies underscores the potential of exosomes as a novel treatment approach for diabetic brain hemorrhage. The ability of exosomes to modulate multiple processes-such as inflammation, neurogenesis, and oxidative stress-highlights their versatility as a therapeutic agent. These promising results provide a foundation for future clinical trials; such trials should be conducted to determine the safety and efficacy of exosome therapy in patients with diabetic brain hemorrhage[3,5].

POTENTIAL ADVENTAGES OVER COVENTIAL THERAPIES

With respect to diabetic brain hemorrhage, exosome therapy has several distinct advantages over conventional treatments. Traditional therapies mainly focus on managing acute symptoms by, for example, reducing intracranial pressure and controlling bleeding, without addressing the pathophysiological mechanisms underlying diabetic brain hemorrhage that contribute to long-term neurological damage. By contrast, exosome therapy targets the main causes of brain injury, including chronic inflammation and impaired neural regeneration, which are concerns in diabetic patients [1]. A major advantage of exosome therapy is its ability to modulate the immune response, with a minimal risk of immune rejection. Conventional cell-based therapies, such as stem cell transplants, often cause immune reactions, necessitating the use of immunosuppressive drugs, which have notable side effects. However, exosomes are less likely to cause such immune responses given their biocompatibility and lack of cell surface antigens that can cause rejection. Thus, exosome therapy is a safer option relative to traditional treatment, particularly for patients with diabetes, who may have compromised immune systems[2]. Exosome therapy also promotes neurogenesis and neuroprotection, which are crucial for long-term recovery from brain hemorrhage. By enhancing the survival and differentiation of neural progenitor cells, exosomes support the regeneration of damaged brain tissue. This is crucial in diabetic patients, who often exhibit impaired regeneration due to chronic hyperglycemia and associated vascular complications. In contrast to conventional therapies, which are mainly palliative, exosome therapy has potential to lead to sustained and improved neurological recovery[4]. Moreover, exosomes have been demonstrated to be promising for reducing oxidative stress and protecting against further neuronal damage. Conventional treatments typically do not directly address oxidative stress; instead, they play roles in managing the immediate aftermath of a hemorrhagic event. The ability of exosome therapy to mitigate oxidative stress represents a significant advancement, and exosome therapy provides a comprehensive treatment approach that can improve long-term outcomes[3,5]. Generally, the targeted approach of exosome therapy for addressing the underlying pathophysiology of diabetic brain hemorrhage-combined with its safety profile and regenerative capabilities-renders this treatment a promising alternative to conventional treatments. As research on the topic progresses, exosome therapy can be integrated into clinical practice and enable more effective and sustained recovery for patients with diabetes[1,6]. Bone marrow-derived mesenchymal stem cell-derived exosomes are particularly rich in growth factors that promote angiogenesis, providing effective and enhanced vascular repair and regeneration capabilities. For example, Wang *et al*[1] demonstrated that bone marrow-derived exosomes loaded with miR-129-5p significantly attenuated neurological impairments after diabetic cerebral hemorrhage by targeting HMGB1, which not only reduced inflammation but also stimulated angiogenesis, leading to improved recovery[1]. The proangiogenic properties of exosomes render them well-suited for recovery from conditions requiring the revascularization of damaged brain tissue. However, although bone marrow-derived exosomes effectively promote angiogenesis, they may not provide the same level of immunomodulation as other exosome sources do. This may be a limitation in scenarios in which controlling the immune response is crucial for preventing further brain tissue damage. However, umbilical cord-derived

Table 2 Comparative analysis of miR-129-5p modulation and high-mobility group box 1 targeting in diabetic and nondiabetic cerebral hemorrhage

Mechanism	Diabetic cerebral hemorrhage	Nondiabetic cerebral hemorrhage	Ref.
miR-129-5p modulation	Regulates neuroinflammation: MiR-129-5p from bone marrow–derived mesenchymal stem cell–derived exosomes modulates neuroinflammation by targeting HMGB1, which reduces neurological impairment and oxidative stress	Modulates neuroinflammation and cellular stress: Similar pathways involving miR-129-5p can modulate inflammation and oxidative stress, but they are less studied in nondiabetic contexts	Wang *et al*[1], 2024; Gómez-de Frutos *et al*[2], 2024
HMGB1 targeting	Attenuates damage: Targeting HMGB1 with miR-129-5p-loaded exosomes can alleviate brain damage by reducing inflammatory responses and promoting cellular repair	Reduces inflammation and promotes recovery: Targeting HMGB1 may reduce inflammation and support recovery, but the specific mechanisms and efficacy may differ because of the absence of diabetes-related complications	Wang *et al*[1], 2024; Cheng *et al*[4], 2024
Impact on neurological outcomes	Improves outcomes significantly: Enhanced targeting of HMGB1 and reduction in neuroinflammation lead to more favorable recovery in diabetic cerebral hemorrhage models	Varied outcomes: The efficacy of HMGB1 targeting in nondiabetic hemorrhages can be variable, with outcomes influenced by the absence of diabetes-related factors	Gómez-de Frutos *et al*[2], 2024; Larsson *et al*[3], 2024
Mechanistic differences	Diabetes-specific effects: The presence of diabetes affects the baseline inflammatory state and cellular response, influencing how miR-129-5p and HMGB1 targeting modify outcomes	General mechanisms: In nondiabetic conditions, the effects of miR-129-5p and HMGB1 targeting are based on standard inflammatory pathways without additional diabetes-related complications	Lv Y *et al*[5], 2024; Southerland *et al*[6], 2024

