

Exosomes as Promising Nanostructures in Diabetes Mellitus: From Insulin Sensitivity to Ameliorating Diabetic Complications

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Abstract: Diabetes mellitus (DM) is among the chronic metabolic disorders that its incidence rate has shown an increase in developed and wealthy countries due to lifestyle and obesity. The treatment of DM has always been of interest, and significant effort has been made in this field. Exosomes belong to extracellular vesicles with nanosized features (30–150 nm) that are involved in cell-to-cell communication and preserving homeostasis. The function of exosomes is different based on their cargo, and they may contain lipids, proteins, and nucleic acids. The present review focuses on the application of exosomes in the treatment of DM; both glucose and lipid levels are significantly affected by exosomes, and these nanostructures enhance lipid metabolism and decrease its deposition. Furthermore, exosomes promote glucose metabolism and affect the level of glycolytic enzymes and glucose transporters in DM. Type I DM results from the destruction of β cells in the pancreas, and exosomes can be employed to ameliorate apoptosis and endoplasmic reticulum (ER) stress in these cells. The exosomes have dual functions in mediating insulin resistance/sensitivity, and M1 macrophage-derived exosomes inhibit insulin secretion. The exosomes may contain miRNAs, and by transferring among cells, they can regulate various molecular pathways such as AMPK, PI3K/Akt, and β -catenin to affect DM progression. Noteworthy, exosomes are present in different body fluids such as blood circulation, and they can be employed as biomarkers for the diagnosis of diabetic patients. Future studies should focus on engineering exosomes derived from sources such as mesenchymal stem cells to treat DM as a novel strategy.

Keywords: diabetes mellitus, insulin resistance, exosome, glucose uptake, lipid metabolism

Introduction

The discovery of exosomes returns to the 1980s, when they were considered debris secreted by reticulocytes.^{1,2} These vesicles with endosomal origin were extensively examined, until ten years after their emergence that, Raposo et al found that exosomes have an antigen-presenting role and they can stimulate T cell response. These exosomes were derived from Epstein-Barr-transformed B lymphocytes.^{3,4} Then, more investigation was directed towards exosomes until their biological functions in cell-to-cell communication were realized. Overall, mammalian cells secrete three distinct kinds of extracellular vesicles (EVs), including exosomes, microvesicles, and apoptotic vesicles among which exosomes are the most well-known and largely investigated ones.⁵ EVs differ in their secretion process, molecular content, and biological functions.⁶ The apoptotic bodies are generated as post-apoptotic remnants of parent cells. The microvesicles emanate from blebbing of cell membrane, and they may contain cytosol parts. The main pathway for the formation of exosomes is endocytosis, and exosomes are vital for preserving homeostasis in cells.⁷ The multivesicular bodies (MVBs) are

considered as the origin of exosomes, and they have a cup shape with particle size of 50 to 150 nm (average size of 100 nm).^{8,9} In 2018, Zhang et al discovered two subcategories of exosomes, including large exosome vesicles (90–120 nm in size) and small exosome vesicles (60–80 nm in size).^{10,11}

After the release from cells, exosomes can transfer various cargoes among cells, and there are proteins on the surface of exosomes that mediate their interaction with receptors available on the surface of target cells.^{12,13} Lipids, proteins, and nucleic acids can be found in exosomes. Cholesterol, sphingomyelin, hexosylceramids, phosphatidylserine, and fatty acids are among the lipid particles that can be found in exosomes.¹⁴ The proteins include endosomal, plasma, cytosolic, and nuclear proteins.¹⁵ It is worth mentioning that two kinds of proteins are found in exosomes. The first category of proteins is related to those involved in membrane transport and fusion, including Rab GTPases and annexins. Other proteins can participate in the biogenesis of exosomes, including ESCRT complex, ALIX, and TSG101. However, there are other proteins in exosomes, including heat shock proteins (HSPs), integrins and tetraspanins, and MHC proteins.^{14,16–20} As it was mentioned, exosomes can also transfer nucleic acids among cells. Based on experiments, microRNA (miRNA) and messenger RNA (mRNA) are present in exosomes.^{21–23} Besides, other kinds of RNA molecules, including lncRNAs, circRNAs, viral RNA, and transfer RNA (tRNA) can be enriched in exosomes.^{23–25}

With respect to the role of exosomes in cell-cell communication and maintaining homeostasis, the present review was dedicated to investigating exosome function in diabetes mellitus (DM). For this purpose, we first discuss exosome biogenesis, isolation, and its role in various diseases to prepare readers for other sections of the manuscript. Then, we briefly describe DM, complications, treatments, and challenges. Next, we specifically discuss the role of exosomes in affecting glucose and lipid metabolism in DM, insulin delivery, affecting β -cell function and gene delivery. Such topics will shed more light on the role of exosomes in the effective treatment of DM and pave the way for translating pre-clinical findings to clinical courses. This overview is different from previously published articles provides a unique and new outline about the role of exosomes in DM.^{26–36}

Exosomes and Diseases

Based on previous statements in the introduction, exosomes are nanostructures (30–150 nm) and can function as communicators among cells.³⁷ The biogenesis of exosomes is still controversial, and despite significant research in this area, this mechanism has not been completely understood yet. The exosome biogenesis begins with the generation of intraluminal vesicles (ILVs) resulting from the elimination of plasma membrane due to inward budding into cells. Therefore, lipid raft domains of plasma membrane can produce endocytic vesicles, which happens very fast, leading to the formation of early endosomes.^{38–43} The destination of early endosomes is completely different based on cargo. For instance, if the aim is to degrade cargo, multivesicular bodies can fuse with lysosomes.^{44–46} Then, maturation of early endosome to late endosome occurs that is accompanied by accumulation of ILVs in multivesicular bodies.^{44,47} Then, multivesicular bodies fuse with the cell membrane to release ILVs as exosomes to extracellular space.^{44,45,47–49} Different kinds of proteins are involved in the process of exosomes formation. Two major kinds of proteins are SNARE and ESCRT proteins. Although reducing ESCRT levels decreases exosome production, it does not completely interfere with exosome formation, showing that exosomes also depend on other proteins for their biogenesis, known as ESCRT-independent mechanisms.^{50,51} The lipids and GTPase are involved in exosome generation from membrane deformation, fission, and fusion.⁵² ALIX, HSPs, and SNAREs participate in exosome formation.^{53–55} Furthermore, the Golgi apparatus transforms the early endosome to late endosome.⁵⁶ Figure 1 demonstrates the biogenesis route of exosomes in cells. Table 1 also summarizes various techniques applied in isolation of exosomes.

Exosomes and their function in various diseases have been identified; for instance, in carcinogenesis, the function of exosomes has been investigated in depth. The exosomes containing circ-0000069 function as tumor-promoting factors and mediate the malignant transformation of pancreatic tumor cells via promoting the expression level of STIL.⁶⁴ Notably, tumor cells also secrete exosomes to promote migration. For instance, a recent experiment has shown the role of exosomes derived from colon cancer cells in increasing migration and invasion of SW480 cells via inducing the Akt/mTOR axis.⁶⁵ The cancer-associated fibroblasts available in the tumor microenvironment can secrete exosomes to down-regulate miRNA-142-5p expression and increase PD-L1 expression in elevating lung tumor progression.⁶⁶ In neurological diseases, such as Alzheimer's disease, exosomes can prevent the accumulation of amyloid-beta (A β) plaques and

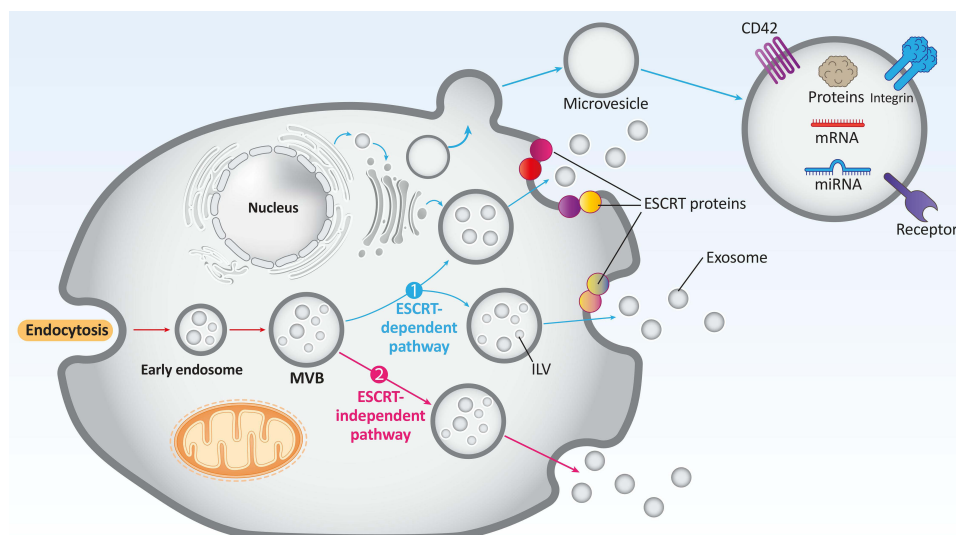


Figure 1 The biogenesis and secretion of exosomes in cells. The biogenesis of exosomes is started from the endocytic pathway. After the formation of early endosomes, they are transformed into multivesicular bodies, followed by two pathways, including ESCRT-dependent and -independent mechanisms, for further processing of exosomes and their secretion. Then exosomes can affect targeted cell based on their cargo that can be proteins, lipids, and nucleic acids.

improve cognitive function by inducing the S1P/SphK axis.⁶⁷ Interestingly, exosomes can deliver therapeutic agents in Alzheimer's disease therapy. The exosomes containing quercetin prevent phosphorylation of tau proteins and reduce levels of neurofibrillary tangles in the treatment of Alzheimer's disease.⁶⁸ In inflammatory bowel disease, exosomes can improve epithelial regeneration and induce repair of the intestinal barrier with TSG-6 overexpression.^{69,70} Based on these studies, exosomes function as therapeutic agents in various diseases, and this review focuses on DM therapy.

