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Diabetes complications and extracellular vesicle therapy

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Abstract
Diabetes is a chronic disorder characterized by dysregulated glycemic conditions. Diabetic complications include microvascular and macrovascular abnormalities and account for high morbidity and mortality rates in patients. Current clinical approaches for diabetic complications are limited to symptomatic treatments and tight control of blood sugar levels. Extracellular vesicles (EVs) released by somatic and stem cells have recently emerged as a new class of potent cell-free therapeutic delivery packets with a great potential to treat diabetic complications. EVs contain a mixture of bioactive molecules and can affect underlying pathological processes in favor of tissue healing. In addition, EVs have low immunogenicity and high storage capacity while maintaining nearly the same regenerative and immunomodulatory effects compared to current cell-based therapies. Therefore, EVs have received increasing attention for diabetes-related complications in recent years. In this review, we provide an outlook on diabetic complications and summarizes new knowledge and advances in EV applications. Moreover, we highlight recommendations for future EV-related research.

Keywords Extracellular vesicle · Diabetic complications · Exosomes · Diabetes · Pathophysiology · Therapy

1 Introduction

Diabetes is recognized as a significant public health problem worldwide, with its global prevalence estimated to be approximately 9.3% (463 million people) in 2019, increasing to 10.9% (700 million) by 2045 [1]. Type 2 diabetes (T2D) is characterized mainly by high blood sugar due to insulin resistance and insufficient insulin production, as well as persistent low-grade inflammation in peripheral tissues [2]. On the other hand, type 1 diabetes (T1D) results from loss of insulin-producing β cells due to autoimmune destruction [3].

It is believed that almost half of diabetic patients are not diagnosed and are thus at higher risk of developing diabetic complications [1]. Diabetic vascular complications broadly occur among T1D and T2D patients and are mainly divided into microvascular and macrovascular. Microvascular complications include peripheral neuropathy, nephropathy, and retinopathy. Macrovascular complications comprise cardiovascular disease, stroke, and peripheral artery disease (PAD) [4]. Diabetic foot ulcers (DFU) have been defined as the result of peripheral neuropathy, PAD, and infection, which accounts for the leading cause of lower limb amputation [5]. Current conventional therapeutic methods for diabetes complications are limited to symptomatic treatments and tighter control of hyperglycemia, which can slow but not halt disease progression and, much less, provide any curative effects. Therefore, there is an urgent need for new therapeutic strategies for diabetes complications affecting the underlying complications' pathological mechanisms [6].

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Cell therapy, explicitly using stromal and stem cells, represent a promising approach to treat diabetic complications. Stem cells are characterized by their self-renewal and differentiation potential [7]. In many regenerative medicine applications, their mechanism of action arises not from their engraftment potential but rather their ability to migrate to an injured site, where they exert a significant part of their effects by releasing a broad spectrum of paracrine factors, either in solution or packaged in extracellular vesicles (EVs), in what has collectively termed the secretome [8–10]. Thus, stem cells and specifically mesenchymal stromal cells (MSCs), act as "mobile drug stores" by releasing anti-inflammatory, anti-apoptotic, immunomodulatory, and proangiogenic factors [9–11]. Cytokines and growth factors were initially considered the only active therapeutic factors of stem cells. However, recent studies support that the underlying therapeutic activity of stem cells is attributed to their released EVs, especially exosomes [12–14]. In addition to stem cells, distant and neighboring somatic cells have also been shown to affect target cells by releasing EVs that can lead to phenotypic changes [15]. EVs have thus received increased attention as a cell-free therapeutic approach [16]. In this review, we discuss current state-of-the-art advances in applying EVs as a treatment for diabetes complications.

2 Extracellular vesicles

2.1 Classification, characterization, and mode of action

Most cells can release membrane-bound vesicles (30–2000 nm) called extracellular vesicles (EVs) containing various substances, such as lipids, proteins, and nucleic acids. EVs act as signal transducers exchanging various components between cells. EVs have been classified into three main subtypes: apoptotic bodies, microvesicles (MVs), and exosomes based on their mechanism of biogenesis [6, 17]. The overlapping size range and density of EVs make their isolation challenging [18]. The apoptotic bodies range from 500 to 2000 nm in diameter, derived from apoptotic cells and express surface markers from their cell of origin [19, 20]. Exosomes range in size from 30 to 180 nm and are marked by specific markers, including tetraspanins (CD9, CD63, and CD81), HSP70, and TSG101 [17, 21]. MVs range from 50 to 1000 nm in diameter; specific MV markers, though less characterized, include flotillin-2, ARF6, and CD40 [22].

Exosomes originate from a multi-step process where the plasma membrane internalizes to form an early endosome, followed by the inward budding of the endosomal membrane to form intra-luminal vesicles (ILVs). At this point, selected cargoes are delivered to the ILVs through endosomal sorting complexes required for transport (ESCRT)-dependent or ESCRT-independent machinery. The endosome is considered a mature multivesicular body (MVB) that contains several ILVs. These MVBs will fuse with the plasma membrane and release the ILVs into the extracellular space, called exosomes (Fig. 1). Exosomes mainly include ESCRT-related proteins (ALIX and TSG101), MHC-I and MHC-II, microRNAs (miRNAs), messenger RNAs (mRNA), long noncoding RNAs (lncRNAs), cytoskeletal proteins, and metabolic enzymes (GAPDH and ATPase) [15, 17, 23].

EV-mediated intercellular communication requires binding to the plasma membrane, followed by activating the plasma membrane receptors and downstream intracellular signaling or by vesicle internalization (endocytosis, micropinocytosis, and phagocytosis) or direct fusion with target cells [15, 24]**.** Released EVs deliver their contents to recipient cells to promote functional changes that further affect their physiological status.

2.2 Biological effects

EVs have been appreciated for their crucial role in cell-to-cell communication and their unique potential as delivery vehicles for various signal molecules. Recently, numerous studies have demonstrated EVs' critical physiological functions, as they have been found in various body fluids such as saliva, urine, blood, and others [25]. Examples of EVs' physiological roles include the maintenance of iron homeostasis [26], presenting antigens between immune cells as an essential part of the acquired immune system [27], and activating the innate immunity of the upper airway against pathogens [28]. On the other hand, some EVs have pathological roles in the development/progression of neurological diseases, cancer, and diabetes [21, 29].

Importantly, EVs have attracted increasing attention as a cell-free alternative approach to current stem cell therapies, with more beneficial properties including lower immunogenicity, tumorigenicity, and higher storage capacity. EVs are derived from various cell types, including stem cells [30], progenitor cells [31], endothelial cells [32], stromal cells [33], and many others. EVs content promotes the repair and regeneration of the injured tissues [16] and are delivered into the injury site through various routes of injection based on the needs of the target disease; including intravenous [34], subcutaneous [35], intradermal [36], subconjunctival [37], intracavernous tissue [30], and loaded by a bioscaffold [38]. The therapeutic potentials of EVs make them good choices for use in different areas of regenerative medicine, as they have been already investigated in lung, liver, and kidney, as well as ischemic heart disease, skin burns and wounds, and stroke [16]. For instance, MSC-derived EVs have a high regenerative potential [39], while EVs derived from endothelial progenitor cells (EPCs) have great

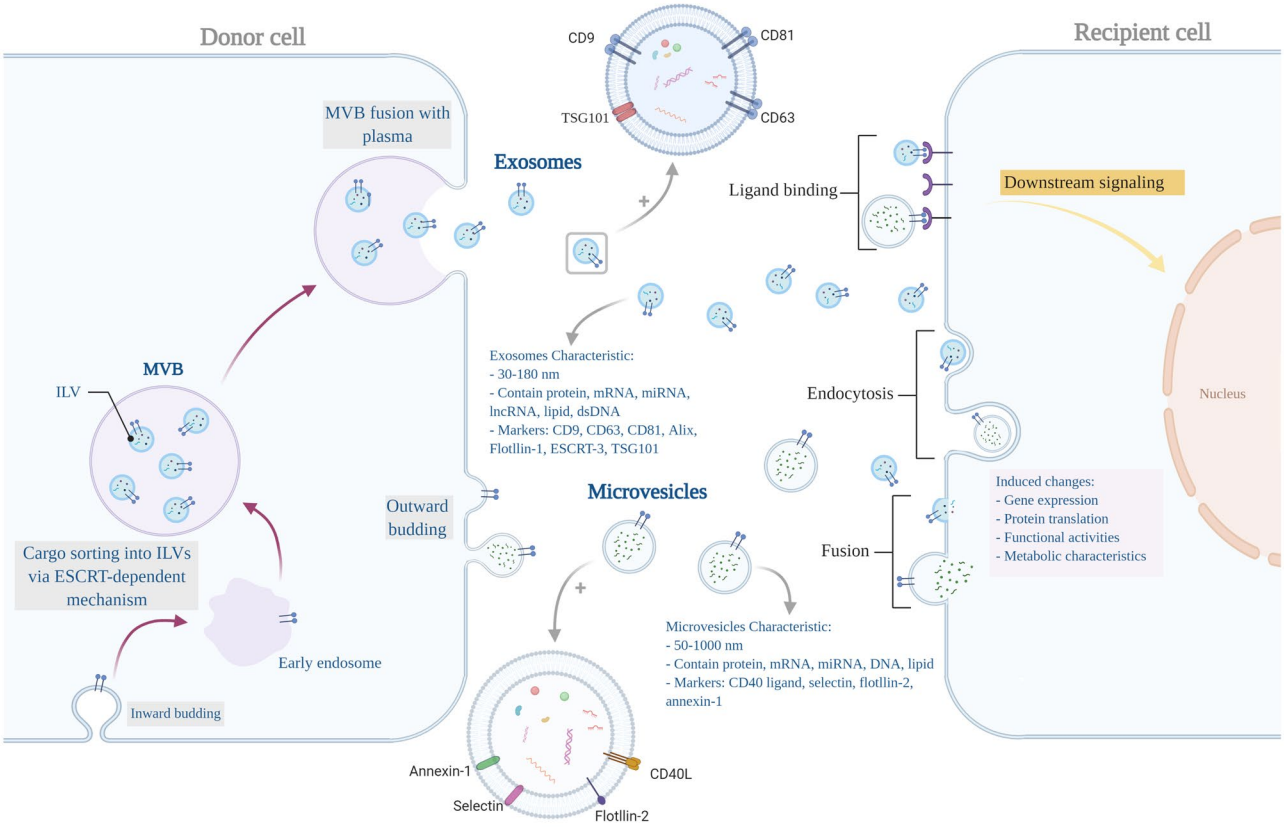

Fig. 1 Extracellular vesicles biogenesis and characteristics; exosomes and microvesicles. ESCRT endosomal sorting complexes required for transport, ILV intra-luminal vesicles, MVB multivesicular bodies

proangiogenic potential [31]. Moreover, the combination of EVs with novel strategies such as engineered bioscaffolds may improve their application [40]. Furthermore, engineering EVs to increase their therapeutic potential and use them for drug delivery makes them a new class of biological nanotherapeutics that can be readily introduced to the precision medicine field [41].

3 EVs for diabetes complications

Evidence suggests that diabetes vascular complications are mainly caused by chronic inflammation and oxidative stress in diabetic patients [42]. Indeed, most diabetes complications are characterized by low tissue regeneration and repair capacity [43, 44]. As EVs demonstrated considerable immunomodulatory and regenerative potential [16, 39], numerous studies have investigated EVs as a new regenerative agent for treating diabetes complications.

Most of the available studies reviewed here used the term "exosomes" while only a few used "EVs". To include all studies and be more scientifically correct, we decided to use "EVs" throughout the paper, unless the exosome validation was specifically shown and confirmed by the authors. This is due to several considerations; initially, many pioneer studies called all the EVs; exosomes; without proper validation and/or being aware of different subclasses of EVs. Also, evidence suggests that it is not trivial to purify a specific EV subtype (e.g., exosomes) based on a single property-based method, such as vesicle size, density, or presence of a specific marker [45]. Even most of the procedures aiming to isolate pure exosomes seem not to be entirely successful [46]. Moreover, using "extracellular vesicle" as one of the keywords in the searching process, we obtained a more significant number of studies to be included.

