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REVIEW

Research progress of extracellular vesicles in type 2 diabetes and its complications

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Abstract

Type 2 diabetes is one of the most common chronic diseases in modern society. However, there is still insufficient research on the pathogenesis, diagnosis and treatment of type 2 diabetes and its complications. Extracellular vesicles are small bilayer vesicles secreted by cells. In recent years, the effect of extracellular vesicles in type 2 diabetes and its complications has aroused extensive attention. The research on the influence of protein and nucleic acids carried by extracellular vesicles secreted by stem cells and inflammatory cells on the pathogenesis of type 2 diabetes and its complications provides new ideas for its diagnosis and treatment. This review focuses on the influence of extracellular vesicles on insulin resistance by regulating inflammation and glucose transporter 4 expression. The second part mainly discusses the research progress and limitations of extracellular vesicles use in treating and diagnosing type 2 diabetes and its complications. This review introduces the current research status of type 2 diabetes and its complications, illustrates the biogenesis of extracellular vesicles, their effect on type 2 diabetes pathogenesis and its complications and their potential as therapeutic tools and diagnostic markers in type 2 diabetes and its complications.

KEYWORDS

diabetes complications, exosomes, extracellular vesicles, insulin resistance, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by hyperglycaemia and insulin resistance.[1] Diabetes, with a prevalence rate of 8.8%, plagues 425 million people globally, and this number is continuously increasing.[2] The latest American Diabetes Association (ADA) guidelines divide diabetes into four types: Type 1 diabetes (T1D), Type 2 diabetes (T2D), gestational diabetes mellitus (GDM) and specific types of diabetes.[3]Currently, T2D is the most common type of diabetes, accounting for about 90% of all diabetic cases.[2] Type 2 diabetes pathogenesis is mainly associated with insulin resistance and progressive pancreatic β-cell apoptosis, but the exact mechanism is unclear. Type 2 diabetes leads to macrovascular (such as cardiovascular disease) and microvascular (such as diabetic nephropathy and diabetic retinopathy) complications if blood glucose levels are under poor control.[4] Historically, the primary therapeutic strategy for reducing T2D incidence and delaying the progression of the complications is intensive glycaemic control. However, much evidence shows that this method can decrease the risk of microvascular complications, with no benefit for macrovascular complications. Exclusion

diagnosis is mainly used to diagnose T2D, usually associated with age, family genetic history, sex, blood pressure, body mass index (BMI) and islet antibody testing.[5] Considering a shortage of research on T2D mechanisms, diagnosis, and therapy, it is urgent to find new biomarkers and therapeutic approaches.

Extracellular vesicles (EVs) with a diameter of about 30–2000 nm are small secreted lipid bilayer vesicles. Based on their biogenesis and size, there are three types of EVs: microvesicles (MVs), exosomes, and apoptotic bodies. Exosomes are the smallest type of EVs, with a diameter of about 40–160 nm (average 100 nm). They were initially isolated from sheep reticular erythrocytes.[6] Extracellular vesicles are widely present in body fluids, such as blood, urine, breast milk, ascites, amniotic fluid, saliva and cerebrospinal fluid. At the same time, EVs contents include protein and nucleic acid (miRNA, mRNA, lncRNA).[7] Extracellular vesicles formation varies among the three subtypes. Apoptotic bodies are formed from the detachment of the plasma membrane, and microvesicles formation is related to membrane lipid redistribution and actin–myosin mechanical contractility. Exosomes formation is a complex process. Firstly, the plasma membrane invaginates and forms the early endosomes. Secondly, the early endosomes develop into multivesicular bodies (MVBs) at the late stage, which carry substances after a second indentation. Finally, MVBs merge with the cell membrane and release the cell content to the extracellular space.[8]

According to the Journal of Extracellular Vesicles Guidelines (2018), there is no single best separation method to isolate EVs. The commonly used separation methods are ultracentrifugation, density gradients, precipitation, immunocapture, size exclusion chromatography and ultrafiltration,[9] and a suitable separation method is selected according to the experimental requirements. Extracellular vesicles play a crucial role in the pathophysiological process, including inducing phenotypic changes of receptor cells, participating in cell–cell communication, transferring proteins and nucleic acids, affecting inflammation, immune regulation, affecting angiogenesis and coagulation.[10] Extracellular vesicles play an important role in T2D and can be used as a medium for cell-to-cell communication in metabolism.[11] One study showed that EVs derived from erythrocytes (CD235a+) are significantly increased in patients with diabetes. This research also indicated that insulin resistance is positively correlated with EVs. Extracellular vesicles in diabetic patients are more likely to be internalized by B cells, inducing monocytes to transform into inflammatory phenotypes.[12] Although many studies have proved that EVs can affect the occurrence and development of T2D and its complications, its specific mechanism is still unclear. Moreover, there is still a lack of research on evaluating their efficacy as T2D markers. Due to EVs' poor storage stability, low yield, low purity, and weak targeting, the clinical application of exosomes is limited.[8]

2 | ROLE OF EXTRACELLULAR VESICLES IN THE PATHOGENESIS OF T2D AND ITS COMPLICATIONS

2.1 | Effects on insulin resistance

Insulin resistance is the main pathogenesis of T2D. As an intercellular communication medium, some researches[13] found that insulin resistance is triggered by abnormal EVs, which can further promote EVs secretion[14] (Figure 1).

