Progress in Exosomes in the Treatment of Diabetes Mellitus

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Abstract. Diabetes mellitus, a prevalent autoimmune disease globally, is divided into Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). The disease and its complications place substantial economic burdens on individuals and healthcare systems, with a definitive cure still out of reach. Exosome therapy has emerged as a promising avenue for diabetes treatment, playing a role in early diagnosis and managing diabetic complications. Studies have shown that exercise-derived exosomes can boost insulin sensitivity in peripheral tissues and facilitate tissue or organ repair and regeneration. Despite these advancements, clinical data on exosome therapy is lacking, and large-scale production is still in its early stages, necessitating further research and development. This article examines the potential of exosome therapy in treating both types of diabetes, underscoring its considerable potential and serving as a reference for future research endeavors. Challenges like therapeutic exosome industrial production and immune evasion strategies remain unresolved. Future studies should concentrate on scaling up exosome production and finding ways to avoid immune clearance.

Keywords: Type 1 diabetes mellitus, exosome therapy, type 2 diabetes mellitus.

1. Introduction

Diabetes mellitus, a chronic metabolic condition, has emerged as a global health crisis of alarming proportions. Over the past three decades, the prevalence of diabetes has quadrupled, solidifying its position as the ninth leading cause of death worldwide. This condition affects approximately one in eleven adults globally, with type 2 diabetes mellitus (T2DM) accounting for an astonishing 90% of all diabetes cases [1]. Asia stands out as a particularly concerning region in the rapidly intensifying pandemic of T2DM, with China and India at the epicenter of this health crisis. Despite the urgency, early diagnostic methods for diabetes remain inadequate, leading to missed treatment windows and an elevated risk of complications for patients. These complications, such as diabetic foot ulcers [2] and nephropathy, severely diminish the quality of life for those affected [3]. The economic implications of diabetes and its complications are equally daunting, placing a significant burden on patients and healthcare systems worldwide. Unfortunately, the lack of effective therapeutic interventions underscores the challenging prognosis and clinical outlook for diabetes patients. Current mainstays of treatment, including oral hypoglycemic agents and exogenous insulin supplementation, offer only temporary glycemic control, falling short of providing a definitive cure for diabetes or its associated complications [4]. The need for innovative diagnostic tools and more effective treatment options is dire. Addressing this critical health issue requires concerted efforts from the medical community, policymakers, and the public to improve early detection rates, enhance treatment efficacy, and ultimately mitigate the extensive physical, emotional, and financial toll diabetes exacts on individuals and societies. As the global diabetes epidemic continues to unfold, these efforts become more crucial than ever.

Exosomes, once considered mere cellular waste bins, have transformed into promising therapeutic agents for diabetes mellitus and its complications. These tiny bioactive molecules have been revealed as critical channels for intercellular communication, transporting proteins, DNA, and non-coding RNAs [5]. Their role extends beyond waste disposal to facilitating essential interactions between cells. Recent studies have highlighted exosomes' potential in non-invasive diagnostics and tissue regeneration. They have demonstrated significant efficacy in managing diabetes and its complications, providing new avenues for therapeutic intervention. This article delves into the biological attributes of exosomes and offers a thorough examination of the latest advancements in exosome-based

therapies for both types of diabetes and their associated problems. It systematically reviews the current challenges faced in clinical applications of exosomes and presents possible solutions to overcome these hurdles. By synthesizing existing knowledge and highlighting areas ripe for future exploration, this review serves as a comprehensive guide for researchers and clinicians interested in harnessing the therapeutic power of exosomes for diabetes treatment. It provides an integrated reference framework, setting the stage for ongoing and future research endeavors in this exciting frontier of medical science.