3.1 Cardiomyopathy

Cardiovascular diseases are the leading cause of death in diabetic patients, mainly due to coronary artery disease, hypertension, and cardiomyopathy. Diabetic cardiomyopathy is characterized by dilatation and hypertrophy of the left ventricle, with diastolic and/or systolic dysfunction. Myocardial fibrosis, myocyte hypertrophy, impaired cellular calcium balance, and damaged myocardial contractile proteins are the most well-known anatomic and physiological changes in the

myocardium, resulting in the development of diabetic cardiomyopathy [47]. Further molecular/cellular mechanisms of cardiomyopathy include abnormal insulin signaling, oxidative stress, lipotoxicity, mitochondrial dysfunction, altered fatty acid metabolism, chronic inflammation, and increased cardiomyocytes' apoptosis [48, 49]. EVs have been investigated for their therapeutic potential to fight abnormalities in diabetic cardiomyopathy (Table 1), mainly through reducing cardiac remodeling and angiogenesis induction (Fig. 2).

3.1.1 Suppression of myocardial remodeling

Cardiac remodeling, including myocardial fibrosis and myocardial hypertrophy, occurs in the early stage of diabetes-related cardiomyopathy, which mainly results in left ventricular diastolic dysfunction [50, 51]. Therefore, suppressing ventricular remodeling might be promising in improving cardiac function.

In the diabetic rat, left ventricular collagen (LVC) is significantly increased, while myocardial tissue lipid metabolism-related enzymes were significantly decreased. Treatment with MSC-exosomes was shown to reduce LVC and fibrosis by inhibiting TGF-β1/Smad2 signaling and induction of lipid metabolism-related enzymes [49]. In addition, exosome treatment reduced Smad2/3 phosphorylation, suppressed the hyperglycemia-induced expression of alpha-smooth muscle actin, and inhibited differentiation of fibroblasts [52]. TGF-β promotes Smad phosphorylation and regulates the proliferation and migration of fibroblasts and collagen I and III synthesis [53, 54]. Cardiac cell apoptosis is among the leading causes of ventricular remodeling [55]; thus, improving cardiac cell viability may abolish the remodeling process. In this regard, parasympathetic ganglionic neuronal exosomes have improved the viability and inhibit apoptosis in hyperglycemic H9c2 cardiomyoblast cell lines [56].

Cardiac injury after stroke is common, and diabetes exacerbates stroke-related cardiac complications [57]. These complications include systolic and diastolic dysfunction resulting from cardiac remodeling, oxidative stress, and excessive inflammation [58]. Exosomes derived from CD133 + umbilical cord blood cells (UC-CD133 +) have improved cardiac systolic and diastolic function after stroke in diabetic mice. In addition, cardiomyocyte hypertrophy and interstitial fibrosis through TGF-β downregulation were also improved upon treatment [59].

3.1.2 Myocardial angiogenesis

Diabetic myocardium shows reduced vascularity due to apoptosis of endothelial cells (EC) and interstitial fibrosis [51]. Therefore, promoting angiogenesis to increase myocardial repair seems to be an avenue for treating diabetic cardiomyopathy.

UC-CD133 + exosome treatment resulted in increased myocardial angiogenesis, possibly resulting from reduced oxidative stress and inflammation in diabetic stroke-related heart injury. UC-CD133 + exosomes also increased cardiac miR-126 expression in diabetic-stroke mice, followed by decreased expression of its target genes, including Spred-1, VCAM, and MCP-1 [59]. Downregulation of Spred-1 induces cardiac neovascularization [60], and decreases in VCAM and MCP-1 expression reduce M1 macrophage activation and infiltration of inflammatory cells into the cardiac tissue after stroke [58]. Wang et al. suggested that HSP20 overexpression in cardiomyocytes, whose reduced expression may contribute to diabetic cardiomyopathy, induces exosome secretion by interacting with TSG101. These exosomes have promoted EC proliferation under in vitro high-glucose conditions and prevent cardiac remodeling in diabetic mice. Since diabetes is closely associated with apoptosis of myocardial ECs and subsequent reduction in capillary density, the authors suggest that HSP20-engineered exosomes might reverse cardiomyopathy by reducing myocardial remodeling and promoting neovascularization [34].

3.2 Myocardial infarction

Diabetes is a risk factor for myocardial infarction (MI) [61]. Ischemia resulting from coronary artery occlusion induces the accumulation of intracellular ions and worsens tissue acidosis. Reperfusion following the restoration of coronary blood flow leads to rapid alterations in intracellular ion concentrations and rapid renormalization of pH, paradoxically damaging cardiomyocytes [62]. Exosomes have been suggested to act as a cardioprotective agent against ischemia/reperfusion injury [63]. Exosomes from non-diabetic rats, human plasma, and human umbilical vein endothelial cells (HUVECs) have been shown to have a cardioprotective effect against hypoxia/reoxygenation injury in diabetic rat cardiomyocytes [64].

3.3 Cognitive impairment

Diabetes increases the risk of developing cognitive impairment by 2 to threefold [65]. Diabetic cognitive impairment (DCI) pathophysiology includes insulin signaling defects, neuroinflammation, dysfunctional swollen astrocytes, vascular abnormalities, decreased hippocampal synaptic plasticity, and oxidative stress-related neuronal damage [65, 66]. Unfortunately, current treatments for DCI are ineffective and limited to hyperglycemic control [65]. Thus, novel approaches like EV treatment with regenerative effects for neurons and/or astrocytes are highly desirable (Table 2).

Table 1 Extracellular vesicle application in diabetic cardiomyopathy and MI

REF	[64]	[34]	[56]	[49]	[59]
OUTCOMES	Induced cardioprotection against IR and reduced apoptosis in cardiomyocytes	Increased cardiomyocytes exosome production, increased angiogenesis, reduced ROS generation and cardiomyocytes apoptosis, improved myocardial function, reduced cardiac fibrosis and remodeling	Improved viability and reduced apoptosis in hyperglycemic cardiomyoblasts	Reduced fibrosis and LVC, increased lipid metabolism-related enzymes	Decreased blood glucose and weight loss, increased cardiac systolic function, decreased interstitial fibrosis and remodeling, increased myocardial capillary density, decreased inflammation and oxidative stress
DOWNSTREAM GENES	/	Interacting with Tsg101	/	TGF-β1, Smad1, FATPs and FA-B-oxidase upregulation	Spred1, VCAM, and MCP-1 downregulation
DOWNSTREAM SIGNALING	/	/	/	TGF-β1/Smad2 suppression	TGF-β suppression
FUNCTIONAL CARGO	/	HSP20 Survivin p-Akt	/	/	miR-126
ASSAY DURATION (IN VIVO)	/	14 weeks	/	12 weeks	4 weeks
ADMINISTRATION ROUTE (IN VIVO)	/	IV injection via tail-vein	/	IV injection via tail-vein	IV injection via tail-vein
EXPERIMENTAL MODEL	In vitro (primary rat cardiomyocytes- cell-based IR model)	In vitro (MCEC line) In vivo (STZ-TG mice model with cardiac-specific overexpression of HSP20)	In vitro (HG-H9c2 cells, a rat cardiomyoblasts cell line)	In vivo (HFD + STZ-SD-rats)	In vitro (mouse brain ECs) In vivo (BKs.cg-m + / + Lepr db/J mice photothrombotic ischemic stroke model)
CONTROL	PBS	PBS WT-exosome	SGN-derived exosome	PBS	PBS
EV ISOLATION METHOD	UC	UC	ExoQuick TC	UC	ExoQuick TC
EV CONCENTRATION	10^8/ml or 0.1 μg, 10^7/ ml (HUVECs)	In vitro (10 μg/ml) In vivo (1 μg/g body weight)	20 μg/ml	100 μg exosomes in 200 μl PBS	20 μg exosomes in 200 μl PBS
EV SOURCE	Human and rat plasma, HUVECs	HSP20 overexpressing cardiomyocytes	PGNs	BM-MSCs	UCDCs (CD133 +)
COMPLICATION	MI	Cardiomyopathy			

MI myocardial infarction, HUVECs human umbilical vein endothelial cells, PBS phosphate buffer saline, IR ischemia–reperfusion, HSP heat shock protein, WT wild type, MCEC mouse cardiac endothelial cells, STZ streptozotocin, SD Sprague Dawley, TG transgenic, PGN parasympathetic ganglionic neurons, SGN sympathetic ganglionic neurons, HG high glucose, BM-MSC bone marrow derived mesenchymal stromal cells, HFD high fat diet, IV intravenous, UCDCs umbilical cord derived cells, ECs endothelial cells, UC Ultracentrifugation

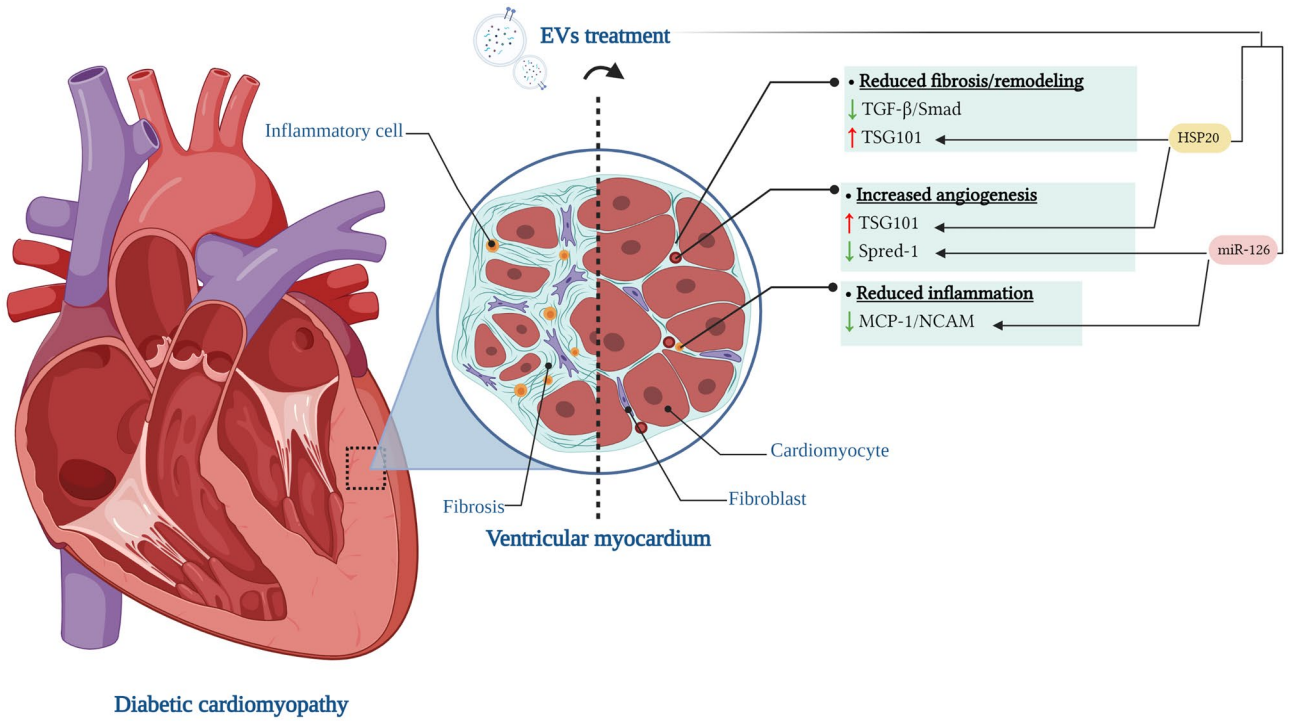

Fig. 2 Extracellular vesicle application in diabetic cardiomyopathy; improve diabetic cardiomyopathy by decreasing cardiac fibrosis and inflammation and augmenting cardiac tissue angiogenesis

Table 2 Extracellular vesicle application in diabetic cognitive impairment

REF	[65]	[71]	[68]
OUTCOMES	Improved learning and memory, decreased mitochondrial damage and oxidative stress, increased synaptic density and plasticity, improved ultrastructural abnormalities in CA1 region	Reduced PrP^c accumulation, improved short-term memory	Improved Cognitive function
DOWNSTREAM GENES	/	/	/
DOWNSTREAM SIGNALING	/	/	/
FUNCTIONAL CARGO	/	miR-146a	/
ASSAY DURATION (IN VIVO)	13 weeks	/	/
ADMINISTRATION ROUTE (IN VIVO)	ICV	ICV	ICV
EXPERIMENTAL MODEL	In vivo (STZ-C57BL/6 J mice)	In vivo (obese diabetic C57BL/ksJ)	In vivo (STZ-C57BL/6 J mice)
CONTROL	aCSF	Scramble loaded BEC-exosomes	aCSF
EV ISOLATION METHOD	UC, sucrose step gradient	UC	UC
EV CONCENTRATION	In vivo (0.5 μg in 2 μl aCSF)	In vivo (2–3 μg per day for 3 days)	In vivo (0.5 μg exosomes in 2 μl aCSF)
EV SOURCE	BM-MSCs (rat)	BECs (mouse)	BM-MSCs (mouse)

aCSF artificial cerebrospinal fluid, BM-MSCs bone marrow mesenchymal stromal cells, STZ streptozotocin, ICV intra-cerebroventricular, BECs brain endothelial cells, PrP^c cellular prion protein, UC Ultracentrifugation

Exosomes derived from rat bone marrow mesenchymal stromal cells (BM-MSCs) have been shown to improve learning and memory in DCI mice by affecting damaged neurons and astrocytes [65]. Previous studies suggested that memory loss correlates with synaptic loss [67]. Diabetic mice also show decreased synaptic density and plasticity. Exosome treatment reverted these mainly through ameliorating oxidative stress and recovered vacuolation

and fragmentation of microtubules in the pyramidal neurons of the CA1 region of the mouse brain. Exosomes also decreased the number of microglia, astrocytic end-foot process swelling, and blood vessel abnormalities [65]. Similar studies confirmed that intracranial injection of mouse BM-MSC-exosomes could ameliorate cognitive dysfunction in diabetic mice [68].