Diabetes Mellitus

DM is a metabolic disease that alters the metabolism of proteins, fats, and carbohydrates.^{71–73} The incidence rate of DM seems to be increasing in different timelines. In 2019, the global prevalence of DM was 9.3%; it appears to be 10.2% in 2030 and higher in 2045 (10.9%). Interestingly, the incidence rate of DM is different in urban and rural areas. Based on estimates, the prevalence of DM is 10.8% in urban areas, while it is 7.2% in rural areas. Furthermore, DM is more common in wealthy countries compared to low-income countries that are 10.4% and 4%, respectively.^{74,75} The incidence rate of DM is more common in the USA, India, and China than other countries in the world.⁷⁶ Various factors can lead to DM development, including lack of insulin secretion, β cell inability to secrete insulin, and reduced insulin distribution in

Table 1 Various Techniques Applied in Isolation of Exosomes

Technique	Remarks	Refs
Ultracentrifugation	-This mechanism isolates exosomes based on size and density -Its benefits are affordability and is considered as a gold option -Low purity is the main disadvantage	[57–63]
Size-based isolation techniques	-This technique isolates exosomes based on their size and molecular weight -It is fast, convenient, and provides high yield -Complex process and the possibility of pore blockage are disadvantages	
Co-precipitation	-A polymer-based technique that employed commercial kits for exosome isolation. -Its advantages are fast procedure and easy to perform. -The disadvantages are low quality of kits and high expenses.	
Immunoaffinity enrichment	-This technique uses immunoaffinity for isolating exosomes - It is expensive to perform, but its benefit is the high purity	

peripheral regions. Type I DM (T1DM) and type II DM (T2DM) are the most common kinds of DM observed in patients in clinical courses.^{77–79} The T1DM is an autoimmune disease in which the immune system inappropriately affects β cells in the pancreas and removes their insulin secretion capacity and decreases serum glucose levels. The treatment of T1DM seems to be vital, and lack of management can lead to severe complications. The T1DM is the most common type in which there is insulin secretion from β cells. However, cells do not respond to insulin, and hyperglycemia occurs. The occurrence of T1DM is more common in obese patients.⁸⁰ Another kind of DM, known as gestational DM, happens in pregnant women and causes a significant decrease in sensitivity to insulin.⁸¹ The exact reason for DM development has not been completely understood. There are a variety of assumptions and experiments to find underlying causes of DM development.⁸² Environmental factors such as malfunction, lack of exercise, infections, and toxins can result in DM development. Genetic alterations and family history of DM are other causes of DM development.^{83,84} The genomic experiments have revealed the role of different gene loci in DM, and most of these genes demonstrate expression in β cells of the pancreas and modulate the response of these cells to apoptosis, inflammation, and immune system.^{85–87}

Various therapeutics have been utilized to treat DM, and each of them has its own advantages and disadvantages. Plant derived-natural products have been used for the treatment of DM due to their capacity in ameliorating diabetic complications. Curcumin is a phytochemical with different pharmacological activities, including antioxidant, anti-inflammatory, and anti-diabetes, among others.^{88–95} Curcumin administration ameliorates apoptosis and oxidative damage in cardiomyocytes during DM, and for this purpose, curcumin induces PI3K/Akt and SIRT1/FOX1 pathways.⁹⁶ Clinical trials demonstrated the role of curcumin in decreasing oxidative stress and inflammation scores in diabetic patients.⁹⁷ Quercetin is another phytochemical that its administration seems to be beneficial in the treatment of different diseases such as Cancer, diabetes, and Cardiovascular diseases.^{98–102} Quercetin induces AMPK signaling to increase SIRT1 expression in inhibiting NF- κ B signaling that is correlated with a decrease in oxidative stress and inflammation and subsequent prevention of DM-mediated atherosclerosis.¹⁰³ Furthermore, a combination of quercetin and vitamin E prevents mitochondrial dysfunction and inhibits apoptosis to alleviate testicular damage in DM.¹⁰⁴ Resveratrol is also a non-flavonoid polyphenol that can decrease oxidative damage and inflammation, and its administration is promising in treating neurological diseases and diabetes.^{105–110} Resveratrol can prevent infertility during diabetes¹¹¹ and its co-administration with dapagliflozin as an antidiabetic agent promotes capacity in lowering glucose levels.¹¹² The nucleic acid-based drugs, including small interfering RNA (siRNA) and short hairpin RNA (shRNA) are utilized in DM therapy. The down-regulation of Cyp4a14 and P2X7 by siRNA ameliorates diabetic nephropathy.^{113,114} Furthermore, CTGF and P2Y12 down-regulation by shRNA ameliorates retinopathy and prevents inflammation in DM treatment.^{115,116} However, these therapeutics have some problems such as poor bioavailability of drugs and degradation of siRNA in serum that for improving their efficacy, application of nanostructures is recommended.^{89,117–120} Noteworthy, recent experiments have focused on using nanostructures in DM treatment. The *Cyperus rotundus*-loaded zinc oxide nanostructures were capable of decreasing inflammation via NLRP3 down-regulation to ameliorate diabetic retinopathy.¹²¹ The empagliflozin is an antidiabetic agent that can be delivered by nanostructures, which in turn enhances its ability to alleviate inflammation and oxidative stress in diabetic neuropathy.¹²² The chitosan-based nanoparticles also deliver metformin for reducing glucose levels.¹²³ The nanoparticles can provide sustained release of drugs in DM treatment.^{124,125} Hence, the application of nanoparticles appears to be promising in DM therapy, and therefore in the next sections, we focus on exosomes as nanostructures in DM treatment.

Exosomes, Glucose, and Lipid Metabolism

The metabolism and uptake of glucose undergo some abnormal alterations in DM. The glucose metabolism significantly decreases in DM and leads to hyperglycemia.¹²⁶ The polymorphism in genes related to glucose metabolism, including OCT3 and GCK, has been reported in T1DM.¹²⁷ The ghrelin system participates in enhancing glucose metabolism in the treatment of T1DM, and hyperbaric oxygen can affect the ghrelin system, which affects glucose metabolism.¹²⁸ The clinical trials on DM patients have shown a potential role for GLP-1 in improving glycemia.¹²⁹ Therefore, studies have focused on glucose metabolism levels in DM.¹³⁰ The deposition of lipid significantly increases in DM patients, making them prone to the development of other diseases such as non-alcoholic fatty liver disease.¹³¹ Enhancing lipid metabolism

by *cola nitida* is beneficial in alleviating hepatic injury in TIIDM.¹³² Thus, this section focuses on exosome functions in affecting lipid and glucose metabolism to pave the way for the treatment of DM patients.

As mentioned before, obesity is one of the factors responsible for insulin resistance and DM development. A recent experiment has focused on the role of exosomes in high-fat diet (HFD) mice. The exosomes were derived from brown adipose tissue, and they could diminish serum glucose levels and body weight. Furthermore, these exosomes decreased lipid deposition in HFD mice. Exosomes promoted oxygen consumption in cells and improved cardiac function. These exosomes were enriched in mitochondrial components and stimulated catalytic mechanisms. Hence, they are promising agents in improving glucose and lipid metabolism and uptake in HFD mice as well as preventing the development of related diseases, including DM.¹³³ On the other hand, based on the cargo of exosomes, they can negatively affect glucose metabolism. High glucose levels induce exosome secretion from macrophages, and miRNA-210 was enriched in these exosomes. For instance, the miRNA-210-enriched exosomes interfere with glucose uptake and for this purpose, miRNA-210 decreases the expression level of NDUFA4. Silencing miRNA-210 expression can promote glucose uptake and prevents diabetic obesity development.¹³⁴ As pathways involved in exosome biogenesis have been identified, future experiments can focus on targeting ESCRT or SNARE proteins in impairing exosome biogenesis and interfering with miRNA-210 delivery to cells to elevate glucose uptake. The exosomes derived from macrophages may not affect insulin-dependent glucose uptake. The stimulation of macrophages by lipopolysaccharide (LPS) mediates exosome secretion from macrophages, and they can induce carbohydrate catabolism. The miRNA-530, chr9_22532, and chr16_34840 show high levels in exosomes derived from LPS-induced macrophages.¹³⁵

The mesenchymal stem cells are another source of exosomes.¹³⁶ These exosomes induce glucose and lipid metabolism and uptake, and significantly diminish gluconeogenesis. Notably, autophagy inhibition impairs the therapeutic impact of mesenchymal stem cell-derived exosomes in DM. More investigation revealed that exosomes induced AMP-activated protein kinase (AMPK) to stimulate autophagy via upregulating LC3-II and Beclin-1 for promoting glucose uptake and lipid metabolism.¹²¹ It is worth mentioning that AMPK has interactions with mammalian target of rapamycin (mTOR) signaling in autophagy regulation,¹³⁷ and future experiments can show how AMPK/mTOR axis regulation by exosomes affects autophagy and subsequently, lipid and glucose metabolism in cells for DM treatment. The exosomes are also able to affect transporters involved in glucose uptake and enzymes. The cardiomyocytes demonstrate capacity in the synthesis and secretion of exosomes that promote the levels of GLUT1 and GLUT4 to elevate glucose uptake. Furthermore, exosomes secreted by cardiomyocytes promote lactate dehydrogenase (LDH) activity to induce the glycolytic process for reducing glucose levels.¹³⁸ Another experiment revealed the role of exosomes derived from hepatic stellate cells in enhancing GLUT1 levels and promoting glucose uptake¹³⁹ that important in DM treatment. These statements highlight the fact that exosomes are potential modulators of lipid and glucose metabolism and uptake in cells. However, one of the limitations of current experiments is the lack of attention to underlying molecular pathways. For instance, it has been shown that exosomes regulate GLUTs in enhancing glucose uptake. However, there is no trace of related molecular pathways that can be the focus of future studies.