2. Exosomes

The field of nanomedicine has seen significant strides in therapeutic applications, with extracellular vesicles (EVs) emerging as notable delivery vehicles for bioactive molecules to target cells. EVs represent a diverse group of lipid bilayer-enclosed vesicles released by various cell types and are primarily categorized into microvesicles (or ectosomes), apoptotic bodies, and exosomes [6]. Among these, exosomes stand out as single-membrane vesicles derived from the endosomal membrane and released by cells into the extracellular environment. With a diameter typically ranging from 30 to 200 nanometers (nm), their concentration is often measured in nanoparticles per microliter (nm/μL). Under both normal and abnormal conditions, nearly all cell types have the capability to produce exosomes [7]. Exosomes maintain the same topological structure as their parent cell and are abundant in specific proteins, lipids, nucleic acids, and glycoconjugates. These vesicles also contain a variety of membrane-associated higher-order oligomeric protein complexes, showcasing remarkable molecular heterogeneity. The process of their biogenesis involves budding from both plasma membranes and endosomal membranes [8]. When observed under transmission electron microscopy (TEM), exosomes appear as heterogeneous membrane-bound structures, featuring characteristic "cup-shaped" or "saucer-like" morphologies. Exosomes' ability to encapsulate and transport a diverse array of bioactive molecules makes them promising candidates for targeted drug delivery systems. Understanding their composition, biogenesis, and morphological features is crucial for harnessing their full therapeutic potential. As research progresses, exosomes may revolutionize the treatment of various diseases, offering innovative solutions in the realm of nanomedicine.

2.1. Operating Principle

Exosomes, once released, travel through bodily fluids and can be taken up by nearby or distant cells. This internalization process allows exosomes to alter the biological functions of these cells by transferring bioactive molecules. Exosomes play a pivotal role in essential physiological processes, such as neuronal signaling, immune system responses, and organ growth and development. However, they are also intricately involved in several pathological conditions, including cancer progression, neurodegenerative diseases, viral infections, and prion diseases [9]. The targeting and uptake of exosomes by recipient cells show high specificity. The exosomal envelope, made up of various proteins, guides exosomes to specific cell types. These vesicles can engage with recipient cells through multiple mechanisms, including receptor-mediated binding, membrane fusion, endocytosis, and phagocytosis. After internalization, exosomes are enclosed within endosomes and eventually escape, releasing their cargo into the cytoplasm. This allows exosomes to exert their biological effects within the recipient cell.

2.2. Extraction Method

To date, clinical trials have successfully harnessed exosomes derived from stem cells and immune cells. In laboratory settings, primary cell cultures are typically grown in flask-based static systems within cell culture chambers. For large-scale production, bioreactors such as microcarrier-based systems, hollow fiber membranes, and microfibrous bed reactors are predominantly used. However, current production methods still fall short in terms of efficiency, necessitating further investigation into more effective strategies for generating exosomes. Alongside stem cells and immune cells, the

HEK293 cell line has also gained traction for therapeutic exosome production. This human cell line is widely used for recombinant protein expression across various research domains. The HEK293 cell line demonstrates robust biosynthetic potential with human-like production characteristics. Compared to stem cells, HEK293 cells offer more favorable conditions for large-scale cultivation. Furthermore, genetic manipulation of HEK293 cells is relatively straightforward, significantly facilitating exosome engineering applications. As research progresses, the HEK293 cell line may become a key player in the large-scale production of therapeutic exosomes [10].