Endogenous rat BM-MSCs can be stimulated to release more exosomes containing higher levels of miR-146a via an enriched environment, including active communication, stress reduction, and exercise. miR-146a has an anti-inflammatory role that can ameliorate cognitive impairment [69]. Conversely, miR-146a downregulation in diabetic mice has been shown to increase cellular prion protein (PrP^c) production, which is implicated in cognitive dysfunction and dementia [70]. Intraventricular delivery of exosomes derived from mouse brain ECs enriched with miR-146a has been shown to decrease PrP^c accumulation and improve short-term memory function in diabetic mice [71].

3.4 Erectile dysfunction

Diabetic men are three times more likely to develop erectile dysfunction (ED) than non-diabetic ones. A normal penile erection depends on neurovascular mechanisms, including corpus cavernosum smooth muscle (CCSM) relaxation and increased arterial blood flow. Diabetic ED is associated with corporal endothelial dysfunction, decreased vascular regeneration, decreased CCSM volume, neural degeneration, and fibrosis [72]. Many studies have demonstrated that EVs can improve endothelial function, endothelial and smooth muscle cell viability, and angiogenesis (Fig. 3) (Table 3).

3.4.1 Endothelial function improvement

Hyperglycemia, excessive oxidative stress, and advanced glycation endproduct (AGE) formation cause cavernosal endothelial malfunction. The main feature of impaired endothelial function is the inability to produce and/or respond to vasodilation mediators, usually caused by the loss of eNOS–eNO levels and activity. This reduces endothelial-induced relaxation of vascular and smooth muscle, leading to diabetic ED [72].

EVs derived from urine-derived stem cells (USCs) have been shown to enhance EC function within the corpus cavernosum (indicated by an increase in eNOS expression), reducing collagen deposition and increasing CCSM cells in the penile tissue, and improving the neurogenic-mediated erectile response (indicated by an increase in nNOS expression) in diabetic rats [30]. Exosomes derived from CCSM cells (CCSMC-exosomes) also demonstrated antifibrotic ability while inducing eNOS and nNOS expression. This

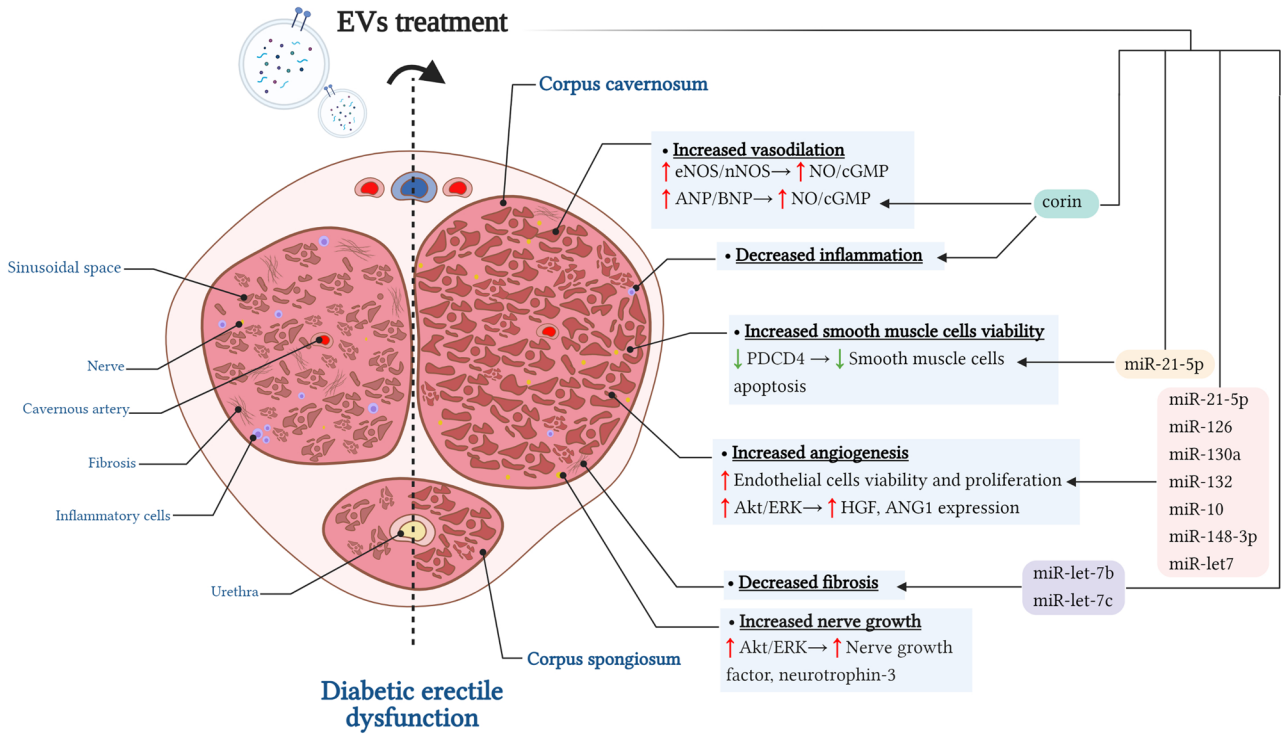

Fig. 3 Extracellular vesicle application in diabetic erectile dysfunction. EVs improve the erection mainly by enhancing cavernous vasodilation and angiogenesis and abolishing tissue fibrosis resulting in increased penile blood flow

Table 3 Extracellular vesicle application in erectile dysfunction

REF	[84]	[74]	[80]	[79]	[75]	[82]	[30]
OUTCOMES	Increased angiogenesis and neurite sprouting in vitro, increased cavernous contents of smooth muscle cells, ECs, pericytes and neuronal cells in vivo, increased ICP	Increased cavernous contents of smooth muscle cells and decreased corporal fibrosis, increased ICP	Reduced apoptosis and increased proliferation of CCSMCs, increased cavernous contents of CCSMCs, increased ICP	Inhibited corporal ECs and smooth muscle cells apoptosis, increased ICP	Increased corporal angiogenesis and nerve content, increased ICP	Induced Angiogenesis in vitro, increased corporal ECs Proliferation, reduced corpus cavernosum fibrosis, increased ICP	Increased corporal ECs content and improved ECs function, increased corporal smooth muscle cell content and decreased collagen deposition, improved penile neural regeneration, increased ICP
DOWNSTREAM GENES	HGF, Ang-1, NGF, neurotrophin-3, and eNOS upregulation, Ang-2 downregulation	nNOS, eNOS, NO, and cGMP upregulation, TGF-β downregulation	PDCD4, Bax, and cleaved-caspase downregulation, Bcl-2 and PCNA upregulation	Bcl-2 upregulation, Caspase-3 downregulation	ANP, BNP, cGMP, and nNOS upregulation, TNF-α, IL-6, and IL-1B downregulation	/	eNOS, p-eNOS, nNOS and CD31 upregulation
DOWNSTREAM SIGNALING	Erk/Akt	NO/cGMP induction	/	/	/	/	/
FUNCTIONAL CARGO	/	/	miR-21-5p	/	Corin	miR-126 miR-130a miR-132 miR-let7b miR-let7c	miR-21-5p miR-let7 miR-10 miR-30 miR-148a-3p
ASSAY DURATION (IN VIVO)	2 weeks	/	4 weeks	4 weeks	2 weeks	4 weeks	4 weeks
ADMINISTRATION ROUTE (IN VIVO)	ICV	ICV	IV	IC	IV	IC	IC
EXPERIMENTAL MODEL	In vitro (HG-MCEC, HG-MCP) In vivo (STZ-C57BL/6 mice) Ex vivo (HG-aortas from C57BL/6 mice, HG-MPG)	In vitro (HG-CCSMCs) In vivo (STZ-SD-rats)	In vitro (HG-CCSMCs) In vivo (STZ-SD-rats)	In vivo (HFD + STZ-SD-rats)	In vivo (STZ-SD-rats)	In vitro (HG-HUVECs) In vivo (STZ-SD-rats)	In vivo (STZ-SD-rats)
CONTROL	HBS, ESCs	BMSC-exosomes, ADSC-exosomes	PBS, exosomes derived from MSC pretreated with miR-21-5p inhibitor, exosomes derived from MSC pretreated with NC-miR	PBS ADSCs	Normal saline, exosomes from corin-silenced ADSCs	PBS	PBS
EV ISOLATION METHOD	Serial extrusion + UC	Ultrafiltration + ExoQuick TC	UC	Ultrafiltration + UC	Ultrafiltration + UC	ExoQuick TC	UC

Table 3 (continued)

REF	[84]	[74]	[80]	[79]	[75]	[82]	[30]
EV CONCENTRATION	In vitro (1 µg/mL) In vivo (1 µg/per 20 µl HBS)	In vitro (100 µg exosomes in 200 µl PBS) In vivo (100 µg exosomes in 200 µl PBS)	In vitro (20 µg) In vivo (100 µg exosomes in 0.2 mM PBS)	In vivo (100 µg exosomes in 0.2 ml PBS)	In vivo (200 µg exosomes in 100 µl PBS)	In vitro (1, 10 µg exosomes per ml) In vivo (10, 100 µg exosomes in 200 µl PBS)	In vivo (100 µg exosomes in 100 µl of PBS)
EV SOURCE	ESCs	CCSMCs	MSCs pretreated with miR-21-5p mimic	ADSCs	ADSCs	ADSCs	USCs (human)

ESCs embryonic stem cells, HBS HEPES-buffered saline, HG high glucose, MCPs mouse cavernous pericytes, STZ streptozotocin, ECs endothelial cells, ICP intracavernous pressure, ICV intracavernous vein, CCSMCs corpus cavernosum smooth muscle cells, BMSCs bone marrow stromal cells, ADSCs adipose derived stromal cells, SD Sprague Dawley, MSCs mesenchymal stromal cells, NC noncoding, IV intravenous, UC Ultracentrifugation, PBS phosphate buffer saline, HUVECs human umbilical vein endothelial cells, IC intracavernous, HFD high fat diet, USCs urine derived stem cells

results in upregulation of the NO/cGMP signaling pathway downregulated in ED [73]. CCSMC-exosome treatment also improved erectile function and was more efficiently taken up by corpus cavernosum than exosomes derived from BM-MSCs and adipose-derived stem cells (ADSCs) [74].

ADSC-exosomes have improved erectile function in diabetic rats via delivery of the enzyme Corin [75]. Corin activates pro-atrial natriuretic peptide (ANP) and pro-brain natriuretic peptide (BNP), known regulators for blood pressure [76]. Moreover, ANP and BNP promote vasodilation through the stimulation of cGMP, a known vasodilatory factor. Indeed, ADSC-exosomes induced the expression of ANP, BNP, nNOS, and cGMP in the CCSM of diabetic rats [75, 77] and suppressed pro-inflammatory factors such as IL-1β, TNF-α, and IL-6 in the cavernous tissues of diabetic rats [75].

3.4.2 Endothelial and smooth muscle cells viability improvement

Diabetes and its related oxidative stressors lead to cavernosal ECs and CCSMCs apoptosis, further affecting penile hemodynamics and ED [78]. ADSC-derived exosomes have been shown to suppress the apoptosis of these cells in diabetic rats. This further led to improved erectile function [79].