Exosomes and β -Cell Function

There are high numbers of Langerhans islets in the pancreas that is estimated to be 1 million, and each islet is composed of approximately 1000 β cells and an overall weight of 0.9 g.¹⁴⁰ The β cells respond to various conditions such as DM and obesity. The interesting point is the β cell mass in obese individuals. The increased levels of insulin in plasma of obese patients, called hyperinsulinemia, is a compensatory process for preventing insulin resistance. Therefore, the mass of β cells enhances in obese patients to induce hyperinsulinemia.¹⁴¹ An obese model in rodents demonstrated enhanced β cell mass up to three times due to obesity.¹⁴² The β cell destruction or their lack of capacity in insulin secretion can be observed in TIIDM, and based on an experiment, the mass of β cells in TIIDM patients over long period of time decreases to near 100%.^{143–145} However, there are some insights in TIIDM that as insulin levels are high in TIIDM patients, the mass of β cells is unaltered in TIID or enhanced. Therefore, β cell function and its mass are important for preventing DM.

An experiment has utilized exosomes derived from mesenchymal stem cells to treat TIIDM. The exosomes were administered to animal models via intravenous route, and after 6 weeks, the animals were examined in terms of insulin and

glucose levels. Based on results, exosomes induce regeneration of β cells in the pancreas and promote their mass that is of importance for promoting insulin secretion in T1DM. In addition to promoting insulin levels, exosomes derived from mesenchymal stem cells significantly diminished glucose levels in serum. Mechanistically, exosomes induce Pdx-1 expression to mediate β cell regeneration and promote insulin secretion. This study provided insights into the biodistribution of exosomes in different organs. The mesenchymal stem cell-derived exosomes show high accumulation in the liver and kidney, and their accumulation is lesser in the lungs and pancreas. Noteworthy, the distribution of these exosomes significantly enhances in the pancreas after 48 h.¹⁴⁶ One of the factors responsible for the onset of DM is cancer, in a way that 30% of patients with pancreatic cancer develop DM. The pancreatic stellate cells (PSCs) are present around the islets and neoplastic lesions. The pancreatic tumor cells and PSCs are able to secrete exosomes, which subsequently impair the normal function of β cells and induces insulin resistance, leading to DM development.¹⁴⁷

As mentioned previously, the expression level of Pdx-1 can induce regeneration of β cells in DM treatment. Exosomes were isolated from mesenchymal stem cells via a centrifugation process, which was then administered to rats via the intraperitoneal route (200 μ g/mL). Noteworthy, these exosomes induced regeneration of β cells and increased insulin secretion. The expression analysis revealed upregulation of Pdx-1, TGF- β , Smad2, and Smad3 in this process.¹⁴⁸ Therefore, based on experiments, exosomes can be beneficial in the treatment of T1DM by preventing the impairment and destruction of β cells. Furthermore, exosomes can be advantageous in treating T1DM via suppressing insulin resistance.¹⁴⁹ The exosome transplantation to diabetic mice is correlated with a decrease in macrophage infiltration in β cell islets and decreases CD31 expression as a marker of endothelial cells that together lead to an increase in insulin levels.¹⁵⁰

One of the strongest points of any set of experiments in this regard is the attention towards underlying molecular pathways involved in the therapeutic impacts of exosomes in DM. The hypoxia or low levels of oxygen can lead to β cell apoptosis and their inability in insulin secretion via triggering endoplasmic reticulum (ER) stress. For inducing apoptosis, hypoxia promotes BIP and Grp94 expression levels. Then, an increase occurs in phosphorylation of eIF2 α , leading to CHOP/p38 axis induction. At the next step, p38 reduces survivin expression while it promotes caspase-3 expression to upregulate PARP, resulting in apoptosis induction. Notably, exosomes derived from mesenchymal stem cells can deliver miRNA-21 that inhibits Grp34 expression. Furthermore, exosomes prevent p38 upregulation to suppress apoptosis in β cells.¹⁵¹ However, the story is not always in favor of β cell function. The M1 polarized macrophages can secrete exosomes. Then, exosomes interfere with normal function of β cells and suppress insulin resistance to develop T1DM. The exosomes derived from M1 macrophages contain high level of miRNA-212-5p that decreases sirtuin 2 (SIRT2) expression. Then, Akt down-regulation and subsequent inhibition of GSK-3 β occurs. Then, nuclear translocation of β -catenin occurs, and it induces F-actin depolymerization. This activity prevents the secretion of insulin vesicles produced in cells and leads to the development of T1DM.¹⁵² Figure 2 summarizes the role of exosomes in modulating β cell function and improving glucose and lipid metabolism.

Exosomes and Insulin Resistance

Insulin resistance is an increasing challenge in the treatment of DM patients, and it means that a shift in insulin concentration-effect curve occurs and it tends to higher concentration levels to exert a similar effect.¹⁵³ The irresponsive of cells to insulin and inducing insulin resistance can be observed commonly in T1DM and some cases, in obese people. The insulin is composed of 54 amino acids, and this peptide is generated in β cells. The insulin function is to significantly promote glucose consumption in cells, and it suppresses hepatic glucose generation. Besides, insulin enhances glucose uptake by cells via upregulating expression and activity of GLUTs such as GLUT4.¹⁵⁴ However, there are some reasons responsible for insulin resistance. For instance, in obese people, fat accumulation results in pro-inflammatory cytokine release, an increase in lipolysis, and reduced adipokine release. These impacts lead to enhanced levels of fatty acid and free glycerol associated with insulin resistance.¹⁵⁵ Recent experiments have focused on the application of nanostructures in reversing insulin resistance. The MgO nanostructures have the capacity of decreasing insulin resistance up to 29.5%.¹⁵⁶ Another study reveals the potential of gadofullerene nanostructures in improving the function of the pancreas and suppressing insulin resistance via inducing the IRS-2/PI3K/Akt axis.¹⁵⁷ This section focuses on the dual role of exosomes in preventing or inducing insulin resistance.