2.1.1 | Inflammatory reaction regulation via M1/M2 macrophage polarization

Insulin resistance and obesity are strongly related to a low-grade inflammation state in the body, in which adipose tissue macrophages (ATMs) play a crucial role. When macrophages are polarized into pro-inflammatory M1 macrophages, they secrete pro-inflammatory cytokines capable of promoting insulin resistance. On the contrary, M2 macrophages have anti-inflammatory effects. Therefore, the M1/M2 ratio relates to insulin resistance.[15] The M1 macrophage activation mechanisms are not fully articulated. However, research has shown that EVs secreted by adipose tissue could promote macrophages to differentiate into M1 macrophages. In 2009, Deng et al. found that adipocyte-derived EVs, which carry the retinal binding protein 4 (RBP4), induce monocytes to depolarize into M1 macrophages through the toll-like receptor 4/toll-interleukine-1 receptor domain-containing adapter-inducing interferon-β (TLR4/TRIF) pathway, and M1 macrophages increase the tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) secretion. Because these two pro-inflammatory factors block insulin in adipocytes, they can induce insulin resistance.[16] In addition, Song et al. proved that EVs from adipose tissue carrying Sonic Hedgehog (Shh) induce bone marrow-derived macrophages (BMDMs) to polarize into M1 macrophages through the Ptch/PI3K signalling pathway, leading to insulin resistance.[17] Zhang et al. showed that miR-155 could be transported to BMDMs through adipocyte-derived exosomes, which leading to BMDMs polarization towards M1 phenotypes by inhibiting the suppressor of cytokine signalling 1 (SOCS1) cascade and regulating janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling, thus promoting insulin resistance.[18] Interestingly, some studies have also shown that EVs can affect insulin resistance by regulating M2 phenotypic polarization. The exosomes from mature adipocytes deliver miR-34a into macrophages to inhibit M2 polarization by decreasing the Krüppel-like factor 4 (Klf4) expression, thereby inducing insulin resistance.[19]