In another study, MSC-derived exosomes containing miR-21-5p also ameliorated ED in diabetic rats through PDCD4 downregulation and consequently reduced CCSMCs apoptosis [80]. Thus, PDCD4 regulates vascular smooth muscle cell apoptosis [81]; it is upregulated in the cavernous tissue of diabetic ED rats and is associated with CCSMCs apoptosis [80].

3.4.3 Angiogenesis induction

Diabetes impairs angiogenesis and vasculogenesis through decreased VEGF expression, reduced number of circulating EPCs, chronic inflammation, and reduced levels and activity of eNO in the cavernous tissue. As a result, poor vascular regeneration exacerbates endothelial dysfunction and thereby aggravates ED [72].

ADSC-derived exosomes promoted angiogenesis through EC proliferation and fibrosis reduction in the corpus cavernosum, which resulted in restored erectile function in diabetic rats. These exosomes contained proangiogenic miR-126, miR-130a, and miR-132, and antifibrotic miR-let7b and miR-let7c [82]. ADSC-derived exosomes were also shown to increase the nerve content in the cavernous tissues of diabetic rats [75]. USC-EVs have also been shown to increase EC proliferation in diabetic rats and promote neovascularization ascribed to proangiogenic let-7, miR-10, miR-30 families, miR-21-5p, and miR-148a-3p expression [30].

To overcome the EV production shortage, some groups have introduced the use of cell-derived EV-mimetic nanovesicles (EMNVs), generated by serial extrusion of cells through filters. These EMNVs are similar to natural EVs, with significantly higher production rates [83]. Kwon et al. showed that EMNVs produced from embryonic stem cells improved erectile function in diabetic mice. This was through induction of penile neurovascular regeneration through activation of cell survival/proliferation signaling pathways (Akt/ERK) and subsequent increases in levels of hepatocyte growth factor (HGF), angiopoietin-1 (ANG1), nerve growth factor, and neurotrophin-3, which are known to be proangiogenic and neurotrophic factors [84]. ANG1 has a vital role in blood vessel regeneration [85], and HGF is a potent proangiogenic factor that stimulates the migration of ECs and pericytes [86]. Furthermore, intracavernous injection of these EMNVs increased the CCSMCs, ECs, and pericytes in diabetic mice cavernous tissue. EMNVs also accelerated microvascular sprouting in the aortic ring and neurite sprouting in the central pelvic ganglion under the high-glucose condition ex vivo [84].

3.5 Nephropathy

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease, causing various changes in the kidney, including hemodynamic alterations, increased oxidative stress, mesangial cell expansion, podocyte injury, development of glomerulosclerosis, and fibrosis [87, 88]. Therefore, protecting podocytes against hyperglycemia-induced injury is beneficial for DN treatment. Since current treatments delay but do not prevent DN development, developing new therapies is essential [88]. EV applications for DN mainly focus on inhibiting podocyte injury under diabetic conditions through four main strategies: regulation of VEGF expression, epithelial-to-mesenchymal transition (EMT) suppression, immunomodulation, and autophagy enhancement (Fig. 4) (Table 4).

3.5.1 Regulation of VEGF expression

There have been contradictory findings on the role of VEGF in DN pathogenesis. Some of the studies suggested that

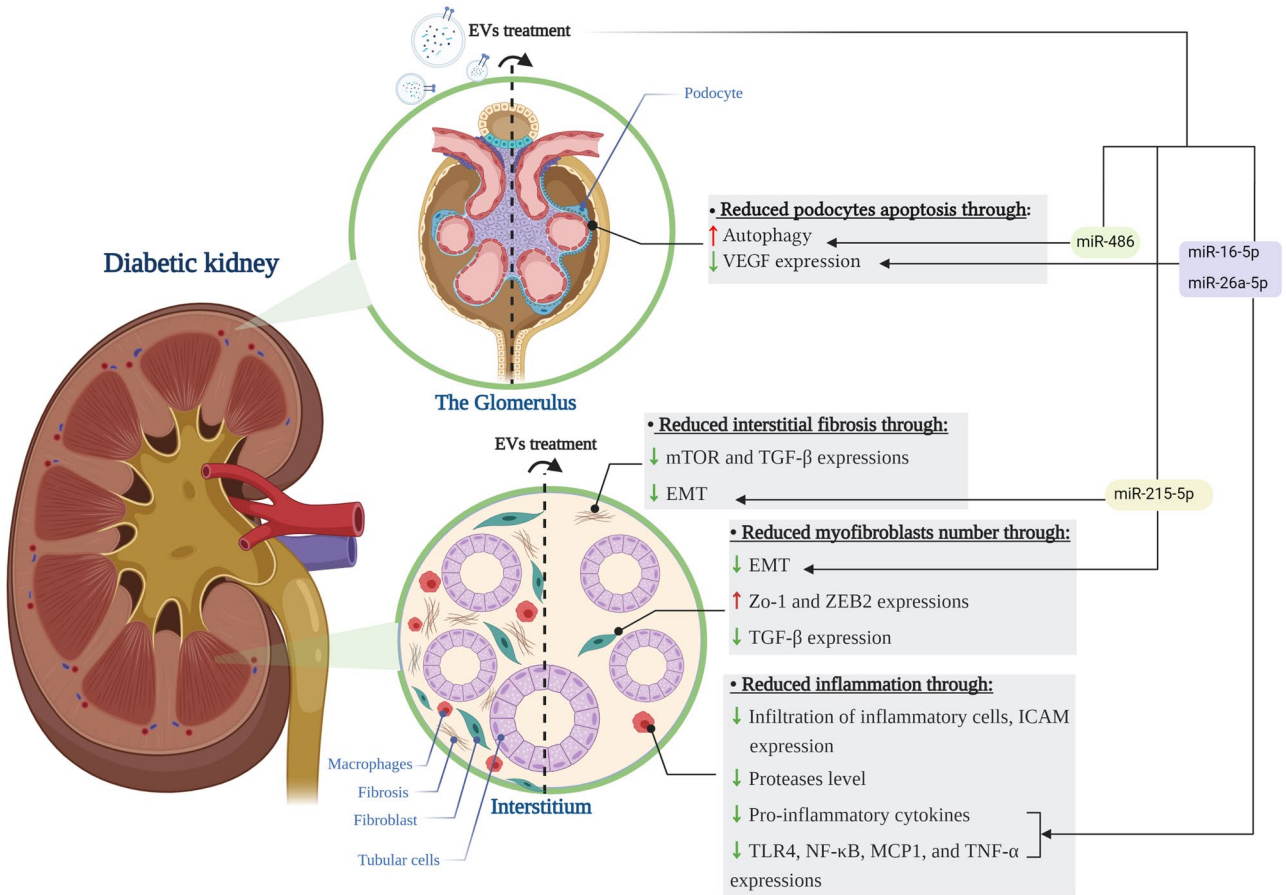

Fig. 4 Extracellular vesicle application in diabetic nephropathy. EVs enhance podocyte survival through different mechanisms. EMT epithelial-to-mesenchymal transition

Table 4 Extracellular vesicle application in diabetic nephropathy

REF	[90]	[91]	[88]	[97]	[98]	[99]	[108]	[101]
OUTCOMES	Prevented podocytes apoptosis	Prevented podocytes apoptosis	Promoted angiogenesis, inhibited podocytes apoptosis	Prevented EMT, reduced BMDCs infiltration and inflammation	Inhibited EMT and fibrosis	Inhibited EMT, migration, and apoptosis of podocytes	Enhanced autophagy, inhibited podocytes apoptosis	Enhanced autophagy, reduced fibrosis
DOWNSTREAM GENES	VEGFA, TNF-α, and MCP-1 suppression	VEGFA and TLR4 downregulation	Caspase-3 downregulation	TGF-β suppression, zo-1 induction in TECs, ICAM-1 downregulation	SNAL1 and collagen-1 downregulation	ZEB2 downregulation	/	TGF-β and collagen inhibition
DOWNSTREAM SIGNALING	/	VEGFA/NF-κB suppression	/	/	/	/	Smad1/mTOR suppression	mTOR suppression
FUNCTIONAL CARGO	miR-16-5p	miR-26a-5p	VEGFA, BMG-7, TGF-β, angiogenin	/	/	miR-215-5p	miR-486	/
ASSAY DURATION (IN VIVO)	12 weeks	12 weeks	12 weeks	8 weeks	4 weeks	/	12 weeks	12 weeks
ADMINISTRATION ROUTE (IN VIVO)	IV via tail-vein	IV via tail-vein	IV via tail-vein	Renal subcapsular space injection (exosomes), IV via tail-vein (cell derivatives)	IV via tail-vein	/	IV via tail-vein	IV via tail-vein
EXPERIMENTAL MODEL	In vitro (HPDCs cultures) In vivo (STZ-SD-rats)	In vitro (MPC5) In vivo (C57BL/ksJ db/db mice)	In vitro (immortalized human podocytes) In vivo (STZ-SD-rats)	In vitro (PRC cultures) In vivo (C57BL/6 GFP-transgenic mice)	In vivo (STZ-NSG mice)	In vitro (MPC5)	In vitro (MPC5) In vivo (C57BL/ksJ db/db mice)	In vivo (STZ-albino rats)
CONTROL	PBS	PBS, miR-26a-5p antagomir	PBS	PBS	Saline, fibroblast-exosomes	PBS	PBS	PBS
EV ISOLATION METHOD	ExoQuick TC	UC	Ultra-Clear tube + UC	Total exosome isolation reagent	UC	UC + exosome extraction kit	UC + exosome extraction kit	UC
EV CONCENTRATION	100 μg exosomes in 200 μl PBS	/	100 μg exosomes in PBS to final volume of 200 μl	5.3×10^7 exosomes particles in 200 μl PBS, 1 mg/ml derivatives	1×10^{10} exosomes particles	/	/	100 μg/kg/dose exosomes in 200 μl PBS
EV SOURCE	hUSCs, miR-16-5p overexpressing hUSCs	ADSCs	USCs	MSCs	MSCs/HLSCs	ADSCs	ADSCs	MSCs

hUSCs human urine derived stem cells, HPDCs human podocytes derived cells, STZ streptozotocin, SD Sprague Dawley, ADSCs adipose derived stromal cells, MPC5 mouse podocyte cells 5, MSCs mesenchymal stromal cells, PRC primary renal cells, TECs tubular epithelial cells, HLSCs human liver stem cells, EMT epithelial-mesenchymal transition, IV intravenous, PBS phosphate buffer saline, UC Ultracentrifugation

VEGF is responsible for DN development. On the other hand, some others have suggested that VEGF can reverse DN progression. Overexpression of VEGF promotes DN by increasing the vascular ECs' permeability and proangiogenic behavior (including proliferation and migration) and via induction of matrix-degrading protease. In addition, VEGF overexpression leads to the thickening of the glomerular basement membrane in DN [89]. Thus, suppression of VEGF overexpression could be a potential strategy to prevent DN development.

While stem cells are generally reported as proangiogenic, their anti-angiogenic behavior may reflect an ability to sense pathological angiogenesis and act against it. Duan et al. indicated that overexpression of miR-16-5p in human USC-derived exosomes suppresses VEGFA expression and protects podocytes against hyperglycemia and apoptosis in vitro and in vivo. Hyperglycemia has been shown to inhibit miR-16-5p and nephrin expression, and promote the expression of VEGFA and TGF-β1 in nephrocytes of diabetic rats, while treatment with exosomes reverted these changes [90]. High levels of miR-26a-5p in EVs derived from ADSCs also led to the inhibition of glomerular podocyte apoptosis, mainly through VEGFA downregulation [91]. DN is characterized by miR-26a-5p downregulation [92].

Interestingly, VEGF's low level could be harmful by reducing podocyte number and progression of renal disease [89]. Therefore, increasing VEGF level could serve as a strategy to ameliorate DN. In another study, exosomes extracted from human USCs ameliorated DN in diabetic rats. These exosomes contained VEGFA, BMG-7, TGF, and angiogenin and inhibited podocyte apoptosis by suppressing overexpression of caspase-3 and promoted glomerular angiogenesis [88]. Considering these contradictory findings, further studies are needed to suggest which strategy (suppression or induction) for VEGF regulation is more effective for DN treatment.

