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Stem Cell-Derived Exosomal microRNAs: An Innovative Approach Towards Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus is described as a lifelong metabolic disorder where the body cannot regulate its blood sugar level. Despite advancement in the treatment modalities, one of the greatest challenges faced today remains early diagnosis and comprehending the pathophysiology of diabetes. Recent studies indicate that the use of exosomes, which contain proteins and microRNAs (miRNAs) isolated from various cells, is becoming increasingly common due to their significant role in cell-cell interactions.

Purpose: This review aims to highlight the rising significance of exosomes and exosomal miRNAs as novel biomarkers and possible therapeutic targets for diabetes diagnosis and treatment.

Methods: A comprehensive review of the recent literature was conducted on the subject of the biological function of exosomes, the diagnostic potential of exosomal miRNAs, and their implication in the development and severity of diabetes. Besides that, special focus was placed on identifying specific miRNA profiles connected to diabetic diseases.

Results: Exosomal miRNAs have been considered highly promising non-invasive markers in the prognosis and early diagnosis of diabetes. Multiple studies show that changes in the expression of miRNAs are positively correlated with the progression of disease and the occurrence of its complications. Treatment using exosomes has shown great potential in the management of the molecular mechanisms of the disease.

Conclusion: Exosomes, mainly the miRNAs contained by them, are recently discovered, fascinating tools that could be used for the diagnosis and treatment of diabetes. Actually, they can be used both as biomarkers and as drugs, which might dramatically change the way of patient care and disease control.

1. Introduction

Diabetes mellitus (DM) is a multifaceted and heterogeneous disease. Its different molecular pathways result in impaired glucose metabolism. Despite all the research, the exact cause of diabetes mellitus is still unclear. Still, genetics and environmental factors play pivotal roles in the development of the disease. It is widely believed that the development of type 2 diabetes (T2D) has a strong genetic component. It has even been estimated that genes can explain 40-70% of the variation in the disease manifestation (Rohde *et al.*, 2021). Type 2 diabetes causes more than 90% of all diabetes cases, and it is very common in developing countries that have low or medium income levels. The number of adults with diabetes in the world in the year 2025 is 589 million, according to the 2025 IDF Diabetes Atlas. It is anticipated that this figure will go up to 853 million by 2050. Even then, in developing countries, the number of diabetes cases is still going to be high mainly because over 75% of people who have diabetes are residents of such countries only (Magliano *et al.*, 2025). Often, the disease is more prevalent among certain ethnic and racial groups, such as American Indians/Alaska Natives, Asian Americans, Hispanics/Latinos, and non-Hispanic Blacks (Rodríguez & Campbell, 2017). Adding to the already complex nature of the disease is the interaction between the production, effects, and metabolism of insulin. Type 2 diabetes is characterized by the combined presence of insulin resistance as well as a deficiency in insulin production, which altogether results in the blood being loaded with excessive sugar. But it is still

not definitely clear what causes insulin resistance together with the inability of beta cells to make sufficient insulin. The prevailing idea is that several factors are simultaneously involved in the etiology (Galicia-Garcia *et al.*, 2020). The treatment of DM involves three main strategies, which are lifestyle changes, use of medication, and, if needed, surgery. The classic treatments of diabetes, such as insulin replacement therapy and metformin and sulfonylurea as examples of oral antidiabetic drugs, besides others like GLP-1 agonists and SGLT2 inhibitors, mainly have as their purpose to regulate blood sugar and relieve the symptoms of the disease; they are not designed to tackle the molecular mechanisms of the disease. The microRNAs administered via stem cell-derived exosomes can be used to treat not only diabetes but also other diseases through the targeting of these: insulin signaling, inflammation, oxidative stress, β-cell functioning, and tissue regeneration at the same time (Gieroba *et al.*, 2025). Due to their potential to target multiple molecular pathways along with minimal immunogenicity and maximum biocompatibility, they are potential candidates for the future treatment of diabetes. The desired outcomes of the treatment are to improve quality of life, prevent or postpone problems, and establish and maintain good glycemic control.

Exosomes are small extracellular vesicles that have a role in immunological control, tissue healing, cell communication, and signaling. The ability of exosomes to target particular cells and tissues is their most significant characteristic. This is because the exosome membrane contains unique surface chemicals that could come into contact with receptors on target cells. EVs are produced by many different cell types, including stem cells, and contain a variety of bioactive chemicals, including microRNAs (miRNAs) (Li *et al.*, 2022). miRNAs are short non-coding RNAs that can suppress or degrade messenger RNA to manage gene expression (O'Brien *et al.*, 2018). It has been proven that a unique set of miRNAs found in exosomes derived from stem cells may regulate a number of biological processes, such as cell differentiation, proliferation, and survival (Yuan *et al.*, 2021). Indeed, it is the unique composition of miRNAs that are contained in stem cell exosomes that makes them an extremely promising therapy for diabetes (Yang *et al.*, 2022). In addition, one should note the inherent ability of exosomes to penetrate through biological membranes, even the blood-brain barrier (Chen *et al.*, 2021).