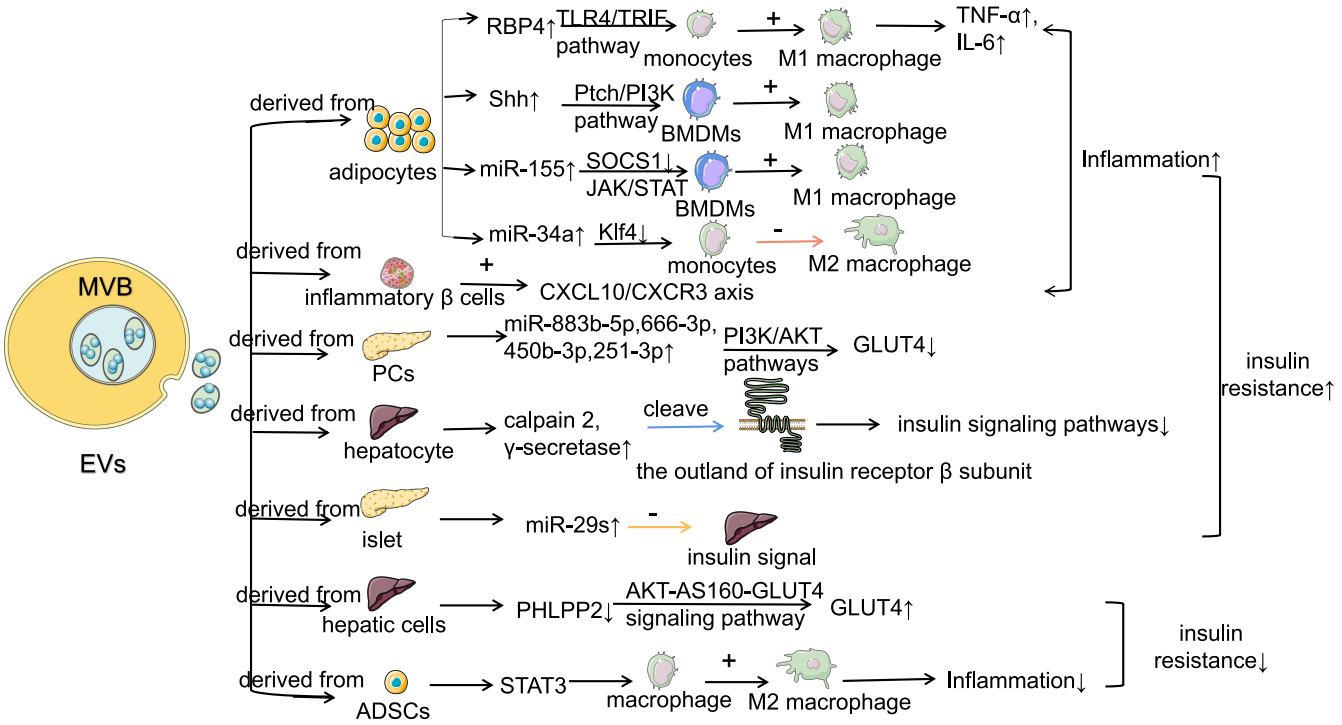

FIGURE 1 The potential mechanisms of EVs in insulin resistance. Summary of the mechanisms by which EVs affect insulin resistance. '↑' indicates a rise in expression level and '↓' represents the opposite. '+' is promoting polarization and '−' is the opposite

Zhao et al. found that exosomes from adipose-derived stem cells (ADSCs) can transfer into macrophages. These exosome-carried active signal transducer and activator of transcription 3 (STAT3) can induce macrophage polarization to the anti-inflammatory M2 phenotype by trans-activating argininase-1, regulating insulin sensitivity.[20] Other studies have shown that besides macrophages and monocyte-derived EVs, dendritic cells and neutrophils also play an important role in the inflammatory process of diabetes and insulin resistance.[21] Javeed et al. showed that EVs secreted by pro-inflammatory β-cell-mediated C-X-C motif chemokine 10/C-X-C motif chemokine receptor 3(CXCL10/CXCR3) axis play a pro-inflammatory role and induce β-cell failure.[22] These studies suggest that EVs from different cells induce and modulate insulin resistance through regulating inflammatory signals.

2.1.2 | Down-regulation of GLUT4 in adipocytes and skeletal muscle cells

Extracellular vesicles and peroxisome proliferator-activated receptor gamma (PPARγ) control glucose metabolism by affecting glucose transporter 4 (GLUT4), which plays an important role in insulin signalling pathways. GLUT4 transports glucose into adipocytes and muscle tissues via insulin to control blood glucose.[23] Manabu et al. fed green tea to hyperglycaemic mice and found that it significantly increased GLUT4 levels and muscle glucose uptake, suggesting GLUT4-mediated glucose transport in adipocytes and muscle tissues.[24] Fryklund et al. showed a sharp decrease in glucose transport in adipocytes accompanied by the decreased GLUT4 protein expression in mice on a high glucose diet. They believed that the glucose transport decline in adipocytes was related to the GLUT4 protein expression changes.[25] On the mechanism by which EVs affect glucose metabolism, many investigations have shown that EVs can carry some microRNAs to affect GLUT4 expression and transport, thus regulating glucose metabolism. Wu et al. demonstrated that miR-130a-3p encapsulated by hepatic cell exosomes could reduce pleckstrin homology domain leucine-rich repeat protein phosphatase 2 (PHLPP2) expression, thereby activating the protein kinase B—the Akt substrate of 160 kDa-glucose transporter 4 (AKT-AS160-GLUT4) signalling pathway in adipocytes, which increases GLUT4 expression and further alleviates abnormal glucose metabolism.[26] Similarly, Wang et al. confirmed that exosomes from pancreatic cancer cells (PCs) carrying miR-883b-5p, 666-3p, miR-450b-3p, and miR-251-3p could reduce GLUT4 expression by regulating phosphatidylinositol-3 kinase/protein kinase B (PI3K/AKT) signalling pathways. Lower GLUT4 expression levels induce insulin resistance in skeletal muscle cells, leading to abnormal glucose metabolism.[27] These studies have shown that various microRNAs carried by various cell-derived EVs can increase or inhibit GLUT4 expression, leading to the alleviation or aggravation of abnormal glucose metabolism.

2.1.3 | Extracellular vesicles affect insulin receptor β-subunit in hepatocytes

After insulin is produced by pancreatic β cells, insulin can regulate the insulin signalling pathway by binding to the insulin receptor on the cell membrane of the target cell to control blood glucose levels. Calpain 2 and γ-secretase secreted from hepatocyte-derived EVs can sequentially cleave the insulin receptor β subunit on the plasma membrane of hepatocytes.[28] Due to the destruction of the insulin receptor, insulin signalling pathways' expression decreases, causing insulin resistance. In addition, Li et al. have shown that miR-29s-rich islet-derived exosomes can inhibit insulin signals in the liver and produce insulin resistance.[29]

2.2 | Effects of extracellular vesicles on other T2D mechanisms

In addition to the aforementioned mechanisms, many other mechanisms can affect T2D progression. Katayama et al. studied the blood of diabetic patients and found that their exosomes carry more miR-20b-5p than non-diabetic patients. Overexpressed miR-20b-5p reduces AKITP abundance and the effect of insulin on glycogen accumulation in human skeletal muscle cells. When the glucose cannot be consumed, it causes an increase in blood sugar levels.[30] Tian et al. showed that macrophage-derived exosomes carrying miR-210 could boost T2D pathogenesis by inhibiting NDUFA4 genes.[31] Guay et al. showed that exosomal microRNAs derived from lymphocytes could promote pancreatic β-cell death.[32]