3.5.2 EMT suppression

Myofibroblasts are key actors in the promotion of renal glomerular and interstitial fibrosis [93]. These profibrotic myofibroblasts are generated by the EMT of tubular epithelial cells (TECs) and glomerular podocytes [94]. One of the crucial factors in EMT induction is TGF-β [95], leading to renal fibrosis [96]. Thus, suppression of the EMT process seems to be a potentially practical approach to reduce fibrosis.

MSC-exosomes were shown to prevent tubular EMT by suppressing TGF-β and increasing the tight junction protein ZO-1. ZO-1 is expressed in TECs and is involved in the renal tubule as a barrier [97]. It has also been shown that exosomes derived from MSCs and human liver stem-like cells improve renal function by preventing and reversing fibrosis in a mouse model via delivering miRNAs and other proteins that reduce collagen-1 and SNAI1 (initiators of EMT) [98].

Moreover, Jin et al. demonstrated that ADSC-exosomes deliver miR-215-5p to podocytes to downregulate ZEB, thus protecting against hyperglycemia-evoked EMT progression, as well as podocyte migration and apoptosis. ZEBs are DNA binding transcription factors with well-documented roles in triggering EMT and cell migration [99, 100].

3.5.3 Inflammation suppression

Inflammatory cells, including macrophages, excessively infiltrate into the diabetic kidney and interact with TECs and further stimulate renal parenchymal cells to produce TNF-α and caspase-3, followed by TEC apoptosis [97]. Therefore, suppressing inflammatory cell infiltration and proinflammatory cytokine production may protect kidneys against detrimental DN development.

Treatment with MSC exosomes has been shown to suppress abnormal immune cell infiltration into the diabetic kidneys and reduce proinflammatory cytokine production by downregulating ICAM-1, an adhesion molecule [97]. Conversely, AGE deposition leads to increased ICAM-1 in TECs and peritubular capillaries [101], which is involved in the inflammatory cells' recruitment into the kidneys [97].

Increased expression of MCP-1 and TNF-α was critical in developing DN by inducing renal inflammation [89, 102]. As mentioned previously, exosomes containing miR-26a-5p lead to the inhibition of podocyte apoptosis mainly by downregulating TLR4, which subsequently inactivates the NF-κB/VEGFA pathway [91]. TLR4 activation stimulates the expression of several proinflammatory cytokines, including TNF-α [103]. In addition, the NF-κB pathway is also involved in glomerular epithelial cell apoptosis and hyperglycemia-induced chemoattractant protein expression (e.g., MCP-1) in mesangial cells [89]. In another study, high levels of miR-16-5p in human USC-exosomes have been shown to suppress MCP-1 and TNF-α expression in the nephrocytes of diabetic rats [90].

3.5.4 Autophagy induction

Autophagy is a catabolic process for the degradation of intracellular components and is responsible for cell homeostasis, whose dysfunction facilitates podocyte injury [104]. Several signaling molecules, including mTOR, are involved in the autophagy process [105]. Activation of mTOR signaling in DN patients suggests that mTOR might mediate podocyte autophagy dysfunction [106]. Consequently, impaired autophagy results in the accumulation of AGEs and collagen in the extracellular matrix, podocytes mitochondrial impairment, and increased hypoxia and endoplasmic reticulum

(ER) stress in tubular cells [107]. mTOR activation is also known to play a vital role in glomerular and tubular cell hypertrophy and podocyte injury [107].

ADSC-exosomes containing a high level of miR-486 have been shown to inhibit Smad1/mTOR signaling pathway in podocytes. mTOR inhibition results in increased autophagy flux which protects podocytes against injury in diabetic mice [108]. MSC-exosomes have also been shown to inhibit mTOR and suppress TGF-β expression, resulting in reduced fibrosis in diabetic rat kidneys [101].

3.6 Stroke

Diabetic patients are 3 to 4 times more likely to experience a stroke, and approximately one-third of stroke patients have diabetes [109]. Diabetic stroke patients have a worse prognosis compared to non-diabetic patients [110]. Altered metabolism, impaired vasculature, and excessive inflammation aggravate vascular and white matter (WM) damage after stroke in diabetic patients [111]. Spontaneous repair that occurs post-stroke can be assisted using neurorestorative agents, such as cell therapy and/or EVs [112]. EVs demonstrated therapeutic potential in diabetic stroke (Table 5) by promoting WM remodeling, immunomodulation, and neovascularization (Fig. 5).

3.6.1 White matter remodeling

Diabetes impairs WM remodeling and oligodendrogenesis after stroke, which delays functional recovery [113]. Exosomes extracted from healthy mouse brain ECs (EC-exosomes) with high levels of miR-126 have been shown to improve neurological and cognitive functional outcomes in diabetic-stroke mice. EC-exosomes also promoted WM remodeling, characterized by increased axon and myelin density in the mouse brain. In addition, these exosomes increased axonal outgrowth in the primary cortical neurons (PCN) under the high glucose condition after oxygen–glucose deprivation (OGD) in vitro [32].

MSC-exosomes isolated from diabetic rats, but not healthy rats, improved functional outcomes after stroke in diabetic rats. Diabetic MSC-exosomes also promoted WM remodeling and increased oligodendrogenesis of diabetic rats' ischemic brains and increased PCN axonal outgrowth in vitro [112]. It has been previously suggested that diabetes or pretreatment with high glucose affects MSC secretome content in a way that improves their therapeutic potential [114]. This may help explain differences in the therapeutic potential of diabetic and healthy donor MSC-exosomes, although further studies are required to determine the exact effects of diabetes on the exosome profile. Moreover, diabetic MSC-exosomes decreased the serum levels of miR-9, increasing the expression of its targets ABCA1 and IGFR1 in the rat's brain. Diabetes is associated with declined activation of the ABCA1 gene [112], which is needed for myelination, neuronal growth, and synaptic function [115]. Decreased ABCA1 activation in the brain worsens neurological function, aggravates blood–brain barrier (BBB) leakage and demyelination, and increases oligodendrocyte and axonal injury after stroke [116, 117].

3.6.2 Immunomodulation

Post-stroke recovery is delayed in diabetic patients because of aggravated inflammation, indicated by increased microglial activation/M1 macrophage phenotype [113]. Therefore, immunomodulatory approaches seem to be promising for diabetic stroke. EC-exosomes decreased the number of M1 macrophages and increased polarization into the M2 phenotype in the diabetic mouse brain after stroke [32]. Moreover, diabetic MSC-exosomes improved the integrity of BBB via augmenting ZO-1 expression, resulting in decreased hemorrhage in diabetic-stroke rats [112]. While stroke is accompanied by impaired BBB integrity and hemorrhage in diabetic patients [111], a leaky BBB facilitates invasion of inflammatory cells and factors that aggravate inflammation and delays brain repair after stroke [118]. Diabetic MSC-exosomes decreased inflammation, indicated by declined proinflammatory microglial/M1 macrophage phenotype and the levels of inflammatory factors such as MMP-9 and MCP-1 in the diabetic mouse brain after stroke [112]. It has been documented that elevated MMP-9 after stroke implicates BBB leakage, neuronal damage, demyelination, and WM injury [119].

3.6.3 Neovascularization

It is now well-known that therapeutic strategies for post-stroke recovery must include cerebral neovascularization that will induce spontaneous recovery mechanisms, including WM remodeling [120]. In this regard, EC-exosomes have been shown to increase vascular density in the ischemic brain of diabetic mice [32].

3.7 Neuropathy

Diabetic peripheral neuropathy (DPN) is characterized by axonal loss and demyelination [121] and involves almost all types of nerve fibers. DPN treatment is currently aimed at relieving symptoms rather than resolving the underlying pathologic process [122].

Exosomes derived from healthy Schwann cells (SCs) have been demonstrated to ameliorate DPN in diabetic mice by reducing peripheral nerve injury. These exosomes improved sciatic nerve motor and sensory conduction velocities (MCV and SCV, respectively) and increased intraepidermal nerve

Table 5 Extracellular vesicle application in diabetic stroke and diabetic neuropathy

REF	[32]	[112]	[121]	[33]
OUTCOMES	Improved cognitive functional, increased axonal growth myelin density, improved vascular density, increased M2 macrophages polarization	Improved cognitive functional, increased axonal growth myelin density, improved BBB integrity and vascular density, increased M2 macrophages polarization	Improved MCV and SCV in the sciatic nerve, increased IENF and mechanical/thermal sensitivity, reduced axonal damage and demyelination, increased neurite growth and SCs migration	Improved MCV and SCV in the sciatic nerve, increased IENF and mechanical/thermal sensitivity, reduced axonal damage and demyelination, reduced inflammation and increased M2 macrophages
DOWNSTREAM GENES	/	miR-9 downregulation, ABCA1-IGFR1 upregulation, ZO-1 upregulation, MMP-9 and MCP-1 downregulation	/	TLR-4, NF-κB p65, IRAK1, TNF-α and IL-1B downregulation IL-10, TGF-β and arginase-1 upregulation
DOWNSTREAM SIGNALING	/	/	SEMA6A, RhoA, PTEN and NF-κB suppression	TLR-4/NF-κB and RAGE suppression
FUNCTIONAL CARGO	miR-126	/	miR-21, miR-27a, miR-146a	miR-17, miR-23a and miR-125b
ASSAY DURATION (IN VIVO)	4 weeks	4 weeks	8 weeks	8 weeks
ADMINISTRATION ROUTE (IN VIVO)	IV injection via tail-vein	IV injection via tail-vein	IV injection via tail-vein	IV injection via tail-vein
EXPERIMENTAL MODEL	In vitro (PCNs and ECs from Wistar rats under OGD condition) In vivo (BKS.Cg-m+/+Lepr db/J mice, photothrombotic stroke model)	In vitro (PCN from Wistar rats under OGD condition) In vivo (HFD+STZ-Wistar rats, MCAo stroke model)	In vitro (mice DRG neurons) In vivo (BKS.Cg-m+/+Lepr db/J (db/db) mice)	In vitro (intraperitoneal macrophages isolated from diabetic mice) *n vivo* (BKS.Cg-m+/+Lepr db/J (db/db) mice)
CONTROL	PBS and Liposome mimic (vehicle control)	PBS, normal MSCs-derived exosome, miR-9 overexpressing MSCs-derived exosome	Saline, FCs-derived exosome, Liposome	Saline (0.9% NaCl)
EV ISOLATION METHOD	ExoQuick TC	ExoQuick TC	Differential UC	UC
EV CONCENTRATION	In vitro (20 ng/ml) in vivo (3×10^{10} particles in the 1 ml PBS)	In vitro (20 ng/ml) In vivo (3×10^{11} particles in the 1 ml PBS)	In vitro (6×10^{9} particles/ml) In vivo (4×10^{10} particles in the 200 µl PBS/mouse)	In vitro (10^{8} or 10^{9} particles/ml) In vivo (1×10^{9} particles per injection)
EV SOURCE	Normal mouse brain ECs	Diabetic rat MSCs	SCs	MSCs
COMPLICATION	Stroke		Neuropathy	

ECs endothelial cells, PBS phosphate buffer saline, PCNs primary cortical neurons, OGD oxygen–glucose deprivation, IV intravenous, MSCs mesenchymal stromal cells, HFD high fat diet, STZ streptozotocin, MCAo middle cerebral artery occlusion, MCP-1 monocyte chemoattractant protein-1, SCs Schwann cells, FCs fibroblasts, DRG dorsal root ganglia, MCV motor conduction velocity, SCV sensory conduction velocity, IENF intraepidermal nerve fiber, UC Ultracentrifugation