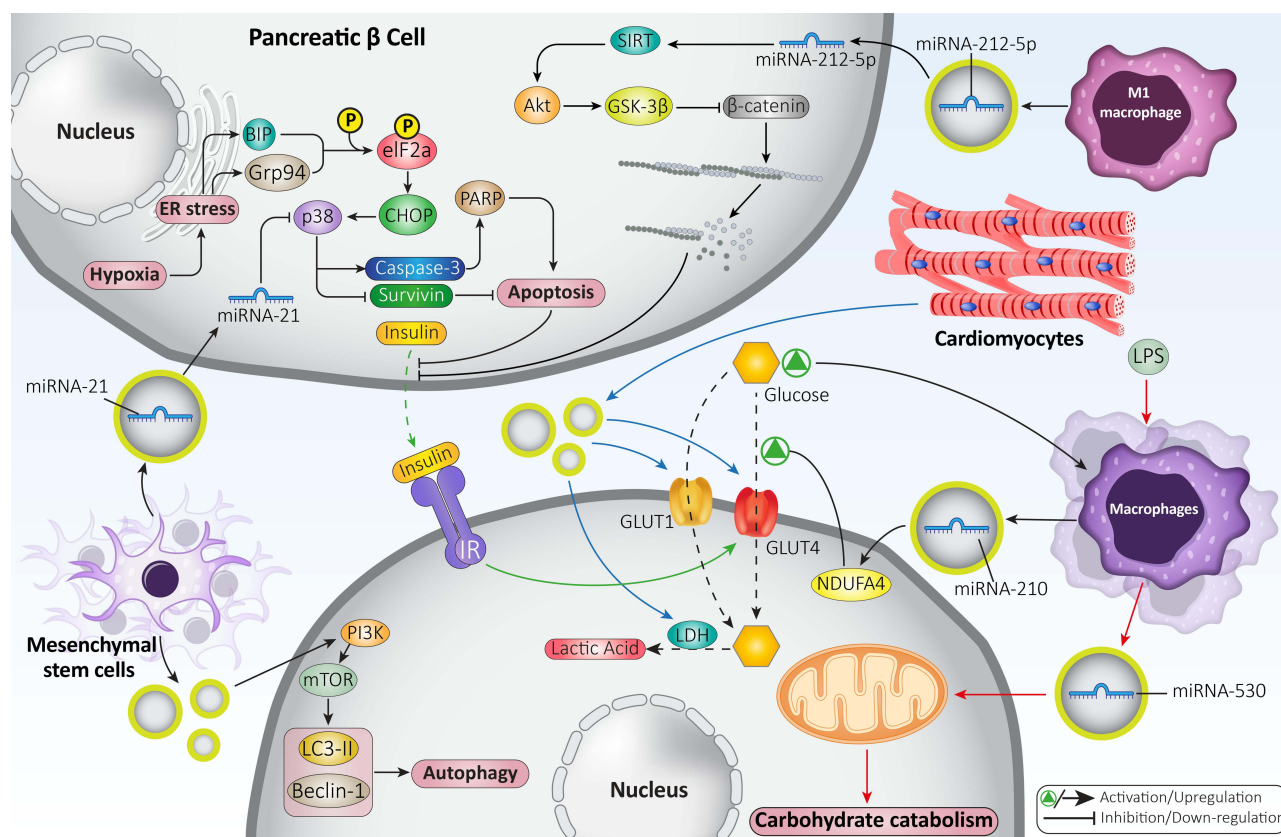


Figure 2 Exosomes in glucose and lipid metabolism as well as regulating β cell function. The exosomes derived from macrophages may contain miRNA-210 and miRNA-530 and are involved in carbohydrate catabolism. The exosomes can increase levels and activities of GLUT1 and GLUT4 to promote glucose uptake and enhance its metabolism in cells. Furthermore, exosomes can enter into β cells to prevent apoptosis and enhance their viability to maintain their capacity in insulin secretion.

Depending on their cargo the exosomes can dually suppress/induce insulin resistance in DM. The exosomes containing Sonic Hedgehog (Shh) can induce insulin resistance and significantly promote glucose levels in T1DM. For exerting such impact, Shh-loaded exosomes induce M1 polarization of macrophages to enhance their pro-inflammatory activity. In this way, Shh-loaded exosomes promote the expression level of Ptch to induce PI3K signaling, leading to M1 polarization of macrophages. More investigation revealed that M1 polarized macrophages and their secreted exosomes reduce expression levels of IRS-1 and HSL in adipocytes. All these interactions and signaling networks lead to insulin resistance and hyperglycemia in T1DM.¹⁵⁸ Previously, it was mentioned that cancer cells could secrete exosomes in triggering DM development and negatively affecting β cells. Noteworthy, exosomes derived from tumor cells can also stimulate insulin resistance in cells. The pancreatic tumor cells have the capacity of exosome secretion, and these nanostructures penetrate into C2C12 myotubes to reduce glucose uptake and mediate lipidosis. The exosomes suppress PI3K/Akt signaling to promote the expression level of FoxO1 and its nuclear translocation. This signaling network diminishes the expression level of GLUT4 to interfere with glucose uptake in cells. Therefore, inhibiting exosome secretion from pancreatic tumor cells or upregulating GLUT4 expression can be beneficial in reversing insulin resistance.¹⁵⁹ Adipose tissue is another source of exosome secretion.¹⁶⁰ The exosome-like vesicles derived from adipocyte tissue can participate in triggering insulin resistance. In this case, exosomes function as a communicator between macrophages and adipose tissue. Macrophages can absorb the exosome-like vesicles after secretion through adipocyte tissue. Then, exosome-like vesicles mediate the differentiation of monocytes to macrophages and induce secretion of IL-6 and TNF- α , resulting in insulin resistance. Silencing TLR4/TRIF axis prevents insulin resistance by these exosomes.¹⁶¹

However, some experiments show that exosomes can function as therapeutic agents in promoting insulin sensitivity, which is important in DM treatment. The consumption of fatty acids (high consumption) can lead to insulin resistance,

and palmitic acid (PA) is among them. The hepatocytes obtain the feature of insulin resistance due to high PA consumption. The PA can induce apoptosis in INS-1 cells, and it diminishes IRS-2 phosphorylation and prevents glucose uptake as a result of insulin induction. The neutral ceramidase (NCDase)-enriched exosomes prevent the generation of reactive oxygen species (maybe in favor of decreasing apoptosis in INS-1 cells) and prevent insulin resistance resulted from high consumption of PA.¹⁶² Another experiment uses umbilical cord mesenchymal stem cells to isolate exosomes and their application in T1DM treatment. These exosomes can promote insulin-induced glucose uptake, and this impact appears to be persistent for at least 48 h. Besides, exosomes decrease levels of leptin, and the expression level of SIRT1 and IRS-1 significantly enhances at mRNA level, showing the capacity of exosomes in elevating insulin sensitivity of adipocytes.¹⁶³

As previously mentioned in the introduction, exosomes are capable of transferring proteins, lipids, and nucleic acids among cells to affect biological events.^{164,165} The miRNAs are among the most well-known cargoes of exosomes and based on the activity of miRNAs, the impact of exosomes on target cells will be different.^{166–168} The miRNA-3075 is suggested to possess anti-diabetic activity via enhancing insulin sensitivity. The exosomes derived from hepatocytes show capacity in inducing insulin sensitivity. These exosomes are enriched with miRNA-3075, and its function is decreasing the expression level of FA2H. The process of insulin resistance is related to the pro-inflammatory function of macrophages. The miRNA-3075-loaded exosomes and their capacity in down-regulating FA2H can pave the way for reversing insulin resistance.¹⁶⁹ Overall, these studies highlight that exosomes can carry various cargoes to affect the insulin sensitivity of cells. Exosomes possess both functions in triggering and inhibiting insulin resistance.^{170,171} However, more experiments are required to evaluate other pathways involved in insulin resistance and their regulation by exosomes. Furthermore, other sources of exosomes from stem cells should be utilized in affecting the insulin sensitivity of cells (Figure 3 and Table 2).

Exosomes and Diabetic Complications

Wound Healing

The wound healing process is delayed in DM, and the patients are prone to chronic non-healing wounds.¹⁷⁴ In diabetic wounds, there are high levels of pro-inflammatory cytokines and proteases as well as low levels of growth factors.^{175–177} More than 70% of DM patients receive diabetic medications, and there is little understanding about the impact of these medications on the process of wound healing. The wound healing process is complicated, and various cellular and molecular mechanisms, including inflammation, proliferation, angiogenesis, collagen deposition and re-epithelization occur.^{178,179} The first step of wound healing is the recruitment of immune cells to eliminate pathogens, and at the next step, wound-associated genes undergo overexpression by cutting epidermal edges to mediate cell migration. The next step is proliferation and migration of fibroblasts to generate wound granulation tissue, and a number of fibroblasts may undergo differentiation to improve wound contraction. Then, angiogenesis occurs, and the wound healing process ends.¹⁸⁰ Disturbance in each of these processes can lead to delayed wound healing. The purpose of the current section is to evaluate the role of exosomes in affecting wound healing in DM.

A recent experiment has revealed the potential of exosomes derived from human amniotic epithelial cells in improving the wound healing process in DM. The exosomes had a cup or spherical shape, and their particle size was 105.89 nm. They were positive for CD63 and TSG101 and their uptake occurs by HFBs and HUVECs. These exosomes were able to elevate the growth and migration of HFBs, while they induced angiogenesis in HUVECs. These exosomes stimulated PI3K/Akt/mTOR axis to induce angiogenesis and improve fibroblast function in enhancing wound healing in DM.¹⁸¹ Therefore, inducing angiogenesis appears to be beneficial in improving the wound healing process in DM. Different molecular pathways have been examined in this case. The overexpression of ERK1/2 results in angiogenesis. The exosomes derived from endothelial progenitor cells enhance the expression level of ERK1/2 to induce angiogenesis and facilitate the wound healing process in DM.¹⁸² Furthermore, vascular endothelial cells are affected by exosomes in modulating the wound healing process in DM. The exosomes derived from endothelial progenitor cells stimulate tube formation in vascular endothelial cells and promote their growth and migration. More investigation revealed the potential of exosomes in promoting expression levels of FGF-1, VEGFA, VEGFR-2, ANG-1, E-selectin, CXCL-16, eNOS, and