This table provides a comparative analysis of the modulation of miR-129-5p and targeting of high-mobility group box 1 in diabetic *vs* nondiabetic cerebral hemorrhage. The differential impact on neuroinflammation, neurological outcomes, and specific mechanisms are highlighted to illustrate the variations in therapeutic efficacy and response between diabetic and nondiabetic conditions. HMGB1: High-mobility group box 1.

exosomes exhibit superior immunomodulatory capabilities. Rich in anti-inflammatory cytokines and miRNAs, these exosomes can significantly reduce the inflammatory response associated with brain hemorrhage. Their ability to mitigate inflammation leads to a favorable environment for tissue repair and regeneration, which is relevant for patients with diabetes with chronic inflammation[2]. Nevertheless, despite their strengths in terms of immunomodulation, umbilical cord-derived exosomes may not be as effective as bone marrow-derived exosomes are in promoting angiogenesis. This limitation may affect their efficacy for revascularizing brain tissue, which is a critical step in recovery from hemorrhage. Combining bone marrow-derived and umbilical cord-derived exosomes may be a more comprehensive therapeutic strategy. Bone marrow-derived exosomes can provide vascular repair, and umbilical cord-derived exosomes can enhance immune regulation. Such a dual exosome therapy can address the multifaceted challenges involved in treating diabetic brain hemorrhage, potentially leading to improved patient outcomes. In general, the choice between bone marrow-derived and umbilical cord-derived exosomes should be guided by the specific therapeutic goals for diabetic brain hemorrhage. Bone marrow-derived exosomes are effective at promoting angiogenesis, and umbilical cord-derived exosomes offer superior immunomodulation. Combining these exosomes may offer a balanced and effective therapeutic approach, alleviating diverse complications in patients with diabetic brain hemorrhage.

CHALLENGES AND FUTURE DIRECTIONS

Despite the potential of exosomes for treating diabetic brain hemorrhage, several challenges should be addressed before it is incorporated into standard clinical practice (Table 3). A major challenge in incorporating it into practice is the lack of standardized protocols for the isolation, characterization, and delivery of exosomes. Variability in isolation, characterization, and delivery processes can result in inconsistent therapeutic outcomes, leading to difficulty in evaluating the efficacy of the therapy. Establishing standardized procedures is essential for ensuring the safety and effectiveness of exosome-based treatments[1]. Another critical concern is determining the optimal dosing and timing for exosome administration. The therapeutic window for exosome delivery in diabetic brain hemorrhage is not well defined. Given the complex interplay of chronic inflammation, oxidative stress, and impaired neural regeneration in diabetic brain hemorrhage, determining the most effective timing for such intervention is crucial. Future research should determine these parameters to maximize the therapeutic benefits of exosomes[2]. The long-term safety and efficacy of exosomes should be thoroughly investigated. Although initial studies have indicated that exosome therapy can reduce neurological impairment and promote neural repair, long-term studies should be conducted to assess its potential side effects, especially in patients with diabetes with comorbid conditions. Ensuring its long-term safety is vital for integrating exosome therapy into standard medical practice[3,4]. Furthermore, the translational gap between laboratory findings and clinical application is a considerable obstacle. Although preclinical studies have highlighted the potential benefits of exosome therapy, translating these findings into clinical practice requires overcoming regulatory, manufacturing, and logistical challenges. This includes producing exosomes at scale while maintaining their therapeutic properties and navigating the complex regulatory landscape governing new medical therapies[6,7]. Although exosome therapy exhibits promise in terms of enabling recovery from diabetic brain hemorrhage, the aforementioned challenges must be overcome to enable the transition of such therapy from preclinical research to widespread clinical use. Continual research is

Table 3 Potential clinical applications and future directions for exosome-based therapies for diabetic neurological complications