The use of exosomes produced by stem cells as a potential therapy for type 2 diabetes is starting to be realized since it was discovered that such exosomes have the potential to not only carry drugs but also regenerate cells. In particular, exosomes derived from stem cells were found to assist the survival of beta pancreatic cells (Soltani *et al.*, 2022). It was shown that exosomes produced by stem cells of the umbilical cord could improve glucose tolerance, boost metabolism in peripheral tissues, and raise insulin sensitivity in diabetes model mice (Sharma *et al.*, 2021). Exosomes derived from mesenchymal stem cells are also found with an immunomodulatory role, in the sense that they are in control of controlling inflammation and autoimmunity, which probably can also be beneficial for type 2 diabetes. Some advantages of using exosomes from stem cells for treating type 2 diabetes include the fact that their administration presents none of the risks that exist with transplanting stem cells, including immune rejection and tumor formation. Exosomes can also be easily obtained and kept at low temperatures for a long time from other sources, such as adipose tissue, bone marrow, and umbilical cord blood (Quiñones-Vico *et al.*, 2021). Thus, exosomes derived from stem cells should be feasible to translate into a safe and efficient strategy for diabetes treatment. Since the advancements in the field of nanomedicine and regenerative biology, the application of stem cell-derived exosomal microRNAs has been identified as the next-generation drug platform, which encompasses targeting, biocompatibility, and regulation on the genetic level. While conventional drugs only act to relieve the symptoms, the use of exosomes offers the potential to regulate pathways that cause insulin resistance, β-cell malfunction, inflammation, and oxidative stress. Moreover, the small size of these particles at the nanoscale gives them more chances of crossing different biological barriers, and they are also naturally targeted at cells, which makes them excellent drug delivery tools for precision medicine, mainly with diabetes patients (Kalluri & LeBleu, 2020; Pegtel & Gould, 2019). In comparison to synthetic nano-vectors like liposomes, polymeric nanoparticles, and dendrimers, exosomes that originate from stem cells display greater biocompatibility, reduced immunogenic potential, enhanced biological stability, prolonged circulation time, and the ability to preferentially target specific cells as a natural feature. They have membrane proteins that exist naturally, which are involved in transporting molecules across the cell membrane and in the communication between and within cells; as such, they result in more targeted therapeutic effects with minimal side effects due to toxicity in normal cells. (Swain *et al.*, 2025). This paper intends to provide an extensive discussion of the therapeutic potential, mode of action, and medication options of stem cell-derived exosomal microRNAs as a novel accessible way of treating diabetes mellitus.

1.1. Isolation and Characterization of Stem Cell-Derived Exosomes

Exosomes refer to nanovesicles of around 30 to 150 nm in size, shed by different stem cells such as mesenchymal

stem cells (MSCs), adipose stem cells (ADSCs), stem cells isolated from umbilical cords, induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs). One should take into account that isolation and characterization of exosomes are very important steps not only in an experiment but also in clinical application down the line (Zhang *et al.*, 2025).

Several methods have been proposed for isolating exosomes, including differential ultracentrifugation, density gradient ultracentrifugation, ultrafiltration polymer precipitation, size exclusion chromatography, immunoaffinity isolation, and microfluidic devices. Of all these isolation techniques, differential ultracentrifugation still stands out as the most common and widely adopted due to the high degree of purity and consistency it brings (Sidhom *et al.*, 2020). Nevertheless, the technique is laborious and instrumental, while precipitation using polymers yields more material, though it is characterized by protein contamination. Size exclusion chromatography provides high purity and vesicle integrity. In recent years, microfluidic systems have proved to be promising since they offer faster processing, a small number of samples, and large-scale applications for clinical purposes. After isolation, detailed exosome characterization is required to verify the identity, purity, and biophysical characteristics of exosomes (Dilsiz, 2024). The MISEV criteria, recommended by the International Society for Extracellular Vesicles, state that exosome characterization must involve analysis of morphology, size distribution, concentration, and expression of particular proteins. Transmission electron microscopy is used to observe the typical cup-shape morphology of exosomes. Nanoparticle tracking analysis and dynamic light scattering are methods for evaluating the particle size distribution and concentration. In addition to these, the following methods are typically used to determine exosomal markers, including CD9, CD63, CD81, TSG101, and Alix, and the absence of non-exosomal markers such as calnexin and GM130: western blotting, ELISA, and flow cytometry (Kim *et al.*, 2025). The development of standardized methods of isolation and characterization is crucial to ensure replicability across studies, reduced variation between batches, and regulatory approval for clinical application. Standardization will be of immense significance in bringing exosomes derived from stem cells that contain miRNAs and which have therapeutic potential for diabetes mellitus into clinically feasible precision medicine approaches.

2. Exosomes, miRNA and Diabetes

Exosomes are derived through the inward budding of the endosomal membrane, which is therefore released upon fusion with the plasma membrane into the extracellular space. The exosomes participate in a wide array of intercellular communication, which has been shown to mediate healthy and pathological cell-to-cell signalling. On the other hand, in physiological conditions, the exosomes are relevant to the process of tissue healing, immunological control, and neural transmission. To illustrate, stem cell-derived exosomes are mainly found to be involved in the regeneration and repair of tissues by most research. Then again, immune system cell-derived exosomes are believed to regulate immune responses (Lu *et al.*, 2023).

Under pathological settings, exosomes have been linked to disease progression mechanisms of different diseases such as cancer, neurological diseases, and cardiovascular diseases. For instance, cancer cells may accelerate the migration of oncogenic molecules to recipient cells that stimulate tumour growth and metastasis. Similarly, exosomes have been demonstrated to carry pathogenic proteins in neurodegenerative conditions such as Alzheimer's and Parkinson's diseases through neuronee-to-neuronee transfer mechanisms (Soria *et al.*, 2017).