2.3 | Extracellular vesicles effects on T2D complications

2.3.1 | Diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is a microvascular complication of T2D. It is characterized by damage to cardiac microvascular endothelial cells (CMECs) and cardiomyocyte (CM) dysfunction, associated with apoptosis. Lu et al. showed that miR-130b-3p carried by adipocyte-derived EVs could negatively regulate AMPKα expression, thereby aggravating diabetic cardiac damage.[33] On the contrary, some researchers found that EVs from different cell tissues protect the heart from diabetic cardiac damage. Reetish et al. demonstrated that parasympathetic ganglionic neuron (PGN)-derived EVs could promote the expression of the anti-apoptotic protein Bcl-2. Moreover, their data also showed that PGN-derived exosomes reverse pro-apoptotic proteins Caspase-3 and Bax.[34] Lin et al. indicated that mesenchymal stem cell (MSC)-derived EVs could reduce diabetes mellitus-induced myocardial injury and fibrosis by restraining the transforming growth factor-beta 1/drosophila mothers against decapentaplegic homologue 2 (TGF-β1/Smad2) signalling pathway.[35] Crewe et al. found that small EVs released by adipocytes can be absorbed by cardiomyocytes, thus protecting them from acute oxidative stress.[36] Therefore, these cell-derived exosomes are expected to become a new therapy for diabetic cardiomyopathy.

2.3.2 | Diabetic retinopathy

Diabetic retinopathy (DR), a chronic complication of T2D caused by poor control of blood glucose, is characterized by retinal pericyte loss and abnormal angiogenesis. It has been reported that some EVs play a crucial role in vascular injury and DR progression. Cao et al. found that MSC-derived exosomal lncRNA SNHG7 could interfere with high glucose-induced endothelial–mesenchymal transition (EndMT) and tube formation of human retinal microvascular endothelial cells (HRMECs) through the miR-34a-5p/XBP1 signalling pathway.[37] These findings may support some new treatment options for DR and other eye diseases. In addition, Li et al. demonstrated that microRNA 17-3p carried by MSC-derived exosomes could suppress STAT1, promoting retinopathy-associated apoptosis.[38]

Moreover, DR is closely associated with Miller cells, which have a significant effect on the maintenance and function of retinal cells. Zhang et al. confirmed that plasma-derived exosomes activate the PI3K/Akt signalling network, which can activate Yes-associated protein (YAP) and develop the fibrogenic activity of Miller cells. The enhanced fibre activity of Miller cells contributes to profibrotic cytokines expression in DR and aggravates the condition.[39]

2.3.3 | Diabetic nephropathy

Diabetic nephropathy (DN) is a severe complication of diabetes with a poor prognosis that impairs kidney structure and function. Jin et al. illustrated that ADSC exosomes enhance miR-486 expression. MiR-486 overexpression can inhibit the drosophila mothers against decapentaplegic homologues 1/mechanistic target of rapamycin (Smad1/mTOR) signalling pathway in podocytes, improving DN symptoms. Therefore, ADSCs-Exo may become a new target for DN treatment.[40] Zhu et al. demonstrated that high glucose-treated macrophages release more exosomes and carry more TGF-β1 mRNA.

These exosomes are transferred to mesangial cells, resulting in increased TGF-β1 expression. TGF-β is considered vital in renal interstitial fibrosis, so they speculated that exosomes carrying TGF-β1 mRNA could promote renal fibrosis.[41] In addition, DN is also associated with tubulointerstitial inflammation. Lv et al. demonstrated that when tubular epithelial cells (TECs) are damaged, miR-19b-3p-enriched miR-19b-3p-enriched exosomes are secreted, and endocytosed by macrophages. Subsequently, miR-19b-3p increases NF-κB expression via directly targeting SOCS-1 to promote the M1 macrophage activation. This process mediates the communication between TECs and macrophages, causing tubulointerstitial inflammation.[42] These studies suggest that EVs may contribute to DN by promoting renal fibrosis and inducing tubulointerstitial inflammation.

