Diabetology & Metabolic Syndrome

REVIEW

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Exosomal MicroRNAs as theranostic tools in type 2 diabetes and its complications: mechanistic insights and clinical implications

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Abstract

Type 2 diabetes is a chronic and progressive metabolic disease, with a steadily increasing global incidence and prevalence, representing a major public health concern due to its substantial impact on morbidity and mortality. Type 2 diabetes is characterized by defective insulin secretion and peripheral insulin resistance, resulting in dysregulated glucose homeostasis. Optimal disease management is critical due to its association with multiple systemic complications, including diabetic retinopathy, nephropathy, neuropathy, foot ulcers, cardiomyopathy, and diabetes-related cognitive impairment. The involvement of exosomes in the initiation and progression of type 2 diabetes has recently gained considerable attention. These nanosized vesicles, secreted by virtually all cell types, play a pivotal role in mediating intercellular communication. This review highlights the potential of exosomes and their molecular cargo, particularly microRNAs, as endogenous biomarkers for the detection and monitoring of type 2 diabetes and its associated complications, while also exploring their emerging therapeutic applications.

Keywords Type 2 diabetes, Diabetic complications, Obesity, Insulin resistance, Extracellular vesicles, Exosomes, MiRNAs, Biomarkers, Therapy

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Background

Type 2 diabetes (T2D), which accounts for 96% of all diabetes cases, is the most common type of diabetes worldwide. As a chronic disease with a steadily increasing global incidence and prevalence, it seriously endangers human health [1]. It is a complex condition influenced by multiple risk factors and strongly shaped by genetic predisposition [2]. The pathophysiology of T2D involves multiple mechanisms, primarily progressive β-cell dysfunction and insulin resistance (IR) [1, 3]. Impaired insulin secretion and sensitivity disrupt glucose homeostasis, leading to increased hepatic glucose output, lipogenesis, and inflammation [4]. Reduced glucose uptake by insulin-sensitive tissues further elevates fasting glucose levels. Chronic hyperglycemia and dyslipidemia induce β-cell glucolipotoxicity, exacerbated by inflammation, ER stress, and oxidative stress, ultimately causing β-cell failure [1, 2]. Notably, insulin sensitivity declines approximately five years before diagnosis, while β-cell activity temporarily increases three to four years prior, indicating compensatory hyperinsulinemia.

Although the treatment of patients with T2D primarily involves education and lifestyle changes, such as dietary adjustments and physical activity, it is crucial to initiate pharmacological treatment promptly [1]. Current pharmacological treatments for T2D focus on enhancing insulin secretion or improving tissue sensitivity to insulin (Table 1) [5, 6]. Although initially effective, these therapies lose efficacy over time due to the progressive decline in β-cell functional mass. Moreover, side effects and high treatment costs often limit their long-term use. This highlights a continued interest in the development of new, more effective, and durable therapeutic approaches [5, 6].

Table 1 Current pharmacotherapy in the treatment of T2D.

In addition to glycemic management, a major concern in T2D is the development of long-term complications [7, 8]. These complications are particularly common in individuals with poorly controlled blood glucose levels. Chronic hyperglycemia contributes to a range of microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy, often leading to vision impairment, kidney failure, and nerve damage. In parallel, macrovascular complications, such as cardiovascular disease, stroke, and peripheral artery disease, also pose significant risks and contribute substantially to morbidity and mortality in patients with T2D. Effective long-term glycemic control is essential to reduce the risk and progression of these complications.

Diabetic retinopathy is a microvascular complication of diabetes mellitus in general and the leading cause of blindness [9]. One of the main risk factors for the initiation of diabetic retinopathy is chronic hyperglycemia, which, together with other factors, causes detrimental effects that lead to microvascular damage and dysfunction of the retina [9]. The complex interplay of multiple molecular pathways precipitates abnormal permeability and ischemia, two changes within the retinal vasculature that constitute a core pathophysiology of diabetic retinopathy. Given that diabetic retinopathy may occur before the diagnosis of T2D and its progression cannot be entirely prevented, it is of great importance to prevent its occurrence at the diagnosis of T2D [10]. As shown in the study by Fernandes Silva et al., an advanced analysis of metabolites associated with diabetic retinopathy may enhance the potential for early detection and diagnosis of this complication [11]. This indicates a need for further investigations of specific biomarkers that can prevent the onset or progression of diabetic retinopathy associated with T2D.

Diabetic nephropathy continues to be a significant contributor to morbidity and mortality among individuals with either T1D or T2D. In Western nations, diabetes stands as the foremost single factor leading to end-stage renal disease [12]. Like in other diabetic complications, hyperglycemia is a leading factor that initiates the development of renal complications, accompanied by other pathogenic processes underlying the development and progression of renal injury, such as the development of glomerular hyperfiltration and hypertrophy, thickening of the glomerular basement membrane, mesangial matrix accumulation, the development of nodular glomerulosclerosis, and increased urinary albumin excretion [13]. Therefore, considering the complex pathophysiology and heterogeneity of renal complications related to T2D, it is of great importance to approach each patient individually. This involves evaluation of disease progression and the patient's response to specific therapy, intending to enhance treatment efficacy and preserve renal function.