Exosomes have also been linked with diabetes development. The role of exosomes in glucose homeostasis and insulin sensitivity regulation has indeed proven to be a major function based on different studies. For instance, studies show that adipocyte exosomes are involved in the development of insulin resistance via the exosomal delivery of miRNAs that hit key players in the insulin signalling pathway (Zhou & Tan, 2020). Also, newly published studies point out a major role of the exosomes from pancreatic beta cells in the regulation of insulin secretion and glucose homeostasis (Li *et al.*, 2021a). Exemplifying exosomes released by beta cells revealed miRNAs governing insulin gene expression and secretion. Furthermore, beta cell exosomes have shown the potential to induce tolerance and dampen inflammation, important mechanisms in preventing the autoimmune system from attacking type 1 diabetes.

Exosomes are small vesicles encircled by a membrane that can be taken up by recipient cells carrying miRNAs. In exosomes, miRNA is still the most dominant form, which not only establishes a paracrine secretory system for cell-to-cell communication but also may even play a role in the development of diabetes. It has been established that exosome-delivered miRNAs can be used therapeutically to treat diabetes. According to a study, exosomal miR-126-3p may be able to improve the development and functionality of pancreatic beta cells that produce insulin. That means exosomal miR-126-3p could represent a new avenue for drug development in diabetes treatment (LaPierre & Stoffel, 2017). Additionally, studies also showed evidence that stem cell-associated exosomes from adipose tissue might be beneficial for decreasing vascular dysfunction in individuals with diabetes, as these exosomes selectively deliver miR-

126 into endothelial cells, thereby reducing disease manifestation. The use of exosomal miRNAs as therapeutic vehicles is one of the most promising techniques to handle diabetic vascular disorders (Zheng *et al.*, 2021).

The therapeutic application of exosomal miRNA-based therapeutics is a rapidly evolving area of research. Another interesting feature is the production of exosomes by stem cells because of their ability to fight inflammation and regenerate. Actually, according to the latest research, it was proved that exosomes from human-induced pluripotent stem cell-derived mesenchymal stem cells increased glucose metabolism and decreased insulin resistance among diabetic rats. Therefore, exosomal miRNAs from stem cells are a promising way to treat diabetes stem cells. Also, stem cell exosomes can be engineered to enhance their therapeutic efficacy.

A number of investigators found a few miRNAs with changed expression in plasma samples from diabetic individuals. A study presented results from 33 miRNAs that showed different levels of expression in patients with type 2 diabetes versus healthy controls. To put it clearly, miR-27a-3p and miR-140-5p are found to be down-regulated, while the expression of miR-29a-3p and miR-222-3p is up-regulated (Pandey *et al.*, 2022). Besides, the team discovered that miR-126-3p showed an opposite relationship with both BMI and HbA1c levels, which means that miR-126-3p may be a reliable marker for the detection and management of diabetes mellitus (Dorcely *et al.*, 2017).

Besides being characteristic signs of diabetes mellitus, circulating changed plasma miRNAs may also play a role in the cause of the disease. According to the study, decreasing the levels of miR-30d-5p, which is a type of microRNA found in the blood of type 2 diabetes patients, causes the pancreatic cells to secrete less glucose-induced insulin. Also, through in vivo studies, the researchers have shown that increasing the miR-30d-5p levels results in increased insulin levels, and the body's ability to handle glucose will also improve (Mao *et al.*, 2022). Furthermore, they demonstrated that enhanced miR-21-5p in the blood of patients with type 2 diabetes causes the fat cells not to respond to insulin by lowering PPAR expression levels. In this experiment, they found that blocking miR-21-5p in diabetic mice resulted in better insulin sensitivity and glucose handling in those animals (Guan *et al.*, 2020).

The pancreatic beta cells are mostly responsible for the production and release of insulin, so they are key in blood glucose level regulation. Typically, a dysfunctional or dead beta-cell causes diabetes. Only a handful of studies have linked exosomal miRNAs to beta-cell injury and death, which is one of the characteristics of diabetes. Certain teams of researchers have found the mechanism of exosomal miRNAs in the regulation of beta-cell damage in T2DM. Obese type 2 diabetic patients had much higher levels of exosomal miR-204-5p in their plasma, which is similar to that observed in media of INS-1 cells exposed to high glucose concentration. This shows exosomal miR-204-5p contributes to the mechanism of beta-cell malfunction and death in T2DM (Włodarski *et al.*, 2020).

According to another study, exosomal miRNAs can help regulate the damage in beta-cells due to gestational diabetes. Moreover, the levels of miR-146a-5p expression were significantly elevated in the conditioned media from INS-1 cells at high glucose concentrations and also in patients with gestational diabetes mellitus. However, the induction of miR-146a-5p expression in INS-1 cells results in cell death and the suppression of GSIS, an index of the proper functioning of beta cells. Conversely, the knockdown of miR-146a-5p in exosomes prevents beta-cell death and enhances GSIS in INS-1 cells. It suggests that exosomal miR-146a-5p could be a contributor to the pathogenesis of beta-cell dysfunction and death in gestational diabete.

Besides this, serum exosomal miR-21-5p turned out much upregulated not only in T1DM patients but also in the cytokine-induced MIN6 cells, a beta-cell line. Firstly, the overexpression of exosomal miR-21-5p resulted in beta-cell death and the reduction of GSIS in MIN6 cells. Still, silencing of exosomal miR-21-5p led to protection against beta-cell damage and the increase of GSIS in MIN6 cells. That means these data indicate that exosomal miR-21-5p may be a factor in the detrimental changes and death of beta cells in T1DM (Lakhter *et al.*, 2018).