2.3.4 | Diabetic peripheral neuropathy

Diabetic neuropathy is another diabetes complication caused by damage to the peripheral and autonomic nervous systems, causing systemic symptoms. Distal symmetric polyneuropathy manifested as a 'stocking and glove' distribution affecting the hands and lower limbs is considered a common form of diabetic neuropathy. Currently, the major pathological changes of diabetic neuropathy are not considered demyelinating neuropathy, but Schwann cells (SC) as the chronic hyperglycaemia target. Wang et al. indicated that SC-derived exosomes reverse diabetes-reduced miRNA (miR)-21, −27a and −146a and diabetes-increased semaphorin 6A (SEMA6A), Ras homologue gene family member A (RhoA), phosphatase and tensin homologue (PTEN) and nuclear factor-κB (NF-κB). They speculate that SC-derived exosomes have a potential role in diabetic neuropathy therapy.[43] The NF-κB pathway is the common downstream pathway that activates diabetic peripheral neuropathy (DPN). Fan et al. used diabetic mice to illustrate that mesenchymal stromal cell exosomes significantly decreased pro-inflammatory cytokines and repressed the inflammatory response through converting macrophages into M2 phenotype with anti-inflammatory effects. In addition, they found that mesenchymal stromal cell-exosomal miRNAs can restrain the TLR4/NF-κB signalling pathway expression, thereby alleviating DPN.[44]

2.3.5 | Diabetic wound

Diabetic patients have a persistent inflammatory response in the wounds, leading to delayed wound healing. Macrophage-derived exosomes can inhibit this inflammatory response. Li et al. found that macrophage-derived exosomes can reduce TNF-α and IL-6 secretion and subsequently inhibit the inflammatory signalling pathway to improve wound healing in diabetes.[45] In addition, diabetic wound (DW) is closely related to fibroblasts function. Li et al. suggested that human keratinocyte-derived exosomes carrying miR-21 could down-regulate phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and reversion inducing cysteine-rich protein with kazal motif (RECK) protein levels. Down-regulation of PTEN and RECK protein levels activates the MAPK/ERK signalling pathway, promoting fibroblasts' function; they concluded that miR-21 has a potential role in DW treatment.[46] Bian et al. speculated that MSC-EVs might inhibit the RAGE pathway and activate the Smad pathway to enhance the fibroblasts' function and promote proliferation.[47] Xiong et al. showed that enrichment of miR-20b-5p in exosomes could inhibit the Wnt9b/β-catenin signalling pathway, thus exerting anti-angiogenic effects and delaying DW healing. They believe that miR-20b-5p inhibitors of circulating exosomes can reverse DW[48] (Table 1).

3 | THE POTENTIAL OF EVS IN THE TREATMENT OF T2D AND ITS COMPLICATIONS

Research on EVs as a treatment for T2D and its complications is still in the preclinical stages, and few findings have been translated into clinical application. Although EVs provide a new treatment direction for T2D and its complications, there is still a lack of corresponding research on EVs' clinical administration route and dosage (Table 2).

3.1 | Research status of association between drug therapy and EVs

The main treatment for T2D patients is drug and insulin therapies. Studies have shown that medication affects the EVs number and content. For example, Ghai et al. treated 31 T2D patients with metformin, showing that EVs-carried miRNAs levels in the patients before the treatment dropped to a level similar to that of healthy controls.[49] Mullins et al. selected exenatide to treat Alzheimer's disease and showed that exenatide reversed insulin resistance in the brain and reduced Aβ42 levels in EVs.[50] However, further research is needed on the effects of drug therapy on EVs, which would provide a new direction for therapeutic interventions and disease surveillance.

TABLE 1 The potential mechanisms of EVs in T2D complications

Active molecule	Source	Disease	Effect	Reference
miR-130b-3p	Adipocyte-derived EVs	DCM	MiR-130b-3p carried by adipocyte-derived EVs aggravates diabetic cardiac damage.	Lu et al.[33]
Bcl-2	PGN-derived EVs	DCM	PGN-derived EVs enhance expression levels of the anti-apoptotic protein Bcl-2, preventing the heart from damage.	Reetish et al.[34]
Unrevealed	MSC-derived EVs	DCM	Decrease diabetes mellitus-induced myocardial injury and fibrosis through restraining TGF-β1/Smad2 signalling pathway	Lin et al.[35]
Unrevealed	Small EVs released by adipocytes	DCM	Small EVs released by adipocytes can be absorbed by cardiomyocytes, thus protecting cardiomyocytes from acute oxidative stress.	Crewe et al.[36]
lncSNHG7	MSC-derived exosomes	DR	Inhibit EndMT and tube formation of HRMECs through interacting with miR-34a-5p/XBP1 signalling pathway.	Cao et al.[37]
microRNA 17-3p	MSC-derived exosomes	DR	MicroRNA 17-3p carried from MSC-derived exosomes can inhibit retinopathy cell apoptosis.	Li et al.[38]
Unrevealed	Plasma-derived exosomes	DR	Aggravate the process of DR.	Zhang et al.[39]
miRNA-486	ADSC-derived exosomes	DN	ADSCs-exo can improve the symptoms of DN by regulating the Smad1/mTOR signalling pathway.	Jin et al.[40]
TGF-β1 mRNA	Exosomes released from macrophages	DN	TGF-β1 mRNA can promote renal fibrosis	Zhu et al.[41]
miR-19b-3p	TECs-exosomes	DN	miR-19b-3p can enhance tubulointerstitial inflammation by promoting the M1 macrophage activation	Lv et al.[42]
Unrevealed	SC-derived exosomes	DPN	Reverse diabetes.	Wang et al.[43]
miRNAs	mesenchymal stromal cell exosomes	DPN	Alleviate DPN through restraining the TLR4/NF-κB signalling pathway expression	Fan et al.[44]
Unrevealed	macrophage-derived exosomes	DW	Reduce the secretion of TNF-α and IL-6 and subsequently inhibit the inflammatory signalling pathway to improve wound healing in diabetes.	Li et al.[45]
miR-21	human keratinocyte-derived exosomes	DW	miR-21 could promote the function of fibroblasts.	Li et al.[46]
Unrevealed	Msc-evs	DW	MSC-EVs might inhibit the RAGE pathway and activate the Samd pathway, to enhance the fibroblasts function and promote proliferation	Bian et al.[47]
miR-20b-5p	Circulating exosomes	DW	miR-20b-5p have anti-angiogenic effects.	Xiong et al.[48]