Application/direction	Clinical application	Future directions	Ref.
Exosome-based delivery of miR-129-5p	Targeted therapy: Exosomes derived from bone marrow mesenchymal stem cells loaded with miR-129-5p can target HMGB1, potentially attenuating neurological impairments in diabetic cerebral hemorrhage	Expand research: Investigate the effectiveness of miR-129-5p-loaded exosomes in broader diabetic and nondiabetic neurological conditions and optimize exosome delivery systems for enhanced therapeutic efficacy	Wang *et al* [1], 2024
Reduction of inflammation through exosomal cargo	Anti-inflammatory effects: Exosomes can deliver anti-inflammatory agents to mitigate neuroinflammation in diabetic cerebral hemorrhage	Explore mechanisms: Study the specific exosomal components responsible for reducing inflammation and their impacts on long-term outcomes in diabetic patients	Gómez-de Frutos *et al* [2], 2024
Exosome-mediated neuroprotection	Neuroprotective strategies: Utilizing exosomes to deliver neuroprotective agents can reduce oxidative stress and cell death in diabetic neurological complications	Develop neuroprotective formulations: Focus on formulating exosomes with neuroprotective agents and assessing their safety and efficacy in clinical trials	Cheng *et al* [4], 2024
Biomarker discovery and monitoring	Diagnostic tool: Exosomal microRNAs can serve as biomarkers for the early diagnosis and monitoring of disease progression in diabetic neurological disorders	Validate biomarkers: Conduct longitudinal studies to validate exosomal biomarkers and their predictive value for disease outcomes	Liao *et al*[8], 2023
Combination therapies	Synergistic approaches: Combining exosome-based therapies with other treatments, such as hyperglycemia management and lifestyle modifications, can enhance overall therapeutic efficacy	Integrate therapies: Explore synergistic effects of combining exosome-based therapies with traditional and novel treatments in clinical settings	Su *et al*[7], 2024
Personalized medicine	Tailored treatments: Personalized exosome-based therapies can be developed on the basis of individual patient profiles and specific disease mechanisms	Customize approaches: Research personalized exosome-based treatments tailored to the genetic and metabolic profiles of diabetic patients	Zeinhom *et al*[9], 2024

This table outlines the potential clinical applications and future research directions for exosome-based therapies for managing diabetic neurological complications. It highlights the current therapeutic uses, anticipated advancements, and areas requiring further investigation to optimize these novel treatments. HMGB1: High-mobility group box 1.

required for standardizing protocols, optimizing dosing and timing, and ensuring the treatment's long-term safety, which will ultimately determine the success of exosome therapy in clinical settings[1,2,4]. Exosomes, which are nanoscale extracellular vesicles that have been gaining attention for their therapeutic potential for treating diabetic brain hemorrhage, can be isolated from the patient's own cells, such as those derived from adipose tissue, bone marrow, or blood. Adopting this autologous approach can reduce the risk of immune rejection and enable personalized therapy tailored to individual needs. For example, exosomes from adipose-derived stem cells are known for their regenerative properties, and those from bone marrow-derived mesenchymal stem cells are effective for promoting angiogenesis and neuroprotection[5,6]. To ensure quality and functionality, several critical steps must be completed in the isolation and purification of exosomes; techniques such as ultracentrifugation, size-exclusion chromatography, and polymer-based precipitation are commonly used. Ultracentrifugation is the gold standard for producing highly pure exosomes; however, it is time consuming and requires specialized equipment. After isolation, to remove contaminants, exosomes must be purified using methods such as density gradient centrifugation and immunoaffinity capture[5,6]. Scalability and consistency are major challenges in exosome production. The current methods are labor intensive and may be difficult to scale to meet clinical requirements. Standardized protocols and scalable technologies are required for producing exosomes efficiently and cost-effectively. Additionally, variability in source material, isolation techniques, and purification methods influences the yield, purity, and biological activity of exosomes, affecting their therapeutic efficacy [5,6]. Research has investigated exosome transplantation for treating neurological conditions such as diabetic brain hemorrhage, with the administration methods including intravenous (IV) and intranasal routes. IV administration facilitates systemic distribution, which is beneficial for ensuring a broad therapeutic distribution. Studies, including that by Wang *et al*[1], have demonstrated that IV administration of exosome-loaded miR-129-5p from bone marrow mesenchymal stem cells can reduce neurological impairment[1]. Intranasal delivery of exosomes is a noninvasive method that can directly target the central nervous system, potentially improving the therapeutic efficacy for brain-related conditions and minimizing systemic side effects[1,2]. Optimal dosing strategies should be devised to maximize therapeutic outcomes while minimizing the risks. Precise dosing regimens specific to different disease severities and target tissues should be developed. Higher doses may enhance therapeutic effects but may pose a risk of adverse effects, and lower doses may be safer but require frequent administration[2]. Monitoring the exosome biodistribution and therapeutic impact postadministration is crucial for optimizing exosome use. Techniques such as fluorescent labeling and nanoparticle tagging facilitate the real-time visualization and monitoring of exosome distribution through imaging modalities such as fluorescence microscopy and magnetic resonance imaging (MRI). These methods can help with refining administration protocols and dosing strategies for exosome therapy by providing insights into exosome migration and accumulation in target tissues[1,4]. Exosomes naturally possess the ability to cross the BBB due to their small size and lipid bilayer composition, which facilitate their fusion with cellular membranes and enable targeted delivery to the brain. Research revealed that exosomes, particularly those from bone marrow mesenchymal stem cells, can deliver therapeutic agents directly to the brain, thus modulating gene expression and promoting neuroprotection[2]. The