In particular, the presence of miR-146a-5p in exosomes from the culture medium of INS-1 cells treated with high concentrations of glucose and in the plasma of gestational diabetes patients was significantly enhanced. However, the increase in miR-146a-5p levels in the cells was associated with beta-cell apoptosis and impaired GSIS, a measure of beta-cell performance. It was established that the miR-27a released by adipocytes through exosomes enhances insulin resistance by reducing the transcription factor responsible for glucose and lipid metabolism – PPAR. Very few studies indicate that miR-27a exosome concentration in obese people suffering from insulin resistance is significantly higher than that of normal-weight counterparts, confirming miR-27a biomarker potential for insulin resistance (Yu *et al.*, 2018). In addition to that, exosomal miR-375 is involved in insulin resistance. In addition, studies indicate that miR-375 with the exosomes represses insulin resistance and obesity caused by the high-fat diet via the control of bacterial tryptophanase (tnaA) and aryl hydrocarbon receptor genes (Kumar *et al.*, 2021). In addition, the results of the research indicated that the expression of miR-375 was highly suppressed among patients with newly developed type 2 diabetes, making it possible to apply the biomarker in the diagnosis of the disease (Patoulias, 2018).

Other than exosomal miR-27a and miR-375, there are some other miRNAs that are also associated with insulin resistance. One such example is miR-96, whose plasma exosomal concentrations in people suffering from type 2 diabetes mellitus are higher as compared to normal people. MiR-96 can make someone insulin resistant through the IRS1 gene (Wang, 2020). It was found out that adipocytes, myocytes, and hepatocytes can take up miR-29b-3p, which is able to regulate the insulin resistance associated with ageing in exosomes (Su *et al.*, 2019). As per this study, exosomal miRNAs are the mechanism that allows for the realisation of the influence of different factors on insulin resistance. According to this study, for example, human adipose-derived exosomal miRNAs can be responsible for insulin resistance by reducing GLUT4 expression (Ebrahimi *et al.*, 2019). From a mechanistic perspective, the exosomal miRNAs modulate numerous intracellular pathways that play a role in the development of diabetes. The function of miR-126 is the induction of endothelial repair through activation of the PI3K/AKT/eNOS signalling pathway and VEGF signalling. On the other hand, the function of miR-21 is the induction of insulin sensitivity by avoiding PDCD4-mediated cell death through PPAR signalling. In the same manner, miR-146a decreases inflammation through inhibition of cytokine production and oxidative stress. Finally, miR-25 regulates immune cell migration through inhibition of CXCR3 expression (Rasmi *et al.*, 2025). The findings show that the microRNAs within the exosomes derived from the stem cells are the ones controlling the signalling pathways that are linked to diabetes mellitus. The various microRNAs have different targets, which range from improving β-cell survival to enhancing insulin sensitivity (Table 1).

Table 1: List of Stem Cell-Derived Exosomal Micrornas, their Molecular Targets and Therapeutic Applications in Diabetes Mellitus

Exosomal miRNA	Molecular Target	Therapeutic Role	Reference
miR-126	VEGF, PI3K/AKT pathway	Angiogenesis and vascular repair	(Zhang *et al.*, 2020)
miR-21-5p	PDCD4, PPARα	Insulin sensitivity and β-cell protection	(Ruan *et al.*, 2011)the molecular mechanisms of β cell death and its regulation are poorly understood. Here we describe a unique regulatory pathway of β cell death that comprises micro-RNA-21, its target tumor suppressor PDCD4, and its upstream transcriptional activator nuclear factor-κB (NF-κB
miR-146a-5p	NF-κB signaling	Anti-inflammatory effects	(Li *et al.*, 2023)
miR-25	CXCR3	Prevention of autoimmune β-cell destruction	(Zhou *et al.*, 2025)
miR-203a-3p	SOCS3	Diabetic wound healing	(Yang *et al.*, 2023)and microRNAs (miRNAs
miR-142-5p	IGF1/VEGF	Diabetic retinopathy management	(Liu *et al.*, 2020)
miR-17-3p	STAT1	Reduction of oxidative stress	(Xu *et al.*, 2018)

3. Application of Stem Cell-Derived Exosomal microRNAs in Diabetes

Exosomal microRNAs derived from stem cells have a completely new approach to change the idea of using cells for therapies to the idea of using cells for regeneration without cells in the area of diabetes. Although the transplantation of stem cells is proven to be effective, its use in the clinic is hindered by a number of issues such as immune rejection, the possibility of tumor formation, and ethical concerns. Then again, exosomes that come from stem cells have the therapeutic materials of the parent cells and, at the same time, do not have the risks originating from the cells, so they are a safer and more scalable option. Note that the effectiveness of the therapy with these exosomes is mainly because of their microRNA content that can affect different signaling pathways at the same time, like the insulin signaling pathway, the inflammatory cascades, the oxidative stress pathways, and angiogenesis. The ability to target multiple things at the same time is really a great thing in diabetes, which is a disease with a lot of different metabolic problems. A summary of key studies highlighting the therapeutic potential of stem cell-derived exosomal microRNAs in diabetes and its associated complications is presented in Table 2.