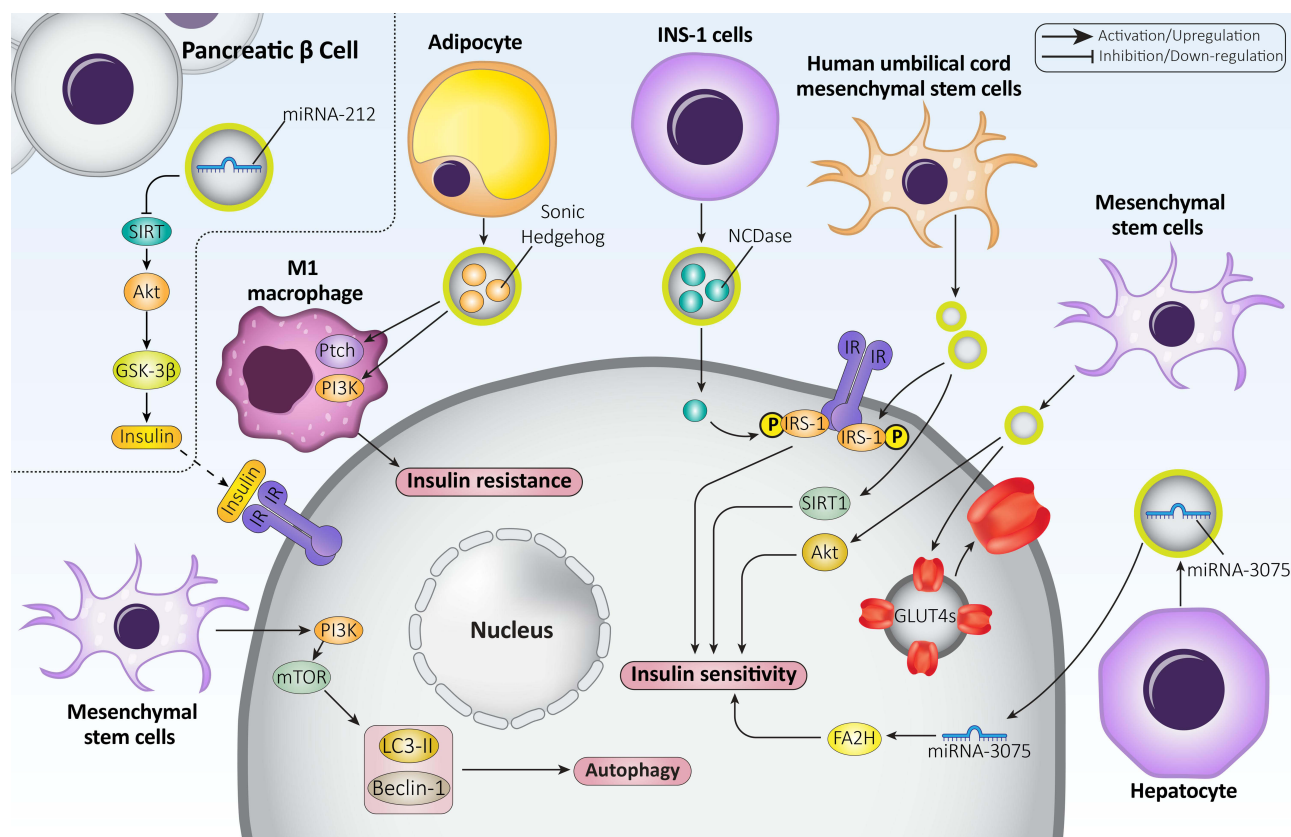


Figure 3 Exosomes and insulin resistance/sensitivity in DM. The exosomes demonstrate dual function in DM and can mediate both insulin resistance and sensitivity. For instance, exosomes derived from M1 macrophages can induce insulin resistance and are rich in PI3K and Ptch; on the other hand, exosomes derived from mesenchymal stem cells and hepatocytes induce insulin sensitivity via affecting molecular pathways such as SIRT1 and Akt as well as transferring miRNAs.

IL-8 for improving the wound healing process in DM.¹⁸³ Hence, Engineering exosomes is advantageous in enhancing wound healing in DM. The expression level of miRNA-31-5p significantly decreases in chronic diabetic wounds, and restoring miRNA-31-5p expression is correlated with the growth and migration of cells in wounds. Loading miRNA-31-5p in exosomes stimulates angiogenesis, fibrogenesis, and reepithelization to promote the wound healing process in DM that are mediated via down-regulating HIF-1 and EMP-1.¹⁸⁴ Furthermore, miRNA-221-3p-enriched exosomes show potential in enhancing wound healing in DM and increasing the expression level of VEGF and CD31 at the protein level and promoting proliferation of cells. Furthermore, miRNA-221-3p-enriched exosomes induce the AGE/RAGE axis in improving the wound healing process in DM.¹⁸⁵ Based on these experiments, exosomes are mainly involved in improving the wound healing process in DM, and different cells, including endothelial and fibroblast cells are affected. Furthermore, various molecular pathways related to proliferation, migration, and angiogenesis are affected, and most of the experiments have focused on the role of miRNAs.

Neuropathy

Approximately 50% of DM patients demonstrate neuropathy due to diffuse and focal nervous system damages.¹⁸⁶ Neuropathy is prevalent among diabetic patients and leads to falls, pain, and reduced quality of life.¹⁸⁷ Diabetic neuropathy is responsible for 10 billion costs annually in the USA.¹⁸⁸ Therefore, efforts should be made in preventing and management of diabetic neuropathy. Notably, anti-diabetic medications have shown potential in ameliorating DM-related brain damages. Anti-diabetic drugs can significantly diminish neuroinflammation and oxidative damage to prevent the development of neurological diseases such as Alzheimer's and Parkinson's diseases. Furthermore, anti-diabetic drugs such as GLP-1R and DPP-4i, among others, can improve neurogenesis and cognitive function.¹⁸⁹ This section is focused on the role of exosomes in diabetic neuropathy.

Table 2 Exosomes in Regulating Insulin Resistance, β Cell Function, Glucose, and Lipid Metabolism

Source of Exosome	Function	Signaling Network	Remarks	Refs
Hepatocyte	Insulin sensitivity	miRNA-3075/FA2H	The exosomes can deliver miRNA-3075 for decreasing FA2H expression and increasing insulin sensitivity	[169]
Human umbilical cord mesenchymal stem cells	Insulin sensitivity	SIRT1 IRS-1	Decreasing leptin levels Upregulating expression level of SIRT1 and IRS-1 in mediating insulin sensitivity	[163]
Mesenchymal stem cells	Insulin sensitivity	IRS-1 Akt GLUT4	Promoting glucose metabolism Increasing phosphorylation of Akt and IRS-1 Elevating membrane translocation of GLUT4	[149]
INS-1 cells	Insulin sensitivity	IRS-2	NCDase-enriched exosomes promote insulin sensitivity via enhancing IRS-2 phosphorylation Increasing insulin uptake in cells Preventing palmitic acid-induced insulin resistance	[162]
-	Insulin resistance	TLR4/NF- κ B	Silencing SIRT1 induces exosome secretion via autophagy inhibition Exosomes induce insulin resistance via triggering TLR4/NF- κ B axis	[172]
Adipocyte	Insulin resistance	Ptch PI3K	Exosomes possess high levels of Sonic Hedgehog Inducing M1 polarization of macrophages via Ptch and PI3K upregulation	[158]
Mesenchymal stem cell	β cell protection	miRNA-21/Grp94/ apoptosis p38/caspase-3/PARP/ apoptosis	The exosomes alleviate ER stress and decrease apoptosis in β cells Exosomes delivering miRNA-21 decrease Grp94 expression to inhibit apoptosis in β cells Exosomes down-regulate p38 expression to prevent apoptosis	[151]
M1 macrophages	β cell dysfunction	miRNA-212-5p/SIRT2/ Akt/GSK-3 β / β -catenin	The exosomal miRNA-212 reduces SIRT2 expression to inhibit Akt/GSK-3 β axis Providing nuclear translocation of β cells Preventing insulin secretion by β cells	[152]
Mesenchymal stem cell	Glucose and lipid metabolism	AMPK/autophagy	Ameliorating T1DM via upregulating AMPK expression, promoting Beclin-1 and LC3 levels, resulting in autophagy Autophagy induction enhances lipid and glucose metabolism in cells	[173]

The apoptosis in neurons can be regulated by exosomes. The administration of paeoniflorin improves the therapeutic impacts of exosomes derived from Schwann cells and promotes homeostasis and integrity of the endoplasmic reticulum. Furthermore, paeoniflorin intervention improves the capacity of exosomes in preventing apoptosis in neurons via down-regulating GRP78 and IRE1 α . These interactions are vital for preventing neuropathy in DM.¹⁹⁰ The exosomes isolated from mesenchymal stem cells demonstrate potential in ameliorating diabetic peripheral neuropathy.¹⁹¹ The underlying molecular pathways affected by these exosomes are of importance. The exosomes derived from mesenchymal stem cells have the capacity of carrying miRNA-146a. The exosomes enriched with miRNA-146a enhance nerve conduction velocity while they can diminish thermal and mechanical stimuli threshold. These exosomes prevent inflammation by monocytes and inhibit endothelial cell activation to ameliorate diabetic neuropathy. The miRNA-146a-enriched exosomes can suppress TLR-4/NF- κ B axis in alleviating diabetic neuropathy.¹⁹² The inhibition of TLR4/NF- κ B axis by exosomes prevents inflammation in ameliorating diabetic neuropathy. More importantly, exosomes derived from mesenchymal stromal cells can decrease M1 polarization of macrophages and promote levels of M2 polarized

macrophages in exerting anti-inflammatory activity.¹⁹³ The neurite outgrowth of neurons and migration of Schwann cells are significantly enhanced by exosomes. In this case, exosomes isolated from Schwann cells are able to promote the maturation of miRNAs, including miRNA-21, -27a, and -146a, while they decrease expression levels of NF- κ B, PTEN, SEMA6A, and RhoA to ameliorate diabetic neuropathy.¹⁹⁴ The miRNA-126-enriched exosomes have demonstrated potential in decreasing infarct size, promoting neurogenesis, and inducing angiogenesis to prevent brain injury in DM. For exerting such protective impacts, miRNA-126-loaded exosomes decrease caspase-3 expression on day 2 and elevate VEGFR2 expression at day 14.¹⁹⁴ The exosomes derived from bone marrow mesenchymal stem cells decrease miRNA-9 expression to provide upregulation of ABCA1, which is important for exerting anti-inflammatory activity and increasing white matter remodeling.¹⁹⁵ Based on these experiments, exosomes are potential therapeutic nanostructures for ameliorating diabetic neuropathy, and more experiments are required to evaluate their impact on molecular pathways.