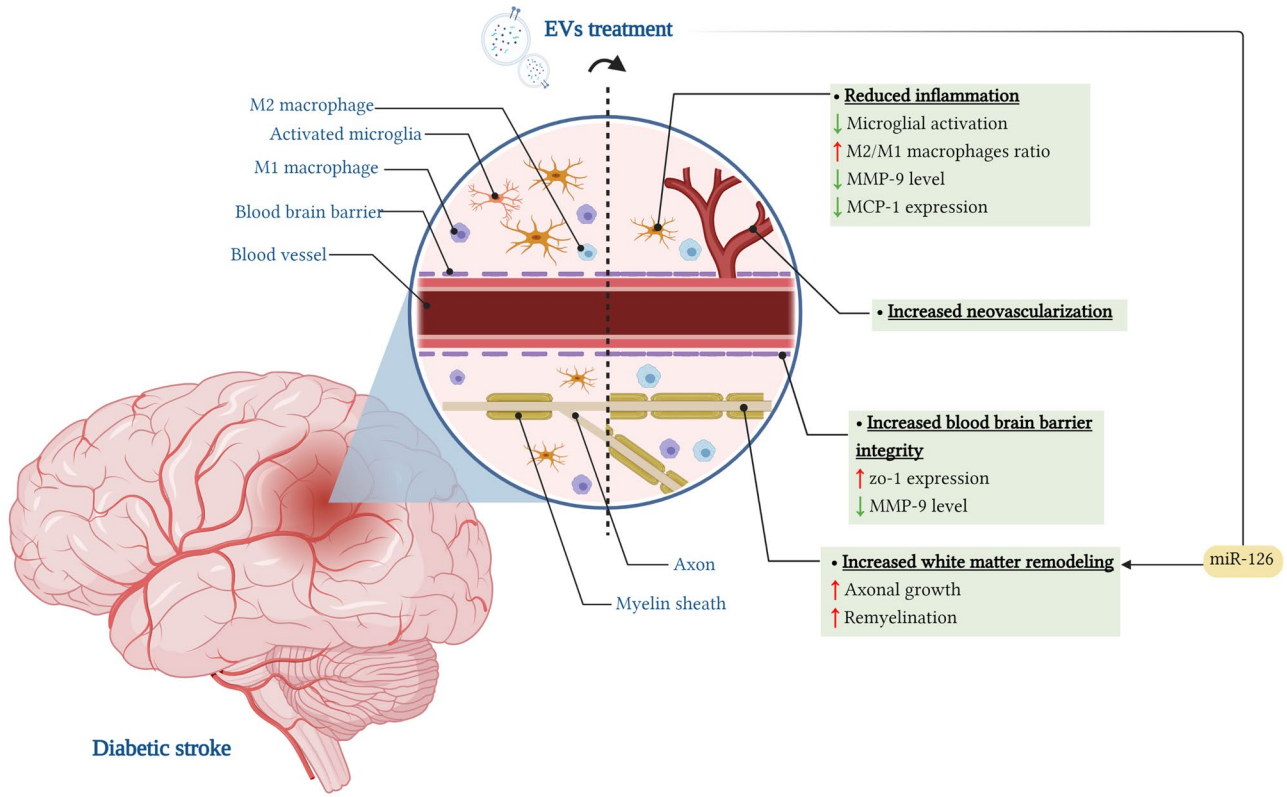

Fig. 5 Extracellular vesicle application in diabetic stroke. EVs treatment modulates inflammation, promotes angiogenesis and neural regeneration after stroke

fiber density, whose reduction is responsible for reduced mechanical and thermal sensitivity, the earliest DPN distal symptoms [121, 123]. Consequently, following exosome treatment, thermal and mechanical sensitivity was improved, demyelination and sciatic nerve axonal damage were reduced, and remyelination improved [121]. In sciatic nerve tissues, DPN has been shown to reduce miR-21, miR-27a, and miR-146a expression [124–126], thereby increasing expression of their direct targets SEMA6A, RhoA, and PTEN, respectively, as well as the indirect target NF-kB. Increased SEMA6A, RhoA, PTEN, and pNF-kB signaling pathways have been shown to damage axons and inhibit axonal growth [127–130]. SC-derived exosome treatment reverted these effects in diabetic mice by delivering miR-21, miR-27a, or miR-146a to the sciatic nerve and promoting upregulation of recipient cell microRNAs [121].

MSC-exosomes have been shown to increase microvascular density in the sciatic nerves. These exosomes have also been shown to reduce M1 macrophages, downregulate TNF-α and IL-1β, and increase arginase-1, IL-10, TGF-β expression, and M2 macrophage polarization. In addition, these exosomes, by delivering miR-17, miR-23a, and miR-125b, partially suppressed TLR4/NF-κB and AGE receptor (RAGE) signaling [33], which are known to increase inflammation and promote macrophages switching to M1, leading to DPN development [131, 132] (Fig. 6) (Table 5).

3.8 Non-healing wounds

The wound healing process consists of four partially overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Several biological mechanisms of these phases are disrupted in diabetic wound healing, mainly due to hyperglycemia, chronic inflammation, arterial dysfunction, hypoxia, and peripheral neuropathy [133]. Therapeutic potentials of EVs for diabetic wounds have been demonstrated, mainly through promoting proliferation and modulating inflammation in the wound bed (Fig. 7) (Table 6).

3.8.1 Inflammation phase

Diabetic wounds are characterized by a persistent inflammatory response after injury, which delays wound closure. The inflammatory cells are immediately recruited into the wound site following the skin injury. A high ratio of M1 to M2 macrophages increases proinflammatory cytokine levels, including IL-1, IL-6, and TNF-α, and elevates MMPs levels responsible for rapid degradation of extracellular

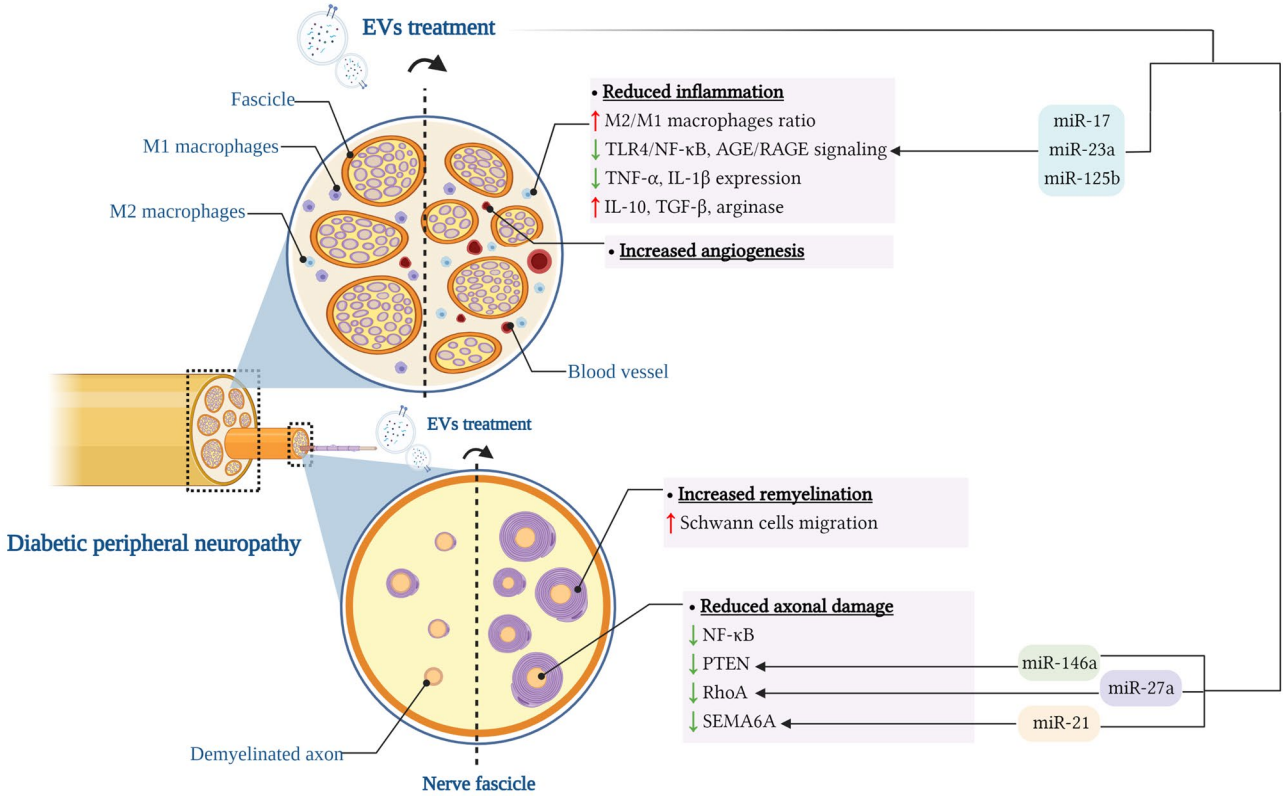

Fig. 6 Extracellular vesicle application in diabetic neuropathy. EVs improve DPN by enhancing nerve regeneration (axonal growth and remyelination), angiogenesis and reducing nerve inflammation. AGE advanced glycation endproducts, RAGE receptor of AGE

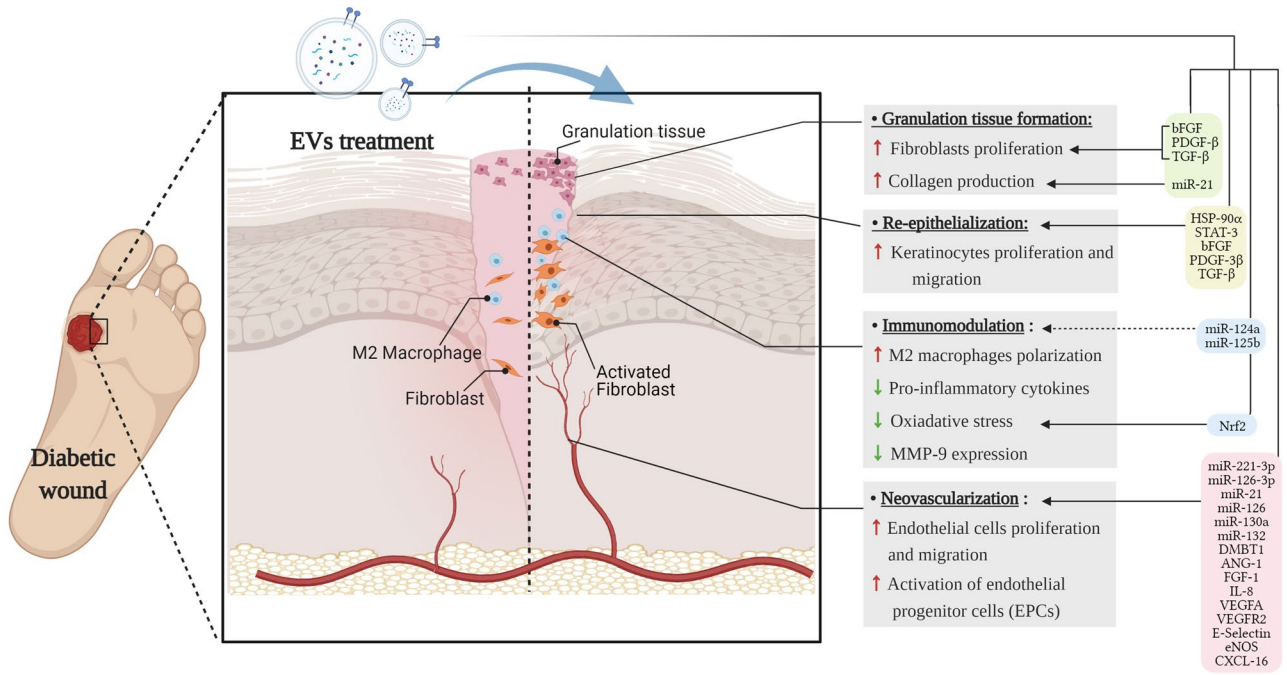

Fig. 7 Extracellular vesicle application in diabetic non-healing dermal wounds. EVs improve the wound healing process mainly through regulating Inflammation and proliferation phases

Table 6 Extracellular vesicle application in diabetic dermal wounds

REF	[135]	[35]	[142]	[147]	[144]	[148]	[154]	[36]	[156]	[157]
OUTCOMES	Reduced inflammation and oxidative stress, activated EPCs, increased angiogenesis and proliferation	Reduced inflammation, increased neovascularization and re-epithelialization	Increased angiogenesis	Increased angiogenesis and blood vessels maturation	Increased angiogenesis	Increased proliferation and migration of keratinocytes, fibroblasts and ECs	Increased angiogenesis	Increased angiogenesis and epithelialization, reduced inflammation, reduced scar formation	Increased angiogenesis and re-epithelialization, increased proliferation and migration of ECs and fibroblasts	Increased neovascularization and re-epithelialization, increased proliferation and migration, and collagen production of fibroblasts
DOWNSTREAM GENES	SMP30 and VEGF upregulation, VEGFR2 phosphorylation, NOX1, NOX4, IL-1β, IL-6, and TNF-α downregulation	IL-6, TNF-α and MMP-9 downregulation	VEGFA, VEGFR-2, CXCL-16, IL-8, ANG-1, E-selectin, eNOS and FGF-1 upregulation	/	VEGF upregulation, p27 and p57 downregulation	/	/	VEGF-A, NF-κB upregulation	/	/
DOWNSTREAM SIGNALING	/	/	/	Erk1/2	AGE/RAGE suppression	/	PI3K/AKT	NF-κB induction	Rho/YAP, Erk and AKT activation	/
FUNCTIONAL CARGO	Nrf2	/	/	? miR-21	miR-221-3p	DMBT1	miR-126	/	bFGF, PDGF-BB, VEGF and TGF-β	HSP-90α, STAT-3, miR-126, miR-130a, miR-132, miR-124a, miR-125b and miR-21
ASSAY DURATION (IN VIVO)	2 weeks	3 weeks	2 weeks	2 weeks	12 days	12 days	2 weeks	2 weeks	2 weeks	3 weeks
ADMINISTRATION ROUTE (IN VIVO)	IV through left femoral vein	SC	SC	SC	Applied directly to the wound	SC	SC	ID	Loaded by sodium alginate hydrogel wound dressing	SC/Directly applied to the wound bed