Table 2: A Few Remarkable Studies Demonstrating the Efficacy of Stem Cell-Derived Exosomal miRNA in Diabetes

Types of Stem Cells	Component (Type of MicroRNA)	Types of Models/Cell Lines Used	Biological Function/Outcomes	Reference
Human umbilical cord mesenchymal	micro RNA-17-3p	Diabetic Retinopathic mice	The gene of interest for MicroRNA-17-3p was determined to be STAT1. In accordance with the results, injecting miR-17-3p reduced blood sugar levels, increased body weight and haemoglobin levels, reduced oxidative damage, and stopped retinal cell loss in DR mice via suppressing STAT1.	(Li *et al.*, 2021c)
Mesenchymal	micro RNA-21-5p	Diabetes mellitus (DM) Erectile dysfunction (ED) rats	Rats with ED and DM recovered as a result of the down-regulation of programmed cell death (PDCD4) and the blocking of CCSMC programmed cell death, which was accomplished by the transfer of miR-21-5p to Corpus cavernosum smooth muscle cells.	(Huo *et al.*, 2020)
Human adipose	micro RNA-21-5p	HaCaT cell line & Diabetic rats	By promoting re-epithelialization, collagen remodelling, angiogenesis, and vascular maturation in rats and stimulating keratinocyte proliferation and dissemination via Wnt/-catenin signalling, E-exos accelerated the closure of diabetic wounds.	(Lv *et al.*, 2020)
Bone marrow mesenchymal	micro RNA-486-3p	Diabetic Retinopathic mice	Toll Like Receptor 4 was a gene of interest for miR-486-3p. Recovering miR-486-3 improved the effects of exosome therapy whereas activating TLR4 reversed it.	(Li *et al.*, 2021b)
Bone marrow mesenchymal stem cells	Micro RNA-133b-3p	Diabetic Retinopathic mice	Inhibiting FBN1 or exosomes from BMSCs, or the upregulation of miR-133b-3p, decreased oxidative stress angiogenesis proliferation, and movement, and promoted apoptosis in mouse retinal endothelial cells treated with high glucose (HG). That means, miR-133b-3p through FBN1 downregulation can reduce angiogenesis and oxidative stress in diabetic retinopathy (DR).	(Liang *et al.*, 2022)
Adipose mesenchymal stem cells	Micro RNA-26a-5p	Mouse glomerular podocytes and MP5 cells	The pathological symptoms of diabetic neuropathy (DN) were examined in relation to the delivery of miR-26a-5p by EVs generated from adipose-derived mesenchymal stem cells (ADSCs). Multiple clinical symptoms indicative of DN were mitigated by miR-26a-5p delivery. EVs also inhibited the high glucose-induced apoptosis of MP5 cells as demonstrated by an upsurge in Bcl-2 and lessening in Bax, cleaved caspase-3 and caspase-3.	(Duan *et al.*, 2020)
Bone marrow mesenchymal stem cells	Micro RNA-221, Micro RNA-423, Micro RNA-1268a	Diabetic mice	One of the significantly expressed miRNAs in diabetic BMSCs-Exos, miR-221, shown in vivo capacities to decrease osteogenesis and promote adipogenesis. Increased levels of miR-221 in healthy BMSCs-Exos decrease the ability to control adipogenesis and osteogenesis. Intriguingly, administration of normal BMSCs-Exos exclusively to BMSCs via the aptamer delivery system increased bone mass, decreased marrow fat buildup, and stimulated bone regrowth in diabetic mice.	(Han *et al.*, 2023)
Umbilical cord mesenchymal stem cells	microRNA-135b-5p and PF-127	Diabetic rat model	Exosome-hydrogel conjugates facilitated the development of the epidermis, decreased the duration of wound healing, and enhanced the formation of hair follicles	(Yang, 2020)

Zhang *et al. (2021) demonstrated* that exosomes discharged by ADSCs exhibit beneficial properties of holding parentally advantageous elements and displaying non-immunogenic, non-carcinogenic, and substantial stability attributes. Lentiviral vectors were employed to transfect ADSCs with genes, allowing for the stable production of significant amounts of exosomes produced from ADSCs. In vivo transplantation of the G-ADSC-Exos enormously enhanced blood circulation, muscular strength, and microvessel count in the ischemic hindlimbs in a T2DM mice model with simple low ligation of the femoral artery. So, stem cells obtained from adipose tissues are known to promote revascularization of different areas of the heart in diabetic mice. But a few limitations still exist, despite successful preclinical results. Firstly, the majority of experiments were conducted only on small animals. Secondly, even the isolation methods, characterization, and dosing regimens of exosomes vary greatly, leading to significant differences in the results. Due to the nature of what exists within exosomes being dependent on the origin of the stem cell from which they originate, replicating the findings becomes difficult. This is the reason why standardization and clinical validation are necessary processes for this research to reach its full potential (Zhang *et al*., 2021).

Additionally, there is further research concerning the ability of exosomes from epidermal stem cells to promote M2 macrophage polarization to enhance diabetic wound healing via the miR-203a-3p/SOCS3 pathway. In other words, the researchers showed that a high concentration of miR-203a-3p within exosomes from epidermal stem cells can positively influence diabetic wound healing through enhanced M2 macrophage polarization owing to the suppression of SOCS3. Nevertheless, these findings provide a new perspective for addressing difficulties associated with diabetic wounds. Key findings of this study include the ability of the miRNA-203a-3p molecule, which is highly abundant in epidermal stem cell-derived exosomes (EpiSC-EXOs), to induce the activation of the JAK2/STAT3 pathway, leading to conversion of macrophages from the pro-inflammatory M1 type to the M2 subtype of macrophages, along with the generation of anti-inflammatory cytokines, to heal diabetic wounds by lowering the expression of SOCS3 in macrophages (Yang *et al*., 2023).