Nephropathy

Nephropathy is another complication of DM that results in end-stage renal disease.¹⁹⁶ The incidence rate of nephropathy appears to be 25%. Various mechanisms are responsible for the development of diabetic nephropathy. Hyperglycemia can result in diabetic nephropathy via generating Amadori products and advanced glycation end products. Furthermore, hyperglycemia significantly enhances levels of ROS via inducing the electron transport chain to mediate diabetic nephropathy.¹⁹⁷ The treatment of diabetic nephropathy is still challenging, and there is a need for the development of animal models to understand its pathogenesis and drug targets effectively. The nanoparticles can provide selective targeting of renal cells and improve the efficacy of anti-diabetic drugs such as Rhein.¹⁹⁸ Furthermore, gold nanostructures can ameliorate podocyte injury and alleviate albuminuria for the treatment of diabetic nephropathy.¹⁹⁹

An experiment has cultured urine-derived stem cells, and exosomes with a particle size of 50–100 nm have been isolated that are positive for CD29, CD73, CD90, and CD44 markers, while they are negative for CD34, CD45, and HLA-DR. The intravenous administration of these exosomes seems to be beneficial in decreasing urine volume and urinary microalbumin secretion. Furthermore, exosomes inhibited apoptosis in podocytes and tubular epithelial cells and enhanced endothelial cell growth in diabetic rats. More investigation revealed that exosomes carried high levels of TGF- β 1, angiogenin, and BMP-7 that are advantageous in enhancing the viability of renal cells and inducing vascular regeneration in DM.²⁰⁰ There have been efforts to enhance podocytes' survival rate to prevent nephropathy in DM. The mesangial cells exposed to high glucose levels can secrete exosomes in triggering podocyte injury and mediating diabetic nephropathy. For inducing podocyte apoptosis, the exosomes transfer TGF- β 1 among cells. The berberine administration is beneficial in decreasing TGF- β 1 transportation by exosomes and reducing its levels to protect podocytes against apoptosis and promote adhesion.²⁰¹ However, exosomes can possess therapeutic impact in diabetic nephropathy. The exosomes derived from mesenchymal stem cells have high levels of miRNA-125b that down-regulates TRAF6 to induce Akt signaling, resulting in autophagy induction and decreasing apoptosis that are of importance for alleviating diabetic nephropathy.²⁰² One of the important molecular mechanisms is autophagy as a programmed cell death process. Overall, autophagy mediates the degradation of organelles and macromolecules that are aged and toxic to main cell homeostasis. Autophagy has both pro-death and pro-survival functions, and its function is context-dependent.^{101,189,203–206} Notably, autophagy with pro-survival function can prevent apoptosis in a cell.²⁰⁷ The exosomes derived from mesenchymal stem cells inhibit mTOR signaling as a negative regulator of autophagy to significantly enhance levels of Beclin-1 and LC3 to induce autophagy and prevent apoptosis in alleviating diabetic nephropathy.²⁰⁸ Based on these two experiments, autophagy induction is beneficial in treating diabetic nephropathy. However, autophagy also has a pro-death role, and this dual function should be considered in future experiments.

Endothelial Dysfunction

Most of the sections of this review focused on the T1DM and T2DM. However, gestational DM also occurs in the second or third trimester of pregnancy, and cells are not responsive to insulin.^{209,210} The gestational DM can occur in 5–20% of pregnancies worldwide. One of the pathologies occurring in gestational DM is endothelial dysfunction.²¹¹ The foeto-placental endothelial dysfunction results from an increase in nitric oxide (NO) synthesis and enhanced transportation of L-arginine.^{212,213} The exosomes derived from the umbilical vein endothelium could induce endothelial dysfunction and

provide a gestational DM phenotype. The transportation of L-arginine is significantly enhanced by using exosomes, and they also enhanced the hCAT-1 and eNOS expression levels. Furthermore, these exosomes induced MAPK signaling to promote uptake of L-arginine in cells. Therefore, suppressing MAPK signaling can prevent the impacts of exosomes in aggravating gestational DM and inducing endothelial dysfunction.²¹⁴ Notably, exosomes are a way of communication between endothelial cells and monocytes. Exposing both monocytes and endothelial cells to high glucose induces exosome secretion. These exosomes can enhance ICAM-1 expression that is a marker of endothelial cell activation.²¹⁵ The importance of this experiment is that ICAM-1 upregulation provides a condition for adhesion of immune cells to vascular wall²¹⁶ and as inflammation occurs in DM, further experiments can focus on reducing ICAM-1 expression in the treatment of DM-mediated inflammation. Another experiment provides more information about the role of exosomes in alleviating endothelial dysfunction and the role of ICAM-1. The endothelial progenitor cells are able to secrete exosomes, and these nanostructures decrease levels of various factors, including malondialdehyde (MDA), superoxide dismutase (SOD), IL-8, and more importantly, ICAM-1 for preventing endothelial dysfunction in DM.²¹⁷ It is worth mentioning that exosomes carrying arginase 1 are able to stimulate endothelial dysfunction in DM.²¹⁸ Based on these experiments, exosomes can effectively modulate endothelial function in DM, and their targeting can be considered as a therapeutic strategy.²¹⁹

Erectile Dysfunction

Erectile dysfunction is defined as the inability to maintain penile erection for at least 6 months.²²⁰ DM is considered as a risk factor for erectile dysfunction.²²¹ This disease decreases men's quality of life and self-esteem, and its incidence rate is at the range of 19–90% and can occur 10 years before the start of DM.^{222–224} Erectile dysfunction is a multifactorial disease. In addition to DM, smoking, cardiovascular diseases, dyslipidemia, hypertension, and obesity are among other factors involved in erectile dysfunction development.²²⁵ The most common factors responsible for erectile dysfunction are vasculogenic factors that mediate arterial inflow or venous outflow disorders.²²⁶

Exosomes were derived from adipose stem cells and administered via the intracavernous route to promote intracavernous pressure and enhance smooth muscle level compared to collagen, revealed by CD31 overexpression. Furthermore, exosomes decrease the expression level of caspase-3, while they promote Bcl-2 expression to prevent apoptosis. Based on results, exosomes derived from adipose stem cells are therapeutic agents for alleviating erectile dysfunction in DM.²²⁷ The adipose stem cell-derived exosomes can induce angiogenesis, increase the proliferation rate of endothelial cells, and prevent erectile dysfunction. Furthermore, these exosomes reduced corpus cavernosum fibrosis. More investigation revealed that exosomes derived from adipose stem cells carried high levels of miRNA-126, -130a, and -132 as proangiogenic factors and miRNA-let7b and -let7c as anti-fibrotic factors.²²⁸ Based on the experiments, preventing fibrosis is the best option in ameliorating DM-induced erectile dysfunction. The exosomes derived from smooth muscle cells enhance smooth muscle content and diminish collagen accumulation to exert anti-fibrotic activity. For this purpose, exosomes upregulate expression levels of eNOS and nNOS to induce NO/cGMP axis in improving erectile dysfunction in DM.²²⁹

Cardiovascular Diseases

The DM can negatively affect the heart and may develop various cardiovascular diseases such as atherosclerosis.^{230,231} The polydatin shows potential in decreasing myocardial injury via down-regulating NF- κ B and inhibition of NADPH oxidase.²³² As NF- κ B signaling is involved in inflammatory processes,²³³ more experiments are required to reveal its role in DM-related cardiovascular diseases. The PLGA-GLP-1 nanocomposites prevent apoptosis and DNA damage and enhance antioxidant activity to ameliorate myocardial injury in DM.²³⁴ Furthermore, endothelium ET-1 enhances inflammation and oxidative damage via NOX1 overexpression to aggravate atherosclerosis in DM.²³⁵

Apoptosis and necrosis are two types of cell death that commonly occur in cardiomyocytes during DM. Hyperglycemia is involved in triggering cell death in diabetic cardiomyopathy, and there have been efforts in using therapeutic nanostructures in alleviating this condition. A recent experiment has shown that exosomes can be secreted and isolated from parasympathetic ganglionic neurons (PGN), and they show capacities in treating diabetic cardiomyopathy. High glucose levels decrease the survival rate of H9C2 cells and induce apoptosis via down-regulation of Bcl-2,

and upregulation of Bax and caspase-3. The exosomes derived from PGN ameliorated diabetic cardiomyopathy and prevented apoptosis.²³⁶ Another negative impact in T1DM is vasa vasorum (VV) angiogenesis, which promotes the possibility of plaque rupture. The insulin resistance adipocytes have the capacity of exosome secretion. These exosomes can be easily taken up by endothelial cells, and in vivo experiment on mice has shown their capacity in penetrating endothelial cells after intravenous administration. Noteworthy, these exosomes contain Sonic Hedgehog, and they can induce VV angiogenesis in aortic plaques. The Gli1 is the downstream target of Sonic Hedgehog, and these exosomes can promote plaque burden in diabetic mice.²³⁷ DM patients are prone to atherosclerosis as one of the cardiovascular complications. The macrophages exposed to high glucose secrete exosomes and promote hematopoiesis, atherosclerotic lesions, and several myeloid cells. Furthermore, these exosomes enhanced cell growth rate and induced changes in metabolic profile via upregulating glycolysis. Further investigations revealed that exosomes derived from macrophages have high levels of miRNA-486-5p that mediate their potential in aggravating atherosclerosis in DM.²³⁸ Myocardial fibrosis is also another challenge in DM. Notably, TGF- β /Smad signaling is involved in fibrosis.⁹⁰ The exosomes isolated from mesenchymal stem cells can reduce the expression level of Smad2 via suppressing TGF- β signaling to ameliorate myocardial fibrosis in DM.²³⁹ Based on these experiments, exosomes can dually induce or inhibit heart injury by carrying various cargoes such as miRNAs in this case. Engineering novel exosomes can be beneficial in preventing DM-mediated cardiac injury.