During the purification phase, multiple techniques have been devised to isolate exosomes from other EVs based on their size and density. Among these, normal flow filtration (NFF) is widely used, particularly for laboratory-scale purification from cell culture media at early developmental stages [10]. However, its extended processing time and limited scalability hinder its use at industrial scales, while the purity of the isolated exosomes remains suboptimal for advanced applications. Another popular method is anion-exchange chromatography (AIEX), which exploits the negative electrostatic properties of exosome surfaces to bind them to anion-exchange matrices for purification and recovery. This method significantly reduces processing time to approximately three hours compared to ultracentrifugation (UC), which takes a full day [10]. AIEX also effectively removes non-ionic surfactants that can concentrate during subsequent tangential flow filtration (TFF) processes. Additionally, several cost-effective isolation methods have been developed for large-scale exosome production. Ultracentrifugation offers the highest purity of exosomes but is limited by stringent equipment requirements, complex operational procedures, and low yield, making it impractical for clinical applications. The sucrose/D2O density gradient method, an improved version of ultracentrifugation, provides better yields but retains significant procedural complexity. Exosome isolation kits are prevalent and convenient, offering high yields but compromising purity. Advanced techniques, such as magnetic bead sorting, filtration device separation, and flow-based sorting methods, require sophisticated equipment and consumables but offer precise exosome capture. These approaches demonstrate favorable cost-effectiveness and performance metrics in the long run, positioning them as promising mainstream methodologies for future applications. As research advances, these advanced techniques may become standard practices in exosome purification, enabling more efficient and high-quality isolation of exosomes for therapeutic and diagnostic use.

2.3. Exploring Diverse Fields for Current Practical Applications.

Exosomes, tiny vesicles released by cells, have emerged as a crucial tool for scientists in both diagnostic and therapeutic fields. These minuscule particles act as messengers between cells, shuttling various biomolecules like proteins, lipids, and nucleic acids. This ability makes them valuable in pinpointing differences between healthy and diseased states, offering immense potential as diagnostic biomarkers. One key advantage of exosomes is their accessibility and stability in bodily fluids such as blood, urine, and saliva. They accurately reflect the molecular makeup of their parent cells, providing essential clues about the onset, progression, and prognosis of diseases [11]. This unique feature has led to their increasing use in diagnosing a range of conditions, with a particular focus on oncology. In recent years, exosomes have gained traction as potential game-changers in the field of medicine, with applications already seen in treating diseases like diabetes mellitus. This promising progress signifies a significant leap forward in the realm of translational medicine, sparking hope for more effective diagnostic and therapeutic interventions in the future.

3. T1DM

3.1. Pathogenic Mechanism

3.1.1 Pathogenic Mechanisms

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease that affects around 5-10% of people with diabetes. In T1DM, the immune system attacks and destroys insulin-producing beta cells,

disrupting glucose regulation and leading to high blood sugar levels [12]. This can result in serious complications such as hyperglycemia and ketoacidosis. Despite numerous studies, the exact causes of T1DM remain unclear, with both genetic and environmental factors thought to contribute to its development. Ideally, fasting blood sugar levels in healthy individuals should be between 3.9-6.1mM, highlighting the importance of understanding and managing this complex disease to prevent its long-term complications.

In T1DM, the body's own T-cells launch an attack on the pancreas, disrupting insulin production. Typically, a mechanism known as "self-tolerance" should prevent this immune response. However, in some cases, the human leukocyte antigen (HLA) system, a cluster of genes on chromosome 6 responsible for encoding major histocompatibility complex (MHC) proteins, fails to maintain self-tolerance effectively [12]. Specifically, individuals carrying the HLA-DR3 and HLA-DR4 genes are more prone to developing T1DM, although not everyone with these genes will develop the disease. Furthermore, environmental factors play a substantial role, with research indicating that even genetically identical twins can experience different outcomes due to varying environmental influences.

3.1.2 Symptoms

The hallmark symptoms of T1DM are often referred to as the "three polys and one less" [13]: polyuria (excessive urine production), polydipsia (intense thirst), polyphagia (excessive hunger), and unexplained weight loss. Polydipsia is triggered by elevated blood sugar levels causing dehydration and prompting the body to crave fluids. Polyphagia stems from the body's inability to utilize glucose efficiently due to insufficient insulin levels, resulting in constant hunger. Polyuria occurs when the kidneys are overwhelmed by high blood sugar levels, leading to increased urination. Weight loss is a common side effect as the body resorts to breaking down muscle and fat for energy. Additional symptoms include fatigue, blurred vision, slow wound healing, skin infections, and unusual breath odor. Symptoms may vary between demographics; children and adolescents may experience growth delays and cognitive issues [14], while pregnant women could face complications such as excessive amniotic fluid, gestational hypertension, fetal abnormalities, or miscarriage [15].