Liu *et al. (2020) recently* investigated the impact of microRNA-142-5p on the onset of diabetic retinopathy, which is associated with damage due to diabetes to small blood vessels, resulting in impairment of retina function and the development of new blood vessels. To induce diabetes, the authors used streptozotocin to create rat models and treated human retinal endothelial cells with a high glucose level. The next stage involved HRECs treated with high glucose and was performed for the examination of the influence of miR-142-5p on cell growth. Indeed, it should be noted that it was established that the effect of the high glucose environment on the expression level of miR-142-5p could nearly fully be restored by means of treatment with miR-142-5p as opposed to the miR-NC group (Figure 1A). VEGF expression level was analyzed by qRT-PCR, showing an increase in the presence of VEGF in high glucose conditions. In addition, an increased amount of miR-142-5p decreased VEGF expression (Figure 1B). In contrast, the analysis using the proliferation test of cells via the CCK-8 assay demonstrated a significantly lower cell viability when miR-142-5p was overexpressed as compared to controls under HG (Figure 1C). Immunofluorescence staining showed that the content of Ki-67, which marks the degree of proliferation, was extremely elevated in the high glucose-treated group of cells, showing a higher rate of proliferation, but it was strongly decreased when cells were exposed to miR-142-5p (Figure 1D). In addition to this, upregulated miR-142-5p and downregulated IGF1 are involved in this signal transduction and have decreased effects of retinal injury in the body. Also, the miR-142-5p/IGF1/VEGF signaling pathway is deeply engaged in the pathogenesis of DR, and increased expression of miR-142-5p may well be an effective treatment against DR (Liu *et al*., 2020).

Zhou *et al*. (2025) also stated that mesenchymal stem cell-derived exosomes with a high miR-25 content are capable of inhibiting T-cell migration, leading to the destruction of T1DM via autoimmunity. Chemokine receptor CXCR3 is seen as one of the key factors that supports the migration of T lymphocytes to pancreatic islet cells, resulting in the cells that produce insulin being destroyed in the body during the development of T1DM. Several research studies demonstrated that microRNA (miR)-25-rich mesenchymal stem cell (MSC)-exosomes were responsible for the down-regulation of CXCR3 in T cells.

In this way, lesser availability of CXCR3 receptors limits T cells' ability to perceive the site of an inflammatory reaction. The number of immune cells coming into the pancreatic islets gets reduced, and so inflammation gets suppressed. Interestingly, beta cells are in fact untouched by these mechanisms. When animals with diabetes received treatment with such exosomes, they showed a significant decrease in their blood glucose levels and, in addition, had better pancreas health. Blocking the action of miR-25 caused all beneficial effects to disappear and highlighted once more the significance of this particular molecule (Zhou *et al*., 2025).