Eye Disorders

The administration route of exosomes appears to be important in their protective impact on the retina. The intravenous administration of exosomes derived from adipose mesenchymal stem cells enhances the thickness of layers and induces irregularity in the ganglionic layer. The subconjunctival administration of exosomes leads to better results compared to intravenous administration and organizes cellular components of the retina in a well manner. The intraocular administration is considered as the best route and improves retinal layers similar to the normal retina. It has been reported that hyperglycemia reduces miRNA-222 expression. The exosomes derived from mesenchymal stem cells promote miRNA-222 expression to ameliorate retinal degeneration in DM.²⁴⁰ Next experiments will shed more light on the function of exosomes in alleviating retinal degeneration and revealing underlying molecular pathways in DM. Based on these experiments, various diabetic complications occur, including neuropathy, nephropathy, endothelial dysfunction, erectile dysfunction, delayed wound healing, cardiovascular diseases, and eye disorders that can be improved or aggravated by exosomes based on the cargo. Various molecular pathways, including VEGF, IRE1 α , Bax, caspase-3, and NLRP3, are affected by the exosomes derived from different sources such as adipose stem cells, mesenchymal cells, and macrophages.^{190,194,200,202,217,219,241–249} Table 3 provides a summary of exosomes and their application in alleviation of diabetic complications. Figure 4 demonstrates the potential of exosomes in alleviating diabetic complications. Figure 5 is also a summary of exosomes in the treatment of DM.

Clinical Application

Exosomes can be considered as biomarkers, and they are isolated from body fluids. A recent experiment isolated placental exosomes from urine at the first, second, and third trimesters of gestation. Five miRNAs, including miRNA-516-5p, -517-3p, -518-5p, -16-5p, and -222-3p, were examined in different periods of pregnancy. The expression level of these miRNA significantly enhanced in healthy women during gestation except miRNA-516-5p. Notably, the expression level of these miRNAs underwent down-regulation in gestational DM and at the third trimester of pregnancy. Therefore, these exosomes can be considered valuable sources for diagnosing gestational DM.²⁵⁶ Noteworthy, the size of exosomes significantly enhances in gestational DM patients, and their concentration is also higher. Various circRNAs undergo down-regulation and upregulation in these exosomes, and most of them are related to affecting miRNA expression, which is important for the diagnosis of gestational DM.²⁵⁷ Another source for diagnosis of gestational DM is the umbilical cord, and the presence of lncRNAs and their interaction with miRNA can be a determining factor for initiation and development of gestational DM.²⁵⁸ Besides, exosomes can be derived from adipocytes. The visceral fat thickness is a factor responsible for the development of gestational DM. The exosomes derived from adipocytes carrying the miRNA-148 family affect gestational DM development, and visceral fat thickness modulates exosomes containing

Table 3 The Role of Exosomes in Improving Diabetic Complications

Diabetic Complication	Source of Exosome	Signaling Network	Remarks	Refs
Atherosclerosis	Macrophage	-	Aggravating atherosclerosis via inducing proliferation and hematopoiesis Enrichment of miRNA-486-5p in exosomes	[238]
Atherosclerosis	Adipocyte	Sonic Hedgehog	The exosomes containing Shh induce angiogenesis, plaque burden, and vulnerability index in aggravating atherosclerosis	[237]
Myocardial injury	Mesenchymal stem cell	TGF- β 1/Smad2	Preventing myocardial injury via TGF- β 1 down-regulating and subsequent inhibition of Smad2 expression	[239]
Wound healing	Amniotic epithelial cells	PI3K/Akt/mTOR	Inducing angiogenesis Improving fibroblast function Stimulating PI3K/Akt/mTOR signaling	[181]
Wound healing	Human endothelial progenitor cells	ERK1/2	Inducing angiogenesis and improving wound healing via triggering ERK1/2 signaling	[182]
Wound healing	Human endothelial progenitor cells	-	Improving endothelial function to facilitate wound healing Upregulating expression levels of FGF-1, VEGFA, VEGFR-2, E-selectin, CXCL-16, eNOS, and IL-8	[183]
Wound healing	-	miRNA-31/HIF-1 miRNA-31/EMP-1	The engineered exosomes containing miRNA-31 improve the wound healing process Down-regulation of HIF-1 and EMP-1	[184]
Wound healing	Endothelial progenitor cells	miRNA-221-3p/VEGF	Improving wound healing process via upregulating VEGF expression and triggering angiogenesis	[185]
Wound healing	Autologous dermal fibroblasts	Akt/ β -catenin	Inducing angiogenesis and cell proliferation Promoting reepithelization and collagen deposition Reducing inflammation Inducing Akt/ β -catenin signaling	[250]
Wound healing	Adipose-derives stem cells	Nrf2	Enhancing Nrf2 expression and increasing vascularization in promoting wound healing	[251]
Wound healing	Mesenchymal stem cells	miRNA-221-3p/Akt/eNOS	Exosomes promote miRNA-221-3p expression to induce Akt/eNOS axis, leading to wound healing process	[252]
Wound healing	Macrophage	-	Exerting anti-inflammatory activity and promoting the wound healing process	[253]
Wound healing	Mesenchymal stem cells	mmu_circ_0000250/ miRNA-128-3p/ SIRT1	Improving wound healing via autophagy induction The mmu_circ_0000250-enriched exosomes promote SIRT1 expression via miRNA-128-3p absorption to induce autophagy and enhance angiogenesis	[254]
Osteogenesis	Mesenchymal stem cells	miRNA-129-5p/ FZD4/ β -catenin	Enrichment of miRNA-129-5p in exosomes Preventing osteoblast differentiation Reducing osteoblastic markers miRNA-129-5p suppresses β -catenin	[255]
Retinal degeneration	Adipose mesenchymal stem cells	miRNA-222	Improving the organization of retinal layers Hyperglycemia decreases miRNA-222 expression Improving retinal repair	[240]

(Continued)

Table 3 (Continued).

Diabetic Complication	Source of Exosome	Signaling Network	Remarks	Refs
Endothelial dysfunction	Umbilical vein endothelium	MAPK eNOS	Exosomes aggravated endothelial dysfunction in gestational DM via inducing MAPK and eNOS expression	[214]
Erectile dysfunction	Adipose-derived stem cells	Bcl-2 Caspase-3 CD31	Alleviating erectile dysfunction via upregulating CD31 and Bcl-2 expression levels, and down-regulating caspase-3 expression	[227]
Nephropathy	Mesenchymal stem cell	mTOR	Exosomes down-regulate mTOR expression to induce autophagy and ameliorate diabetic nephropathy	[208]
Neuropathy	Mesenchymal stromal cells	TLR4/NF- κ B	Improving neovascular function Preventing inflammation Decreasing M1 polarization and promoting M2 polarization of macrophages Inhibiting TLR4/NF- κ B axis	[193]

the miRNA-148 family.²⁵⁹ The miRNA-125 and miRNA-144 are two miRNAs with differences in expression level in pregnancy and gestational DM. The expression level of miRNA-125 decreases in circulating exosomes and placenta, mediating gestational DM development. The miRNA-144 shows upregulation in circulating exosomes in the third