Abbreviations: DCM, diabetic cardiomyopathy; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; DW, diabetic wound; EndMT, endothelial–mesenchymal transition; HRMECs, human retinal microvascular endothelial cells; IL-6, interleukin 6; MSC, mesenchymal stem cells; PGN, parasympathetic ganglionic neuron; SC, Schwann cells; STAT3, signal transducer and activator of transcription 3; T2D, type 2 diabetes; TECs, tubular epithelial cells; TGF-β1/Smad2, transforming growth factor-beta 1/drosophila mothers against decapentaplegic homologs 2; TLR4/TRIF, toll-like receptor 4/toll-interleukine-1 receptor domain-containing adapter-inducing interferon-β; TNF-α, tumour necrosis factor alpha.

TABLE 2 List of EVs as treatment tools for T2D and its complications

Active molecule	Source	Disease	Effect	Reference
STAT3	ADCS-derived exosomes	T2D	STAT3 induce anti-inflammatory M2 phenotypes, resulting in significant improvement in glucose tolerance and insulin sensitivity.	Zhao et al.[20]
Unrevealed	HucMSC-exosomes	T2D	Alleviated T2D by reducing insulin resistance and β-cell damage.	Sun et al.[51]
miRNAs	Circulating exosomes	T2D	Improve the glucose tolerance in recipient mouse by regulating fibroblast growth factor-21 expression.	Thomou et al.[52]
PDGF-BB	CD31+EVs	T2D	Reduce the apoptosis of vascular smooth muscle cells	Togliatto et al.[53]
microRNA-126	Endothelial particles	DCM	Endothelial particles promote vascular endothelial cell repair	Jansen et al.[54]
Unrevealed	EVs from BMSCs	DPN	Improve DPN.	Singh et al.[55]
Unrevealed	Human umbilical cord-derived mesenchymal stem cell-derived exosomes	DW	Improve the wound healing ability.	Yang et al.[56]
MiR-192	EVs extracted from bone marrow stem cells	DR	Released miR-192, which delayed the inflammatory response and angiogenesis of DR.	Gu et al.[57]
Unrevealed	ADSC-Exo	DN	Reduce the podocyte apoptosis.	Jin et al.[40]
Unrevealed	Bone marrow MSC-derived exosomes	DN	Reverse the progression of fibrosis	Grange et al.[58]

Abbreviations: ADSCs, adipose-derived stem cells; BMSCs, bone marrow mesenchymal stromal cells; DCM, diabetic cardiomyopathy; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; DW, diabetic wound; HucMSC, Human Mesenchymal Stem Cell; MSC, mesenchymal stem cells; STAT3, signal transducer and activator of transcription 3; T2D, type 2 diabetes.

3.2 | Extracellular vesicles as tools of treatment of T2D

Extracellular vesicles can cross biological barriers, easily obtain from body fluids and remain stable in circulation without degradation. Extracellular vesicles secreted by some cells can carry nucleic acids, proteins and small molecule drugs to the receptor cells to play a corresponding role. Increasing studies have been made on EVs as T2D treatment in recent years. Many studies demonstrated that some exosomes from stem cells might have potential therapeutic effects on T2D. Zhao et al. found that exosomes from adipose-derived stem cells (ADSCs) can transfer into macrophages. These exosome-carried active STAT3 can induce macrophage polarization to the anti-inflammatory M2 phenotype by transactivating arginase-1, regulating insulin sensitivity. There are limitations to applying ADSC-derived exosomes in clinical treatment, and the route and frequency of exosome administration also need to be considered.[20] Sun et al. injected HucMSC exosomes into the tail vein of high-fat diet-fed mice with T2D. The exosomes effectively alleviated T2D by reducing insulin resistance and β-cell damage in the injected mice.[51] The above research expounds that EVs from stem cells can become a new direction for T2D treatment in the future. In addition, Thomou et al. found that circulating exosomal miRNAs originate mainly from adipose tissue, and that brown adipose tissue transplant could improve the glucose tolerance in recipient mice by regulating the fibroblast growth factor-21 expression.[52] Togliatto et al. proved that PDGF-BB carried by CD31+EVs could be used to treat diabetes by reducing the apoptosis of vascular smooth muscle cells.[53]