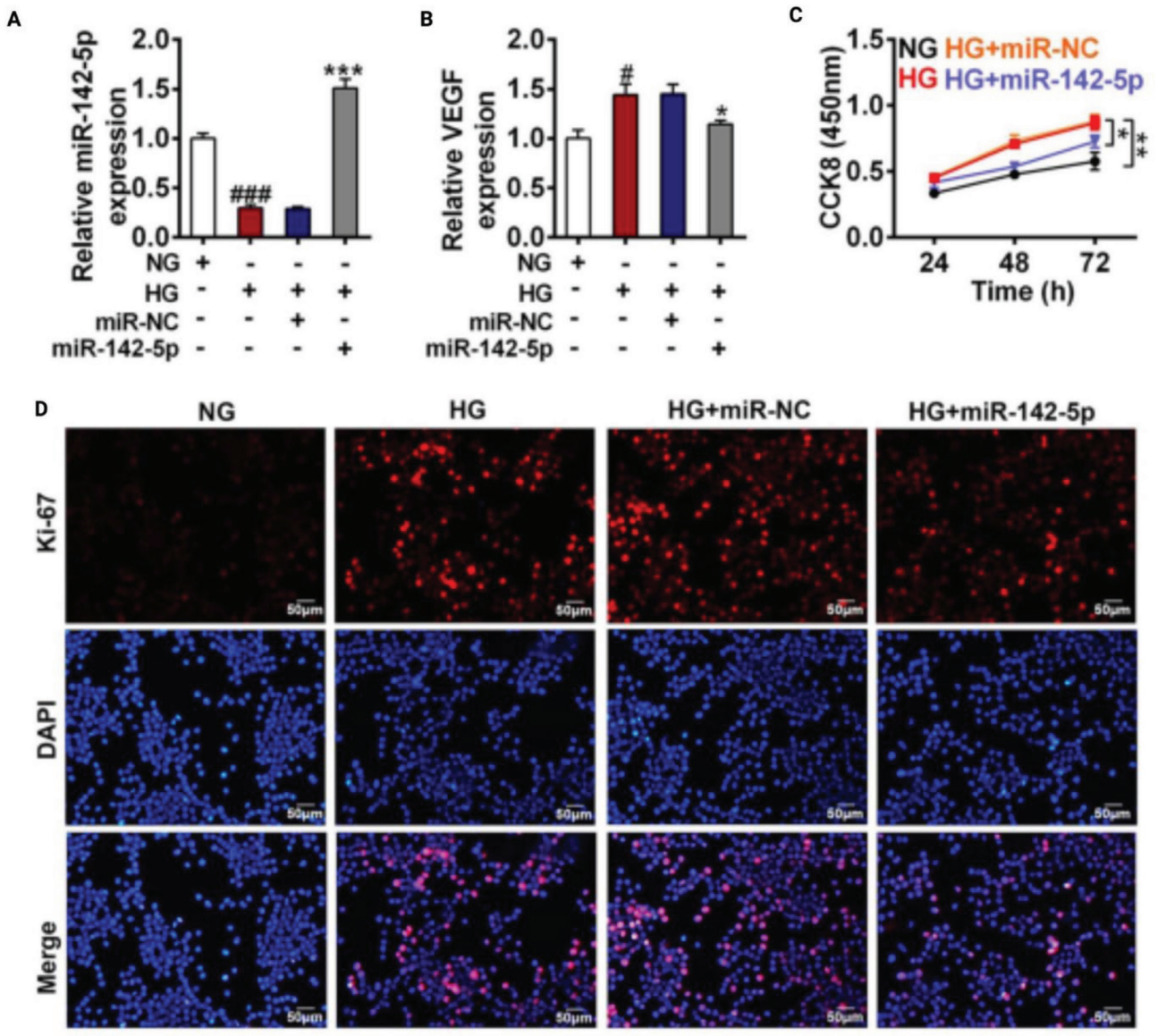

Figure 1: (A and B) The influence of miR-142-5p mimics on miR-142-5p and VEGF levels was measured by qRT-PCR upon HG treatment. (C) Effects of miR-142-5p overexpression on the HRECs' viability were evaluated by CCK8 under HG conditions. (D) Effects of miR-142-5p mimic on the Ki-67 staining were assessed by IF assay insult to HG treatment. Reprinted from Liu *et al.* (2020) under open access license.

4. Future Perspectives and Clinical Translation

The development of microRNAs in exosomes from stem cells has brought about new paths for personalized medicine in the treatment of diabetes. Even though there is hopeful evidence from preclinical studies, the effective clinical application of this technique is dependent on solutions to various scientific, technological, and regulatory hurdles. One significant future direction of great relevance is the redesign of exosomes to increase their therapeutic potential. Approaches such as genetically altering parent stem cells, improving the efficacy of cargo delivery, and decorating the surface of exosomes are the main focus of research to gain higher targeting specificity biological activity. Engineered exosomes have demonstrated much greater regenerative and anti-inflammatory potential. Mostly in diabetic conditions like chronic wounds and vascular impairments. Another major focus of present research is the combination of exosomes with advanced biomaterial-based delivery systems, e.g., hydrogels and nanoscaffolds. These systems offer the possibility of controlled release and delivery of exosomal cargo to the site, which results in getting more retention at the

target site and, thus, improves therapeutic effects. Actually, studies now show that treatments based on exosomes greatly stimulate angiogenesis, the growth of fibroblasts, and remodeling of the extracellular matrix, thereby causing diabetic wounds to heal at a quicker pace with tissue regeneration (Jin *et al.*, 2025).

Personalized therapy with exosome technology has gained huge traction recently. One individual's exosome can reveal a completely different microRNA profile from another person's, so the differences in these microRNAs can actually be very informative. They reflect the person's metabolism, diabetes risk, or existing disease state. In fact, clinical findings support the idea that some exosomal microRNAs are related to curing diabetes or preventing the progression of diabetes by regulating glucose and insulin. Because of this, this tailor-made treatment is also highly effective, as it can help reach precisely those areas that need it, like pancreatic β-cells, the liver's fat tissue, and the blood vessel's lining. So, the healing effect can be dramatically strengthened, and the adverse reactions can be minimized (Wang *et al.*, 2025). Researchers have found that miRNAs present in the exosomes can influence important pathways that are essential for metabolic diseases like insulin resistance and inflammation. Furthermore, the exosomes derived from stem cells not only promote the viability of β-cells but also increase insulin sensitivity. In other words, they are an excellent means of turning disease around rather than simply alleviating symptoms (Li *et al.*, 2024). Beyond these benefits, the issues of standardization and scaling up are still major obstacles for the clinical use of these technologies. One major reason for the poor repeatability between the studies is the use of different exosome separation methods, their unloading/expression, and dose forms. To enhance the performance, purity, and consistency of the exosomal preparations, scientists are looking into additional approaches, for example, size-exclusion chromatography and microfluidics. Besides, treatment validation and approval for human use necessitate several well-controlled and thorough in vivo and clinical investigations. It is also very important to consider safety and legal aspects. Exosomes are better tolerated by the human body than synthetic delivery platforms and can hardly elicit an immune response. Though long-term studies are required to determine their biodistribution, possible side effects, and effects on non-target cells. Presently, the lack of uniformity in the regulatory systems for exosome-based therapies is a significant barrier to their introduction into the market. Moreover, the translation of stem cell-derived exosome therapy into the clinic is impeded by various factors, such as individual variability between donors, differences in cargo content of the exosomes according to the stem cells they originate from, low yield of the products, and lack of standardized quality control criteria. Further questions arise with respect to stability of the product over time, reproducibility between production batches, and appropriate dosage regimes. The resolution of these problems is crucial for the translation of the therapy into practice.

In addition, microRNAs in exosomes derived from stem cells are a revolutionary means for diabetes treatment, as they combine the features of regenerative medicine and nanotechnology. Their capacity to influence complicated molecular mechanisms together with native targeting features and low toxicity make them viable options for future diabetes therapies (Zhang *et al.*, 2024). Still, for these therapies to make a successful transition from research labs to clinical practice, they should break down barriers in engineering standardization and scalability and meet regulatory requirements. It is highly expected that more interdisciplinary investigations will harness their capability in tailoring medicine for diabetes, leading to the complete realization of their potential.

5. Challenges Involved in Delivery of miRNAs

The number of medicines developed on a microRNA (miRNA) basis against diabetes mellitus has been increasing. Though their administration in the clinical environment still encounters many problems. One of the biggest problems is the instability of miRNAs under physiological conditions, as naked miRNAs can be very easily and rapidly degraded by the body's own ribonucleases present in the blood and tissues. This leads to a very short circulation half-life, the time during which miRNAs are active in the body (Diener *et al.*, 2022; Rupaimoole & Slack, 2017). Besides, miRNAs are small, negatively charged, and hydrophilic molecules, which a lot limits their capability of passing through the lipophilic cellular membrane. This causes poor cellular uptake when no proper delivery systems are used (Chen *et al.*, 2015).