Table 6 (continued)

REF	[135]	[35]	[142]	[147]	[144]	[148]	[154]	[36]	[156]	[157]
EXPERIMENTAL MODEL	In vitro (peripheral blood EPCs) In vivo (STZ-SD-rats)	In vitro (HG-HUVECs) In vivo (STZ-SD-rats)	In vitro (HEMC-1) In vivo (STZ-SD-rats)	In vitro (HMEC-1) In vivo (STZ-SD-rats)	In vivo (STZ-C57BL/6 mice)	In vitro (HaCaT and HSFs and HMECs) In vivo (STZ-SD-rats)	In vitro (HUVECs) In vivo (STZ-SD-rats)	In vivo (STZ-C57BL/6-mice)	In vitro (HMEC-1) In vivo (STZ-SD-rats)	In vitro (HMECs) In vivo (B6. lepr db/db mice)
CONTROL	PBS	PBS	PBS	PBS	PBS	PBS	PBS	PBS, MenSCs	/	PBS
EV ISOLATION METHOD	ExoQuick Exosome precipitation solution	UC	UC	UC Ultrafiltration	Centrifugation, Exosome separation solution	Centrifugation Ultrafiltration ExoQuick-Exosome-precipitation-solution	UC	UC	Ultrafiltration + UC	Ultrafiltration
EV CONCENTRATION	In vitro (10 and 50 μg/ml)	In vitro (500 μg/ml) In vivo (100 μg/ml, 1 mg/ml)	In vitro (100 μg/ml) In vivo (100 μg/ml)	In vitro (2×10^{10} or 1×10^{11} particles/ml) In vivo (2×10^{10} or 1×10^{11} particles in 200 μl of PBS)	In vivo (0.1 μg/μl)	In vitro (100 μg/ml) In vivo (200 μg exosomes in 100 μl PBS)	In vitro (50 μg/ml) *In* vivo (100 μg exosomes in 100 μl PBS)	10 μg exosomes in 100 μl PBS	1% v/v	In vitro (1 or 10 μg/ml) In vivo (5 or 50 μg exosomes in 200 μl PBS)
EV SOURCE	ADSCs, Nrf2-overexpressing ADSCs	Macrophages (RAW 264.7 cells)	EPCs	hUCB-EPCs	EPCs	USCs	Defroxamine preconditioned BM-MSCs	MenSCs	PRP	Fibrocytes

ADSCs adipose derived stromal cells, EPCs endothelial progenitor cells, STZ streptozotocin, SD Sprague Dawley, PBS phosphate buffer saline, IV intravenous, HG high glucose, HUVECs human umbilical vein endothelial cells, SC subcutaneous, HEMC-1 human microvascular endothelial cell line, ECs endothelial cells, hUCB human umbilical cord blood, HaCaT human skin keratinocytes, HSFs human skin fibroblasts, USCs urine -derived stem cells, DMBT1 deleted in malignant brain tumors 1, AGE advanced glycation end products, RAGE receptor for advanced glycation end products, UC Ultracentrifugation, ID intradermal, MenSCs menstrual blood stem cells, PRP platelet-rich-plasma, v/v volume/volume

matrix components. Excessive inflammation at the wound site reduces angiogenesis and re-epithelialization. Therefore, inflammation modulation represents a promising therapeutic strategy in diabetic wounds [133].

Nrf2 is a transcription factor with a protective role against oxidative stress [134]. Exosomes from Nrf2-overexpressing ADSCs by suppressing oxidative stress and proinflammatory cytokine expression (including IL-1β, IL-6, and TNF-α) have been shown to prevent the high glucose-induced impairment of EPCs. Moreover, Nrf2-enriched exosome treatment promoted wound healing in diabetic rats by reducing inflammation and oxidative stress, resulting in increased angiogenesis and granulation tissue formation in the wound bed [135].

It has also been demonstrated that macrophage-derived exosomes decrease proinflammatory cytokines (including IL-6 and TNF-α) production in ECs. Inhibition of inflammatory cytokine production led to reduced inflammation at the wound site and further improved neovascularization and re-epithelialization of skin wounds in diabetic rats. In addition, these exosomes also effectively downregulated MMP-9 expression in the diabetic wound, which is ordinarily upregulated in response to excessive inflammation [35, 136].

In another study, exosomes extracted from menstrual blood-MSCs (MenSCs) have been shown to ameliorate non-healing dermal wounds in diabetic mice by reducing inflammation via induction of M2 macrophage polarization at the wound site [36].

3.8.2 Proliferation phase

Neovascularization occurs at the wound site, which includes angiogenesis and vasculogenesis. Vasculogenesis is the EPC-dependent de novo generation of new blood vessels [137]. Meanwhile, keratinocytes migrate and initiate re-epithelialization, which covers the new connective tissue (granulation tissue). However, in diabetic wounds, neovascularization is impaired. EPCs are damaged, and their recruitment from the bone marrow to the wound site is abolished [138]. Fibroblasts and keratinocytes exhibit decreased differentiation, proliferation, and migration ability [139, 140], and growth factor levels are low [141]. Therefore, promoting the proliferation and migration of these cells seems to be necessary for diabetic wound healing. In this case, EVs, specifically stem cell-derived exosomes, have shown promising pro-proliferative potential [16].

EPC-exosome treatment has been shown to accelerate skin wound closure in diabetic rats through improving ECs' angiogenic function, including cell differentiation, proliferation, and migration. Proangiogenic molecules including FGF-1, eNOS, IL-8, ANG-1, E-selectin, VEGFA, VEGFR-2, and CXCL-16 also had increased expression [142]. EPC-exosomes also accelerated skin wound healing in diabetic mice similarly to the rats. Improved angiogenesis has also been ascribed to high levels of miRNA-221-3p in exosomes. miRNA-221-3p likely antagonizes AGE/RAGE signaling. AGEs impair EPC function, thus inhibiting wound neovascularization and healing [143]. miRNA-221-3p was also shown to reduce p27 and p57, negative cell cycle regulators, thus promoting the proliferation of vascular cells [144]. Also, human umbilical cord blood EPC-exosomes have been shown to promote angiogenesis, and maturation of blood vessels in diabetic rats. These exosomes are shown to be enriched in miR-21 [145], which can induce angiogenesis by activating the Erk1/2 pathway [146] and subsequently promote angiogenesis [147].

USC-exosomes have also been shown to stimulate angiogenesis and accelerate wound closure in diabetic mice, mainly through the proangiogenic protein DMBT1, which is highly expressed in USC-exosomes. In addition, USC-exosomes could also effectively induce the migration and proliferation of vascular ECs, keratinocytes, and fibroblasts in the diabetic wound bed [148].

Exosomes released from human MenSCs enhanced angiogenesis through VEGFA upregulation, promoted epithelialization by inducing NF-κB signaling, and reduced scar formation by decreasing the collagen I/III ratio and the cell count in the granulation tissue [36, 149, 150].

Hypoxia preconditioned MSC-exosomes was shown to have higher therapeutic properties than normal exosomes [151]. Deferoxamine is a hypoxia mimetic agent [152], which can activate hypoxia-related genes and increase the proangiogenic ability of MSCs [153]. Deferoxamine-preconditioned human BM-MSC-exosomes improved EC angiogenic function and promoted neovascularization more efficiently compared with non-preconditioned exosomes. In addition, these exosomes had a higher level of miR-126 which induces the PI3K/AKT pathway leading to enhanced skin wound recovery in diabetic rats [154].

Platelet-rich plasma (PRP), a platelet concentrate obtained from whole blood centrifugation, has been widely used for chronic non-healing wounds such as diabetic wounds [155]. PRP-exosomes accelerated cutaneous wound closure in diabetic rats, mainly through activation of rho/YAP, while inducing angiogenesis through Erk/Akt signaling. In addition, PRP-exosomes encapsulated bFGF, PDGF-BB, VEGF, and TFG-β [156].

Preconditioning fibrocytes via TGF-β, PDGF-b, and FGF2 changes their exosome content profile. These exosomes showed better wound healing promotion in a dose-dependent manner through enhancing neovascularization and re-epithelialization of wound beds in diabetic mice [157]. HSP-90α and STAT-3, which induce re-epithelialization and production of wound healing-related growth factors [158], were abundant in these exosomes [157]. Fibrocyte-exosomes also contained miRNAs with proangiogenic

(miR-126, miR-130a, miR-132), and immunomodulatory (miR-124a, miR-125b) functions [157].

3.8.3 Exosome-loaded wound dressings

Exosomes are currently mainly injected subcutaneously around the wound, where they do not directly contact the injury site. To provide a more clinically-friendly application, exosome-loaded wound dressings seem to be helpful. In addition, biodegradable materials like chitosan work well as wound dressing, with the drug-delivery ability and antimicrobial properties [159]. Thus, using exosomes combined with such wound dressing agents represents a promising future application (Table 7).

Synovium mesenchymal stromal cells (SMSCs) induce cell proliferation in connective tissue and angiogenesis by upregulation of miR-126-3p [160, 161]. Exosomes derived from miR-126-3p overexpressing SMSCs were shown to improve the angiogenic function of human ECs by activating PI3K/AKT and MAPK/ERK pathways. Combined with the chitosan solution in a hydrogel form, these exosomes promoted the diabetic rats' wound healing by augmenting angiogenesis, epithelialization, granulation tissue generation, and collagen deposition [160].

Gingival mesenchymal stromal cells (GMSCs) exosomes loaded on a chitosan/silk porous hydrogel accelerated the healing process in diabetic rats' cutaneous wounds. Indeed, GMSC-exosomes also stimulated nerve growth and increased nerve density in the wound bed [162].

In order to use an ideal multifunctional scaffold, Wang et al. utilized a polysaccharide-based FEP hydrogel scaffold for delivering the ADSC-exosomes into mice diabetic wounds. This scaffold shows antibacterial activity, hemostatic ability, anti-ultraviolet performance, and pH-dependent exosome release. In comparison with pure exosomes, exosome incorporated FEP hydrogel induced higher levels of neo-vascularization, granulation tissue generation, collagen deposition, re-epithelialization, prohibition of the scar, and skin appendage generation in the mice diabetic wounds. These outcomes are proposed due to the long-term and continuous release of ADSC-exosomes and the multifactorial properties of FEP hydrogels [38]. Wang et al. also used FHE hydrogel (composed of PF-127, oxidized hyaluronic acid, and EPL) loaded with AD-MSC-exosomes. FHE is a multifunctional and antibacterial polypeptide-based dressing. Exosome-loaded FHE was shown to accelerate diabetic wound healing [40]. Moreover, PF-127 can fit into irregular-edged diabetic wounds. PF-127 itself can retain and attain a sustained release of exosomes directly into the wound bed [163]. Yang et al. showed that loading umbilical cord-derived MSC (UCMSCs) exosomes on the PF-127 hydrogel improved exosomes' therapeutic effects, promoting rat diabetic wound healing. These exosomes enhanced angiogenesis through VEGF and TGF-β1 upregulation [163]. TGF-β1 is a known growth factor that modifies the interaction between the mural and ECs [164, 165].

In a recent study, human UCMSC-derived exosomes, encapsulated in a nano hydrogel scaffold composed of polyvinyl alcohol (PVA)/alginate, sped up the healing rate of rats diabetic wounds (higher than exosome injection alone) by promoting angiogenesis and the ERK1/2 signaling pathway [166].