immunogenicity of exosomes is another key consideration. Autologous exosomes, which are derived from a patient's own cells, are less likely to trigger an immune response, rendering them ideal for transplantation. However, immune rejection may occur, particularly for allogeneic exosomes. Ongoing research is crucial for understanding and mitigating adverse immune reactions[7]. Overall, exosome transplantation is a promising therapeutic strategy for central nervous system disorders including diabetic brain hemorrhage. Advances in administration techniques, dosing strategies, and tracking methodologies can lead to a more comprehensive understanding of the exosome biodistribution and pharmacokinetics. Exosomes' ability to cross the BBB and their low immunogenicity indicate they have potential as a novel treatment modality. Future research should focus on refining treatment approaches to enable the successful transition of exosome-based therapies from the laboratory to clinical practice.

CONCLUSION

The use of bone marrow-derived mesenchymal stem cell-derived exosomes for treating diabetic cerebral hemorrhage is a notable advancement in terms of targeted therapies for neurological complications related to diabetes. Because they mitigate neuroinflammation and promote neural repair, mesenchymal stem cell-derived exosomes have promise for reducing neurological impairment in diabetic cerebral hemorrhage[1]. The insights that have been obtained through research enhance the understanding of the complex pathophysiology of diabetic brain hemorrhage and provide a foundation for innovative treatments tailored to this patient population. Mesenchymal stem cell-derived exosomes can target neuroinflammation and oxidative stress and thus can be considered a novel therapy with the potential to significantly improve clinical outcomes[2]. The successful translation of these findings into clinical practice is critical. For exosomes to be established as a standard treatment option, ongoing research must address the long-term safety, efficacy, and optimal delivery methods for mesenchymal stem cell-derived exosomes. Given the severe impact of diabetic cerebral hemorrhage on patients, these exosomes offer new hope for improving patient care and recovery[4,5]. Although research results regarding such therapy are promising, several challenges remain. The progress in research on exosomes highlights the importance of continued exploration in this field. Exosomes have the potential to revolutionize the treatment of diabetic cerebral hemorrhage; thus, the development of mesenchymal stem cell-derived exosomes and similar therapies is crucial for addressing the neurological complications of diabetes[1,4]. Exosome therapy offers notable advantages over traditional stem cell transplantation, especially for neurological conditions including diabetic cerebral hemorrhage. Exosomes, as cell-free therapeutics, present several benefits relative to stem cell approaches, including a reduced risk of tumorigenesis, a lower likelihood of immune rejection, and enhanced feasibility in terms of practical use. A primary concern of stem cell transplantation is the risk of tumor formation, particularly when embryonic or induced pluripotent stem cells are used; such cells are prone to uncontrolled proliferation[1]. By contrast, exosomes are nonliving and do not carry the same risk, rendering them a safer alternative for therapeutic use. Immune rejection is another key concern in stem cell therapies; thus, careful matching of donor and recipient tissues is required, as well as long-term immunosuppressive treatment[2]. Exosomes derived from autologous cells or immunologically privileged sources, such as umbilical cord tissue, are less likely to trigger immune responses, reducing the need for immunosuppressive therapies and enhancing patient safety[4]. Exosomes also offer practical advantages in terms of storage, handling, and administration. In contrast to stem cells, which require complex procedures for expansion and processing, exosomes can be isolated, purified, and stored for extended periods without a notable loss of functionality[3]. This stability simplifies logistical management and clinical application of exosome treatment. Moreover, exosomes can be administered through less invasive routes, such as intravenous or intranasal routes, potentially improving patient compliance[5]. Another key benefit of exosomes is their ability to cross the BBB. Studies have demonstrated that exosomes can effectively penetrate the BBB and deliver therapeutic payloads directly to brain tissues, which is essential for treating neurological conditions requiring targeted delivery[1]. The small size and lipid bilayer composition of exosomes facilitate their passage through the BBB, rending them an attractive option for treating diseases such as diabetic cerebral hemorrhage. In summary, the safety profile, practical advantages, and effective tissue penetration of exosomes render them as a promising alternative or adjunct to traditional stem cell therapies. The growing body of research supporting the usefulness of exosomes indicates that they have therapeutic potential for complex neurological conditions.

FOOTNOTES

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