3.3 | Extracellular vesicles as tools for the treatment of type 2 diabetes complications

Recently, some studies have used EVs to slow the development of T2D complications, such as DCM, DPN, DW, DR, and DN. Jansen et al. found that endothelial particles could promote vascular endothelial cell repair by delivering microRNA-126. These results suggest that endothelial particles may have a therapeutic function in vascular disease.[54] Singh et al. fused the exosomes secreted by bone marrow mesenchymal stromal cells (BMSCs) with liposome-containing polypyrrole nanoparticles to form an

TABLE 3 Possible candidate markers of EVs in T2D and its complications

Cargo	Expression	Circulating source	Compared subject	Effect	Reference
miR-10b miR-23-3p	Increased	Serum	$n = 52$ control versus $n = 100$ individuals with prediabetes	Two miRNAs highly regulated in the PREDM group as compared with the CT group	Parrizas et al.[59]
miR-23a miR-192	Increased	Plasma	Control subjects versus T2D subjects	Exosomal levels of miR-23a and miR-192 were significantly higher in T2D subjects	Liu et al.[61]
EVs	Increased	Intestinal microbes	Control subjects versus T2D subjects	EVs may be caused by the increase of intestinal permeability of T2DM patients	Nah et al.[62]
miRNAs		Plasma CD31+EVs	Control versus T2D-C versus T2D-NC subjects	miRNAs shuttled by plasma CD31+EVs have more diagnostic potential than whole plasma miRNA levels	Prattichizzo et al.[63]
EVs	Increased	plasma	Euglycaemia versus Diabetes	Insulin resistance increases EVs secretion	Freeman et al.[64]
miR-92a	Decreased	serum	Control versus cAMP	Exosomal miR-92a concentrations in serum were inversely correlated with human brown fat activity	Chen et al.[65]
mRNA	Increased	Urine	Healthy versus Diabetic versus DKD subjects	Urinary EV UMOD mRNA levels are progressively elevated from T2DM to DKD groups	Yamamoto et al.[66]
miR-30b-5p	Decreased	Urine	T2DKD versus T2DNRF versus CCKD	Reduced miR-30b-5p is associated with renal impairment	Zang et al.[67]
AEBP1 mRNA	Increased	Plasma	T2D versus DKD subjects	The expression of AEBP1 mRNA of plasma EVs increased significantly in DKD	Tao et al.[68]
miRNA-21 miRNA-126	Increased	Plasma	Healthy versus Diabetic versus DKD subjects	miR measurement in EVs may improve the biomarker sensitivity of these miRs for microvascular injury in DKD	Florijn et al.[69]

Abbreviations: CCKD, controls with chronic kidney disease; CT, control subjects; DKD, diabetic kidney disease; PREDM, prediabetes; T2D, type 2 diabetes; T2D-C, type 2 diabetes-complications; T2DKD, type 2 diabetes mellitus and DKD; T2D-NC, type 2 diabetes-non-complications.

exosomal complex, and injected it intramuscularly into a DPN rat model. They found that the morphology, muscle mass, and integrity of the gastrocnemius muscle of mice injected with the exosome system returned to normal, improving the DPN.[55] Currently, DW treatments are still inadequate. Many studies have shown that exosome therapy can promote DW healing. Yang et al. induced a diabetic mouse model and applied human umbilical cord-derived mesenchymal stem cell-derived exosomes wrapped in thermosensitive PF-127 hydrogel to treat wounds. The results suggest that these exosomes can improve wound healing. However, some problems, including potential tumorigenicity, limited tissue targeting, rapid expansion and inactivation at room temperature, limit the clinical application of exosomes in DW.[56] To examine the effects of EVs in DR caused blindness, Gu et al. injected EVs extracted from bone marrow stem cells into the vitreous of diabetic mice. These EVs released miR-192 and delayed the inflammatory response and angiogenesis in DR.[57] Recent studies have found that EVs can be used for DN treatment. Jin et al. found that ADSC-Exo treatment of DN mice significantly reduces podocyte apoptosis.[40] Grange et al. used bone marrow MSC-derived exosomes to reverse fibrosis progression in diabetic mice.[58] Altogether, these studies demonstrate that stem cell-secreted EVs have great potential in treating T2D and its complications.