3.8.4 Exosome as a drug carrier to the wound site

EVs are supposed to be ideal delivering vehicles for nucleic acid-based drugs [167]. The higher production yield of EMNVs [83] makes them a potential candidate to deliver therapeutic molecules/drugs. EMNVs released from H19-overexpressing HEK293 cells have been shown to efficiently transport lncRNA-H19 into ECs under hyperglycemia and restore angiogenic function and proliferation of ECs through Akt activation. Moreover, loading EMNVs into sodium alginate hydrogels improved angiogenesis, epithelialization, collagen alignment, and remodeling at the wound site, and therefore helped the process of wound healing in diabetic rats [168].

3.9 Retinopathy

Diabetic retinopathy (DR) is a major diabetes complication [169], involving microvascular impairment and degeneration of the retina [170], which, if left untreated, can lead to severe visual impairment and even loss of vision [169]. Recently, Safwat et al. demonstrated that intraocular or subconjunctival injection of adipose MSC-derived exosomes containing miR-222 leads to retinal tissue repair in diabetic rabbits [37]. miR-222 can inhibit excessive angiogenesis associated with the severity of DR by regulating STAT5A protein expression [171]. Furthermore, reduced miR-222 expression in the diabetic rabbits' retinal tissues correlates to retinal damage [37].

3.10 Salivary gland hypofunction

Salivary gland dysfunction in diabetes can cause xerostomia, characterized by a reduced amount of saliva secretion [172]. Xerostomia itself aggravates oral candidiasis infection in patients with diabetes. Moreover, the salivary glands of diabetic rats show increased fibrosis and degeneration [173]. Recently, Abubakr et al. suggested that BM-MSC-exosomes reduce blood glucose levels in diabetic rats. Notably, these exosomes also improved the salivary glands function (indicated by reducing serum amylase and salivary IgA levels) and reduced fibrosis, degeneration, and apoptosis in the salivary glands through downregulation of the TGF-β/Smad3 pathway [173]. TGF-β upregulation leads to reduced

Table 7 Extracellular vesicle application in diabetic dermal wounds (loaded by wound dressing), diabetes-related salivary glands hypofunction, and diabetic retinopathy

REF	[160]	[162]	[168]	[163]	[38, 40]	[166]	[173]	[37]
OUTCOMES	Increased angiogenesis, epithelialization and granulation tissue formation	Increased angiogenesis and re-epithelialization, improved collagen deposition and remodeling, increased nerve growth/density	Increased angiogenesis and re-epithelialization, improved collagen deposition and remodeling	Increased granulation tissue formation, angiogenesis, and epithelialization	Increased angiogenic, granulation tissue formation, epithelialization and generation of the skin appendages, improved collagen deposition	Increased angiogenesis and accelerated wound healing	Reduced salivary gland fibrosis, improved salivary gland function, reduced blood glucose	Reduced blood glucose, reduced retinal injury, increased level of miR-222 in the retina
DOWNSTREAM GENES	/	/	/	VEGF and TGF-β upregulation	/	VEGF upregulation	/	/
DOWNSTREAM SIGNALING	PI3K/AKT and MAPK/ERK activation	/	AKT activation	/	/	ERK1/2	/	/
FUNCTIONAL CARGO	miR-126-3p	/	lncRNA-H19	/	/	/		? miR-222
ASSAY DURATION (IN VIVO)	2 weeks	2 weeks	2 weeks	2 weeks	3 weeks	18 days	5 weeks	12 weeks
ADMINISTRATION ROUTE (IN VIVO)	Loaded by chitosan hydrogel wound dressing	Loaded by chitosan/silk porous hydrogel sponge	Loaded by sodium alginate hydrogel wound dressing	Loaded by pluronic F127 hydrogel	Loaded by FEP /FHE hydrogel	Loaded by PVA/alg hydrogel	IV	IV, SC, IO
EXPERIMENTAL MODEL	In vitro (HEMC-1) In vivo (STZ-SD-rats)	In vivo (STZ-SD-rats)	In vitro (HMEC-1) In vivo (STZ-SD-rats)	In vitro (HUVECs) In vivo (STZ-SD-rats)	In vitro (HUVECs) In vivo (STZ-ICR-mice)	In vitro (HUVECs) In vivo (STZ-SD-rats)	In vivo (STZ-albino-rats)	In vivo (STZ-rabbit)
CONTROL	/	/	Wild type HEK292-derived EMNVs	PBS, Hydrogel only, exosome only, DMEM	Exosome alone, FEP/FHE alone	Exosome alone, nano- hydrogel alone	PBS	PBS
EV ISOLATION METHOD	Ultrafiltration + UC	Centrifugation and MVCO hollow fiber membrane	Ultrafiltration + UC	ExoQuick TC	Differential centrifugation	Differential centrifugation	UC	UC
EV CONCENTRATION	1.2 ml of exosomes solution (50 wt%) in chitosan solution	150 μg exosomes in 100 μl PBS	In vitro (50 μg/ml) In vivo (1% v/v)	In vivo (100 μg exosomes in 100 μl PF-127 gel) In vitro (1.3 ml exosomes)	1 μg exosomes in 100 μl FEP/FHE	In vitro (100 μg/ml) In vivo (300 μl)	100 μg/kg/dose in 0.2 ml PBS	100 μg/ml PBS
EV SOURCE	SMSCs, miR-126-3p overexpressing SMSCs	GMSCs	H19 overexpressing HEK293 cells	hUC-MSCs	Adipose-MSCs	hUC-MSCs	BMSCs	Adipose-MSCs (rabbit)
COMPLICATION	Wound						Salivary glands hypofunction	Retinopathy

SMSCs synovium mesenchymal stem cells, HMEC-1 human microvascular endothelial cell line, STZ streptozotocin, SD Sprague Dawley, ECs endothelial cells, PBS phosphate buffer saline, GMSCs gingival mesenchymal stem cells, HEK292 human embryonic kidney 292, EMNV extracellular vesicles-mimetic nanovesicles, UC Ultracentrifugation, hUC-MSCs human umbilical cord mesenchymal stem cells, MSCs mesenchymal stromal cells, HUVECs human umbilical vein endothelial cells, PVA/alg polyvinyl alcohol alginate, BMSC bone marrow stromal cells, IV intravenous, SC subconjunctival, IO intraocular

salivary gland function due to excessive interstitial fibrosis [174]; thus, suppressing TGF-β expression seems to be a potential therapeutic target in diabetes-related salivary gland hypofunction.

4 Concluding remarks

EVs' low immunogenicity, low neoplastic transformation probability, low abnormal differentiation, high resilience, and ability to act locally and systemically make them potential cell-free alternative candidates to current cell-based therapies. Additionally, the EV lipid bilayer membrane protects bioactive cargos from degradation and body clearance, extending their circulation half-life. Hence, it gives EVs a superior advantage for therapeutic interventions.

We have reviewed the advances in EV applications as novel therapeutics for diabetes complications. EVs have demonstrated acceptable results in diabetes micro- and macrovascular complication therapy by affecting the pathophysiology of the complications (Fig. 8). Expanding the EV therapy to other diabetic complications, including diabetes-related peripheral artery disease and limb ischemia, cataracts, and gestational diabetes-related maternal problems, seems to be the next step. Gestational diabetes is defined by glucose intolerance during the last two semesters of pregnancy [175]. Increased risk of preeclampsia and gestational hypertension, which occur due to gestational diabetes [176], may represent exciting targets for future EV therapies.

However, there are still several challenges to overcome for introducing EVs for clinical application, including uniformity, stability, long-term efficacy and safety, large-scale production, lack of a unified isolation/preparation method, identifying efficient administration doses [177, 178], and frequency of administration for each specific complication. Moreover, EV stability varies based on their source and preparation method, and there is no standard procedure for evaluating EVs stability [177]. Several strategies have been tried to scale up EVs released from cells, including increasing intracellular calcium [179], serum deprivation [180], hypoxic-condition [181], using nanoparticles [182], and creating immortalized cells via introducing oncogenes

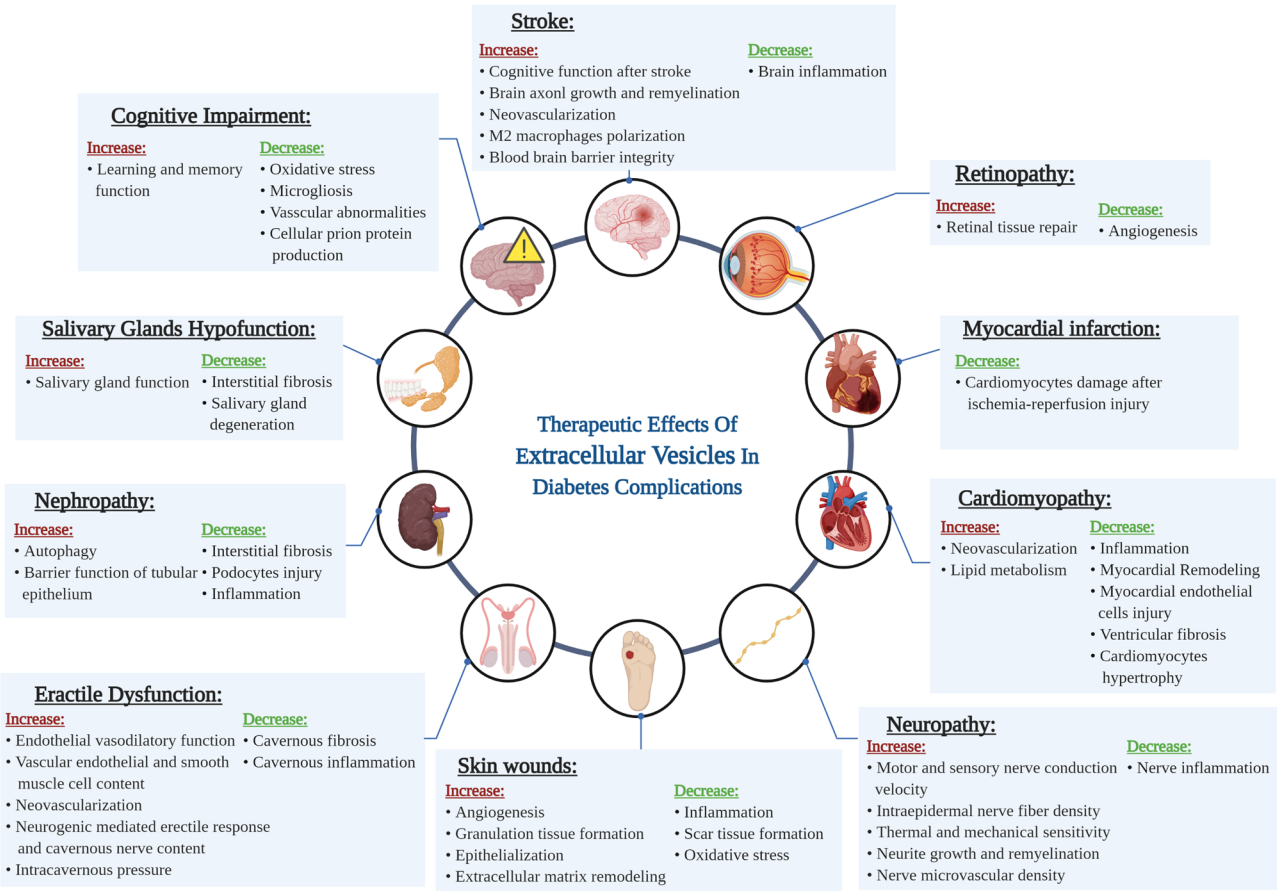

Fig. 8 Extracellular vesicle application in diabetic complications. Systemic or local administration of EVs showed considerable improvement of different complications

to primary cells [177]. Large-scale production of EVs through extrusion or filtration of cells (e.g., EMNVs) provides another method [84]. Moreover, currently used EV isolation methods include ultracentrifugation, ultrafiltration, density-gradient centrifugation, precipitation, immuno-affinity capture, and size exclusion chromatography [183, 184] cannot isolate different EV subtypes efficiently. Thus, there remains a need for a standardized isolation workflow so the process is robust and reproducible across different laboratories. In addition, the specific roles and detailed characterization of the molecular composition of various EVs, the potential of other EV sources, and preparations for diabetes complications therapy should be further investigated. For instance, priming or preconditioning of cells has been demonstrated to improve the therapeutic effect of the derived EVs [185, 186]. Thus, further investigations are needed to reveal the full potential of stem cells priming on their EVs' therapeutic potential.

Advances in various aspects of EV research and overcoming the obstacles mentioned above will pave the way for translating the EVs application for efficient diagnostic and therapeutic purposes and allow for long-term evaluation of EV therapy.

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Declarations

Conflict of interest The authors have nothing to disclose.

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