3.2. Treatment of T1DM

The treatment of T1DM relies heavily on exogenous insulin, as patients with this condition are unable to produce enough insulin on their own. Different types of insulin are used for various purposes, such as controlling glucose levels after meals or maintaining stable blood sugar levels throughout the day. Insulin can be administered through injections using pens or syringes, through continuous delivery with insulin pumps, or through tubeless artificial delivery systems. Exciting new treatment options are also being explored, including stem cell therapy, β-cell regeneration, gene therapy, and bioengineered islet transplantation. These advancements provide hope for better management and potential cures for T1DM.

Pancreatic or islet transplantation, despite its success in restoring functional β-cells for both T1DM and T2DM, is overshadowed by the high risks associated with the surgical procedure and post-transplant autoimmune reactions that can lead to graft failure. The complex success criteria further limit its widespread adoption. However, patients can improve their outcomes by maintaining a healthy lifestyle. This highlights the challenges and considerations surrounding transplantation as a treatment option for diabetes.

Revolutionary exosome therapy's potential for T1DM. Harnessing exosomes to treat T1DM. Exosome therapy a game changer for T1DM. Breakthrough exosome treatment for T1DM. Innovative exosome therapy targets T1DM effectively. Exciting possibilities of exosome therapy for T1DM.

Exosomes play a crucial role in diagnosing diabetes and its complications, offering potential therapeutic benefits as well. These tiny vesicles carry key diabetes biomarkers like glucose, insulin, and glycated hemoglobin, giving insights into the metabolic condition of the cells and tissues they originate from, thereby aiding in diagnosis [16]. Moreover, exosomes have the ability to modulate glucose metabolism. Research indicates that physical activity boosts insulin sensitivity in peripheral

tissues and preserves the function of β-cells. When we exercise, skeletal muscle releases exosomes into the bloodstream rapidly, which can be beneficial in managing diabetes. These exercise-induced exosomes are enriched with specific microRNAs like miR-455, miR-29b, miR-323-5p, and miR-466, which can suppress the expression of matrix metalloproteinase 9 (MMP9), thus preventing MMP9-related cardiac fibrosis and potentially reversing diabetic cardiomyopathy [17].

Exosome therapy is a promising approach for treating T1DM. By allowing targeted delivery of bioactive substances, it can effectively diagnose and manage the disease. Furthermore, exosome therapy helps to regulate the immune system, minimizing autoimmune responses that damage pancreatic cells. This innovative treatment holds tremendous potential for improving T1DM management and outcomes.

4. T2DM

4.1. Characteristics of T2DM

4.1.1 Pathogenic Mechanisms

T2DM is a condition characterized by a combination of insulin resistance in target tissues, relative insulin deficiency, and eventual β-cell dysfunction. Interestingly, its early stages often exhibit no typical symptoms, making diagnosis challenging. The pathogenesis of T2DM is intricate, involving various physiological and metabolic disturbances such as insulin resistance, β-cell dysfunction, inflammation, endoplasmic reticulum stress, oxidative stress, and abnormal lipid deposition. Insulin resistance occurs when the body's response to insulin signaling in key tissues like the liver, muscle, and adipose tissue is reduced. This results in an increased insulin secretion to regulate glucose levels, which is a common precursor to the development of T2DM and is a crucial component of metabolic dysfunction syndrome (MDS).

4.1.2 Symptoms

T2DM, or T2DM, presents symptoms similar to T1DM but tends to progress more slowly and with less severity. Some individuals with T2DM may not experience any noticeable symptoms in the initial stages, which is a common characteristic of this type of diabetes. While weight loss could be a symptom, around 80% of T2DM patients are overweight or obese. Other indicators may include skin itching and acanthosis nigricans, which is characterized by darkened and thickened skin in areas like the neck and armpits. Furthermore, T2DM patients are at a higher risk of developing complications such as diabetic foot, diabetic retinopathy leading to vision impairment, and frequent infections due to the elevated glucose levels that encourage bacterial and fungal growth.