4 | EXTRACELLULAR VESICLES AS POTENTIAL BIOMARKERS IN T2D AND ITS COMPLICATIONS

Early and pre-diabetic forms of T2D are mostly asymptomatic and difficult to diagnose, leading to missed optimal timing for treatment. However, in recent years, EVs have been a promising new biomarker for diagnosing T2D and its complications. Not all pre-diabetic patients develop diabetes. After 4 years of follow-up of pre-diabetic patients, Parrizas et al. found significant increases in miR-10b and miR-23-3p in serum exosomes of subjects who developed diabetes. This suggested that these serum exosomal miRNAs may serve as diagnostic markers for diabetes. Due to the lack of standardized methods for the isolation and quantification of exosomal miRNAs, it is difficult to apply them in the clinical setting.[59] Saravanan et al. found that exo-miRNAs 29b-3p and 216a-5p appeared earlier than other indexes after islet damage.[60] Similarly, Liu et al. demonstrated that exosomal miR-23a and miR-192 are potential diagnostic T2D biomarkers.[61] Nah et al. studied the relationship between EVs derived from intestinal microbes and intestinal barrier in T2D patients. They found that the correlation between EVs in faeces, serum and urine of T2D patients was significantly consistent, which might be caused by increased intestinal permeability. Therefore, intestinal EVs can be used as biomarkers of the intestinal barrier.[62] Prattichizzo et al. showed that miRNAs shuttled by plasma CD31+ EVs have more potential than whole plasma miRNA in diagnosing diabetes and its complications.[63] Freeman et al. found that insulin resistance increases EVs secretion associated with diabetic oxidative stress and inflammatory responses. These results suggested that plasma EVs can be used as diagnostic markers of T2D.[64] Chen et al. demonstrated that the concentrations of exosomal miR-92a in serum inversely correlate with human brown fat activity, suggesting that serum exosomes have diagnostic value.[65] At present, DN diagnosis is mainly based on serum creatinine and urinary protein excretion, but these markers have low diagnostic sensitivity and are easily affected by diet. Therefore, more sensitive markers are urgently needed to identify early diabetic renal damage. Yamamoto et al. tested urinary EVs mRNA on 242 subjects, and found that these mRNAs are highly sensitive to DN recognition and are expected to be useful biomarkers for identifying DN progression and stages.[66] Diabetic kidney injury patients usually present lipoprotein metabolism disorder and dyslipidaemia. Zang et al. suggest that the urinary exosome miR-30b-5p was positively correlated with dyslipidaemia, which indicated that urinary exosome miR-30b-5p might become a potential marker for DN diagnosis.[67] However, urinary EVs are susceptible to various reasons, such as drinking water and urinary tract infections. Tao et al. found that the AEBP1 mRNA expression in plasma EVs increased significantly in DN, which allowed to distinguish T2D from DN.[68] Florijn et al. showed that circulating microRNAs among EVs, especially miRNA-21 and miRNA-126, are important markers of diabetic microvascular injury in DN.[69] These studies suggest that EVs may be a potential diagnostic marker for T2D and its complications (Table 3). However, these achievements are rarely translated into clinical applications, mainly due to the small sample size. Furthermore, the lack of standardization of methods for isolating and quantifying exosomal miRNAs makes it challenging to apply them in the clinic.[59]

5 | CONCLUSION

In recent years, increasing evidence suggested that EVs as the potential aetiology of T2D and a key to its complications. Extracellular vesicles regulate the inflammatory response by affecting the M1/M2 macrophage polarization and thus affect insulin resistance. Glucose metabolism can be affected by regulating GLUT4 expression levels. Insulin resistance is induced by cutting insulin receptors. There are many other mechanisms by which EVs can regulate T2D,

such as stimulation of glycogen accumulation and NDUFA gene inhibition. These vesicles can also participate in the development of diabetic complications such as diabetic nephropathy, diabetic cardiomyopathy, and diabetic retinopathy through various pathways. In general, the occurrence and development of T2D and its complications is associated with abnormal molecules carried by EVs, including proteins and nucleic acids, but the specific pathogenesis is still unclear. Notably, some EV contents, such as mRNA, are expected to be potential diagnostic indicators in patients with T2D and complications. At present, hypoglycaemic drugs in clinical treatment can also have corresponding effects on EVs, but there is not enough research in this regard. A small number of studies have also demonstrated the therapeutic effect of EVs in animal models of diabetes.

In addition, EVs have shown great potential as a natural drug delivery system. The EVs' bilayer protects its cargo from removal by the body, thereby prolonging its circulating half-life. Some therapeutic agents, including small molecule drugs, RNA, proteins, and oligonucleotides, can be preloaded into chemically or biologically modified EVs. Therefore, EVs can be used as drug carriers to treat T2D. At present, relevant animal experiments have successfully applied EVs in treating T2D and its complications, especially for stem cell-derived EVs, but the clinical application is still lacking. Studies on the relationship between EVs and various diseases are still in the screening stage of diagnostic markers, and only a few studies have transformed them into marker diagnostic reagents. Therefore, the application of EVs in the diagnosis and treatment of T2D and its complications, and the evaluation of disease progression still need to be further examined.

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CONFLICT OF INTEREST

The authors state that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors were involved in the conception, drafting and review of the article outline and subsequent drafts. All authors critically reviewed the manuscript and approved the final version for submission.

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SUPPORTING INFORMATION

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