Another big problem this field faces is that the existing miRNA therapeutics cannot be delivered to a specific tissue or cell, and this is very much needed for the treatment of diabetes, where miRNAs should selectively target pancreatic cells, liver, skeletal muscle, adipose tissue, or vascular endothelium to bring about the desired therapeutic effects (Guay & Regazzi, 2013). Non-specific microRNA distribution can silence genes unintentionally, and in return, it may cause unexpected changes in metabolism. The thing that makes this problem even more challenging is that in reality microRNAs have the property that a single microRNA may regulate several target genes and signalling pathways simultaneously. This way, the risk of modulating complicated gene networks involved in insulin signalling, glucose balance, lipid metabolism, and inflammatory

responses is even increased (Rottiers & Näär, 2012). Immune system activation is another important issue in delivering miRNA effectively. The miRNAs given from outside or their carriers can be recognised as alien to the body, and this way activates the body's immune system, which results in an immune response through toll-like receptors and the release of proinflammatory cytokines (Chakraborty *et al.*, 2020).

One of the primary concerns in the field is the toxicity of the delivery carriers, such as cationic lipids, polymers, and inorganic nanoparticles, which are frequently utilised for miRNA therapy. Because diabetes is a chronic illness that requires ongoing care, this is primarily concerning. Repeated administration of these carriers can cause cumulative toxicity, lower biocompatibility, and result in poor patient compliance. Besides this, due to the fast clearance and short time activity of miRNAs, optimum dosing and sustained therapeutic effects are still a challenge which require the frequent dosing schedule (Rupaimoole & Slack, 2017). Also, pathological consequences related to diabetes such as poor blood vessel formation, oxidative stress, thickening of the extracellular matrix, and diminished blood flow contribute to the failure of miRNA-loaded systems to efficiently reach and penetrate the target tissues. Besides, issues on large production, batch-to-batch consistency, shelf-life stability, and the absence of uniform regulatory guidelines for miRNA-based therapies continue to hinder their progression from preclinical studies to clinical treatments. Of all delivery systems, exosomes stand out because they are of natural origin and have an inherent ability to target specific cells. But problems related to large-scale production, cargo loading capabilities, and regulatory harmonisation are still major hurdles that should be overcome for exosomes to be translated into clinical settings.

6. Conclusion

Exosomal microRNAs from stem cells are revolutionising therapeutics for diabetes mellitus and stand to take the place of symptom-control-oriented therapies with precision- and disease-modifying-based ones. Bringing together the principles of regenerative medicine, nanotechnology, and molecular biology, these nanoscale vesicles have this exceptional benefit due to their natural biocompatibility, ability to deliver the drugs selectively, and capacity to regulate complex gene networks involved in insulin resistance, β-cell dysfunction, inflammation, and oxidative stress. Our review of the topic reveals that exosomal miRNAs are excellent non-invasive biomarkers to detect the disease early and to make the prognosis. Besides, they can be considered highly potent therapeutic agents that help in bringing back metabolic balance and in preventing the complications of diabetes. Their diverse functions include the promotion of angiogenesis, the enhancement of β-cell survival, the increase of insulin sensitivity, and the modulation of immune responses, which interestingly suggests their supremacy over the standard drug-based treatment methods. Many promising discoveries have been made so far, but the field is still at the edge of clinical translation due to problems related to the standardisation of methods for exosome isolation, production at large scale, cargo heterogeneity, and various regulatory aspects. For the technique to be reliable and repeatable, a more thorough understanding of the molecular pathways and long-term safety issues with clinical practice is essential. The complete therapeutic spectrum of exosomal miRNAs will be revealed in the future through the synergistic impacts of advanced engineering techniques, biomaterial-assisted delivery vehicles, and patient-specific medications. Stem cell-derived exosomal microRNAs, through cross-disciplinary research and technological breakthroughs, strive to change the very notion of therapy for diabetes, leading to finely tuned, highly potent, and patient-specific means of treatment which will have a very positive impact on health across the globe. Although there have been considerable developments in the field, there are still major gaps in knowledge about biodistribution of exosomes, proper dosing regimens, scaling up the manufacturing process, safety, and proper isolation processes. Future research in this area should concentrate on engineering exosomes with better targeting abilities, biomaterial-based delivery methods, and multicentric clinical trials to enable the bench-to-bedside transition.

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Authorship Contribution

Garima and Ritamay Sau have contributed to the work through the process of conceptualization, data curation, investigation, and writing-original draft. Neeraj Mittal has contributed to the validation, formal analysis, and project administration of the manuscript for editing purposes. Meenakshi Dhanawat has contributed to the validation and conceptualization. Pramila Chaubey has contributed to the work through the process of conceptualization and data curation.

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Declarations

The authors confirm that this manuscript is original, has not been published previously, and is not under consideration for publication elsewhere. The final version of the manuscript has been approved by all authors.

Conflict of Interest

The authors declare that there is no conflict of interest regarding this manuscript.

Data Availability Statement

Data sharing is not applicable to this article, as no new data was generated or analyzed.

Human and Animal Rights

No animals or human participants were involved in this study.

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The authors declare that artificial intelligence (AI)-assisted tools were used solely for language enhancement, grammar checking, and improving the readability of the manuscript.

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