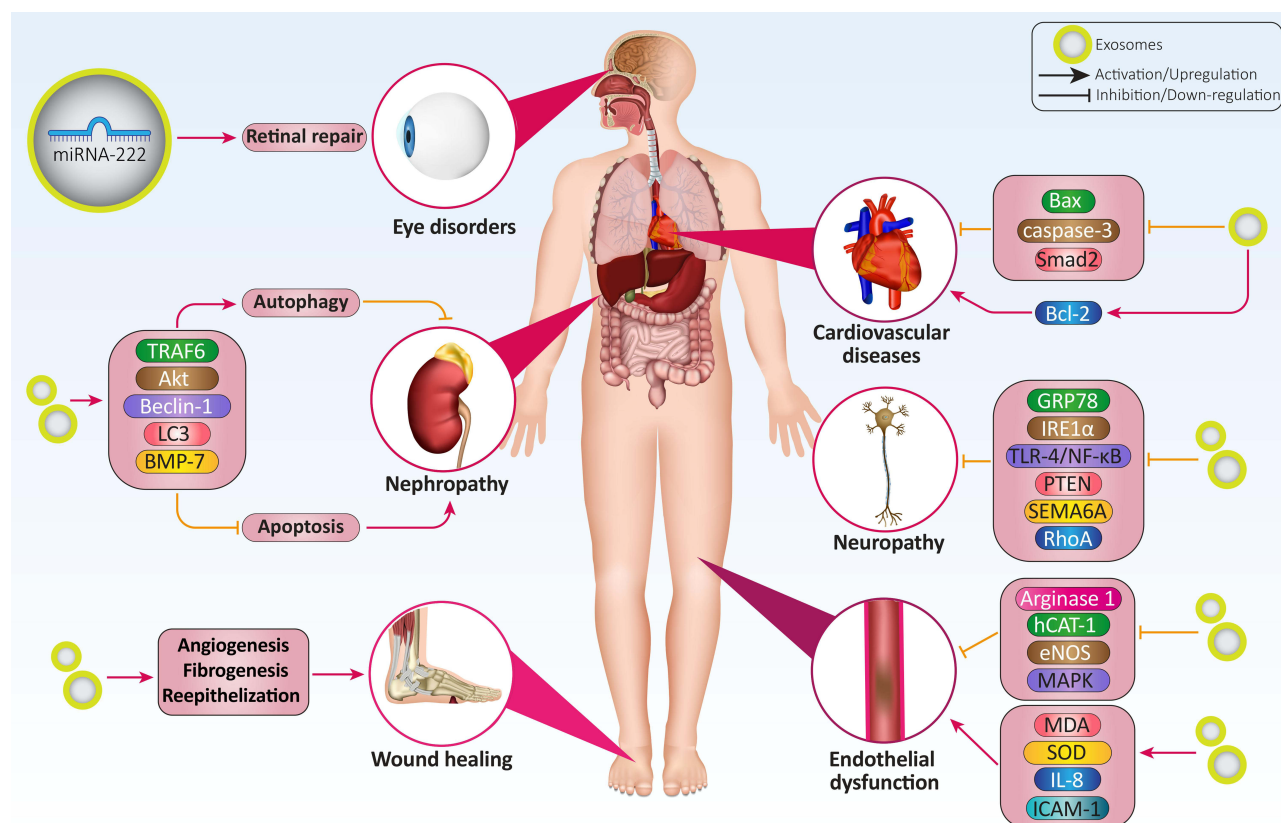


Figure 4 Exosomes and diabetic complications. The various kinds of diabetic complications, including eye disorders, cardiovascular diseases, nephropathy, neuropathy, delayed wound healing, and endothelial dysfunction, can be ameliorated by exosomes. Neuropathy and nephropathy are the most common diabetic complications. Apoptosis, autophagy, angiogenesis, and fibrogenesis are among the most common molecular mechanisms affected by exosomes in alleviating diabetic complications.

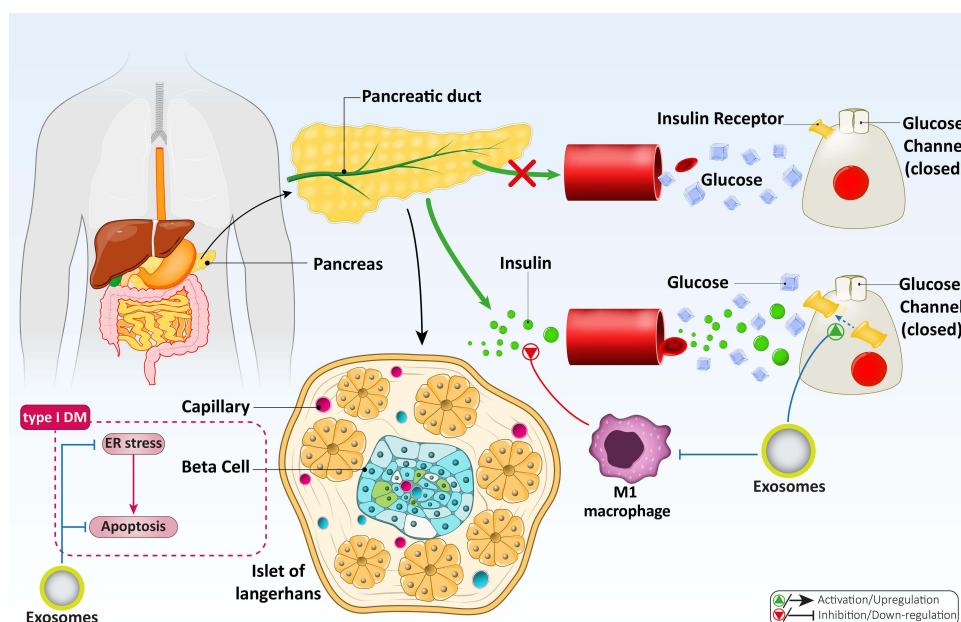


Figure 5 A summary of exosomes and their potential in DM treatment. This schematic demonstrates that glucose and lipid metabolism, viability and survival of β cells, and important molecular mechanisms such as apoptosis and ER stress are tightly regulated by exosomes to provide new insight into the treatment of DM and its complications.

trimester of pregnancy and induces gestational DM development.²⁴⁴ The exosomes can deliver free fatty acids from the bloodstream to cardiac tissue that may result in metabolic disorders such as DM.²⁶⁰ The expression level of lncRNAs H19 and MALAT1 undergoes abnormality in exosomes. The exosomes derived from T1DM patients confirm the aforementioned statement. The expression level of lncRNA MALAT1 decreases in serum exosomes of T1DM, while lncRNA H19 shows an increase in expression level.²⁶¹ Based on these experiments, exosomes can be considered as non-invasive or minimally invasive diagnosis of DM.^{262–264}

Conclusion and Remarks

In recent years, therapeutics for the treatment of DM have been developed in a growing trend and the reason of high incidence rate of this metabolic disorder and altered lifestyle. The DM can occur in both developing and developed countries, and it is more common in urban areas than rural areas due to the lifestyle. In DM, hyperglycemia occurs, which can lead to complications and negative impacts on cells, such as cell death and reduced viability. The present review aimed to investigate the role of exosomes as nanostructures in the treatment of DM.

The glucose uptake and metabolism, as well as lipid metabolism, undergo changes during DM. Exosomes can enhance the metabolism of glucose and lipid in DM. The impact of exosomes will be different based on cargo. For instance, miRNA-210-enriched exosomes inhibit glucose uptake, while exosomes triggering AMPK signaling can induce autophagy which enhances glucose and lipid metabolism. The interesting point is that exosomes can affect β cells in DM. Exosomes derived from pancreatic cancer cells impair β cell function and result in DM development. Noteworthy, exosomes can also promote regeneration and function of β cells via upregulating expression levels of Pdx-1, TGF- β , Smad2, and Smad3. Therefore, exosomes possess both pro-diabetic and anti-diabetic activities. The same story occurs in insulin resistance. The miRNA-3075-enriched exosomes induce insulin sensitivity, while exosomes decreasing expression levels of IRS-1, HSL, and PI3K/Akt, can stimulate insulin resistance. The diabetic complications, including retinal degeneration, osteoporosis, diabetic wound healing, atherosclerosis, neuropathy, and nephropathy, can be dually regulated by exosomes. The interesting point is the clinical trials evaluating the function of exosomes in DM patients, and based on these studies exosomes can be derived from various sources such as urine to detect gestational DM in the third trimester of pregnancy. The enrichment of miRNAs, lncRNAs, and circRNAs in exosomes determines the function of exosomes in DM and their biomarker role. Although different experiments have explored the role of exosomes in DM,

some limitations remain that should be the focus of future studies. Most of the studies have disregarded the underlying molecular pathways affected by exosomes in DM. Furthermore, surface modification of exosomes or loading cargo in exosomes can promote their therapeutic activity in DM treatment that has been overlooked by current experiments.

Abbreviations

EVs, extracellular vesicles; MVBs, multivesicular bodies; HSPs, heat shock proteins; mRNA, messenger RNA; miRNA, microRNA; tRNA, transfer RNA; lncRNA, long non-coding RNA; circRNA, circular RNA; DM, diabetes mellitus; ILVs, intraluminal vesicles; A β , amyloid-beta; T1DM, type I DM; T2DM, type II DM; NF- κ B, nuclear factor-kappaB; Akt, protein kinase-B; PI3K, phosphoinositide 3-kinase; siRNA, small interfering RNA; shRNA, short hairpin RNA; HFD, high-fat diet; LPS, lipopolysaccharide; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; LDH, lactate dehydrogenase; GLUT, glucose transporter; PSCs, pancreatic stellate cells; ER, endoplasmic reticulum; SIRT2, sirtuin 2; Shh, Sonic Hedgehog; NCDase, neutral ceramidase; PA, palmitic acid; NO, nitric oxide; SOD, superoxide dismutase; MDA, malondialdehyde; PGN, parasympathetic ganglionic neurons; VV, vasa vasorum.

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Author Contributions

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

Disclosure

Amir Reza Aref is the vice president at Translational Sciences, Xsphaera Biosciences Inc. The authors declare no other potential conflicts of interest for this work.

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