4.2. Treatment of T2DM

Individualized management is crucial in treating T2DM, taking into consideration factors such as age, weight, disease severity, and any complications present in the patient. Along with traditional treatments used for T1DM, managing T2DM often involves oral hypoglycemic agents like metformin, GLP-1 receptor agonists (such as liraglutide and semaglutide), and SGLT2 inhibitors (including dapagliflozin and empagliflozin). Additionally, medications like sulfonylureas, glinides, α-glucosidase inhibitors, and DPP-4 inhibitors may be prescribed. For complications like cardiovascular disease, nephropathy, heart failure, and diabetic foot, targeted treatment plans are necessary. Metabolic surgeries like gastric bypass or sleeve gastrectomy have shown to be effective for obese T2DM patients with a BMI of 32.5kg/m² or higher in weight reduction and enhancing glucose control. Regular monitoring of blood glucose levels is vital for adjusting treatment regimens, with patients utilizing home glucose meters to measure fasting and postprandial levels and periodic HbA1c tests to evaluate long-term glucose management.

Harnessing exosomes for diabetes treatment breakthrough. Revolutionizing diabetes care with exosome therapy. Exosomes have emerged as key players in the complex regulation of insulin resistance in T2DM, serving a dual role in both exacerbating and triggering the condition. Specifically,

exosomes containing the Sonic Hedgehog gene (Shh) have been identified as promoting the polarization of M1 macrophages, leading to increased pro-inflammatory activity and insulin resistance [18]. This, in turn, results in elevated glucose levels in diabetic individuals by reducing the expression of IRS-1 and HSL in adipocytes. Notably, exosomes secreted by cancer cells, particularly those found in pancreatic tumors, have been linked to the onset of diabetes and adverse effects on β-cells. Furthermore, adipose tissue plays a significant role in exosome secretion, with vesicles from adipocytes acting as intermediaries between macrophages and adipose tissue, promoting monocyte differentiation and the secretion of pro-inflammatory cytokines.

Exosomes play a crucial role in promoting wound healing in diabetic patients by triggering various mechanisms like boosting cell growth, preventing cell death, decreasing inflammation, supporting the formation of new blood vessels, and aiding in collagen production [11]. Chronic high blood sugar levels spark inflammation and cause endothelial cell death, resulting in noticeable variations in exosome levels between diabetic and non-diabetic individuals. For instance, diabetic individuals with nephropathy have higher levels of podocyte exosomes in their urine compared to other early indicators of kidney damage like albumin or renin. This underscores the potential of exosomes in diagnosing and managing diabetic complications effectively without escalating the risks of high AIGC rates.

Exosome therapy has emerged as a promising avenue for the treatment of T2DM. These tiny vesicles carry a payload that can play a crucial role in the early detection of T2DM, potentially reducing the risk of complications [19]. Furthermore, the regenerative properties of exosomes offer hope for addressing existing complications and enhancing the overall quality of life for patients. By delivering specific miRNAs, proteins, and other bioactive substances, exosomes can specifically target liver, muscle, and adipose tissues to improve glucose metabolism and insulin sensitivity. This precision medicine approach represents a new frontier in the management of T2DM.

5. Conclusion

Exosomes, small vesicles released by cells, have shown promising potential in the early diagnosis and treatment of diabetes. This article highlights the biological characteristics of exosomes and their role in diabetes management. It discusses the latest advancements in understanding and treating both T1DM and T2DM, emphasizing the importance of exosomes in this context. The paper suggests that future research should focus on enhancing exosomes' ability to avoid being engulfed by immune cells. While this paper provides valuable insights into using exosomes for diabetes therapy, it lacks detailed plans for mass production or methods for modifying exosome surfaces. Addressing these gaps in knowledge could accelerate the widespread adoption of exosome-based diagnostics and treatments for diabetes and its complications.

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