Diabetic neuropathy is the most prevalent long-term complication of diabetes, among which diabetic peripheral neuropathy occurs in around 50% of individuals with T2D [14, 15]. Diabetic peripheral neuropathy is characterized by distal-to-proximal loss of peripheral nerve function, which leads to sensory disturbance, neuropathic pain, and impaired motor function, ultimately affecting the quality of life. As hyperglycemia is the primary risk factor for this condition, current treatment focuses on glycemic control alongside pain management [16]. In addition to diabetic peripheral neuropathy, diabetic autonomic neuropathy is also a commonly present complication of T2D and can lead to significant dysfunction in individual organs, such as the heart (cardiovascular autonomic neuropathy) [17, 18]. By definition, diabetic autonomic neuropathy is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes"

Table 1 Current pharmacotherapy in the treatment of T2D

Group of Agents	Examples	Administration	Physiological effects	Glucose-lowering efficacy	Advantages	Disadvantages
Biguanides	Metformin	Oral	↓ Hepatic glucose production, ↑ Insulin sensitivity ↑ GLP-1	High	No hypoglycemia, weight neutral, cheap	Diarrhea, nausea, vitamin B12 deficiency, lactic acidosis
Sodium/glucose cotransporter 2 inhibitors	Dapagliflozin, Empagliflozin, Canagliflozin, Ertugliflozin	Oral	↑ Renal glucose excretion	Intermediate	No hypoglycemia, ↓ weight (intermediate), ↓ blood pressure, renoprotective, ↓ CV events	Urinary/genital infections, polyuria, dehydration
Sulfonylureas (2nd generation)	Gliclazide, Glimepiride, Glyburide	Oral	↑ Insulin	High	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, ↑ weight
Meglitinides	Nateglinide, Repaglinide	Oral	↑ Insulin	High	Short onset of action, lower postprandial glucose	Hypoglycemia, ↑ weight
Dipeptidyl peptidase 4 inhibitors	Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin	Oral	↑ Insulin, ↓ Glucagon, prolong endogenous GLP-1 action	Intermediate	No hypoglycemia, weight neutral	Angioedema/urticaria and immune-mediated dermatologic effects, ↑ risk of pancreatitis
GLP-1 receptor agonists	Exenatide, Liraglutide, Dulaglutide, Semaglutide	SC/Oral*	↑ Insulin, ↓ Glucagon, ↑ Satiety, slow gastric emptying	High to very high	No hypoglycemia, weight loss (intermediate to high), ↓ CV events	Gastrointestinal side effects
Dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists	Tirzepatide	SC	↑ Insulin, ↑ Insulin sensitivity, ↓ Glucagon	Very high	No hypoglycemia, weight loss (high)	Gastrointestinal side effects
Thiazolidinediones	Pioglitazone	Oral	↑ Insulin sensitivity, ↑ Glucose utilization ↓ Free fatty acid release	High	Lower insulin requirements ↓ blood pressure	Peripheral edema, congestive heart failure, weight gain, bone fractures, macular edema
Insulin	Rapid-acting (aspart, lispro, glulisine), Short-acting (human regular) Intermediate-acting (human NPH) Long-acting (glargine, detemir, degludec) Biphasic	SC	↑ Glucose utilization, ↓ Hepatic glucose production, and other insulin actions, ↓ Lipolysis	Very high	Known safety profile	Hypoglycemia, ↑ weight, fluid retention,

*Semaglutide is also available in oral formulation. Glucagon-like peptide 1 (GLP-1), cardiovascular (CV), subcutaneous (SC), ↑ increase, ↓ decrease

[17]. Although often underestimated, this complication leads to a high rate of morbidity and mortality [19]. Moreover, when clinically diagnosed, there is no unique and completely effective therapy for this disease, so the management and treatment are primarily based on glycemic control, multifactorial interventions, and lifestyle modifications [16].

Diabetic foot ulcer is a devastating complication of diabetes characterized by lesions that are often accompanied by infections, which can lead to the development of gangrene and non-traumatic amputation, and, in some cases, death. It is a multifactorial problem with underlying pathology that includes neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot, as well as impaired wound healing [20]. There are several classification systems based on the ulcer size, depth, ischemia, infection, and neuropathy by which the severity of diabetic foot lesions can be determined [21].

These classifications, together with the identification of pathogen-causing infection, enable the proper management and treatment of diabetic foot problems; moreover, because diabetic foot ulcers are among the most preventable late-stage adverse outcomes of diabetes [22]. Although management of this complication includes prevention as the first step, when it occurs, it demands multidisciplinary treatment, which includes surgical debridement, dressing, wound off-loading, vascular assessment, control of infection, glycemic control, and adjuvant therapies [22].

The worldwide incidence of wounds related to diabetes, in general, is approximately 20% [23]. Diabetic wound healing is a multifaceted and dynamic process that involves cell migration, proliferation, fibrogenesis, angiogenesis, and re-epithelialization, processes that are impaired in T2D and lead to the development of chronic ulcers with a high possibility of amputation of lower extremities. Current therapeutic approaches primarily revolve around conservative measures such as dressings, pressure offloading, surgical debridement, revascularization, infection control, and glycemic management [24, 25] combined with the administration of growth factors, various cytokine modulators, anti-inflammatory drugs, matrix metalloproteinase inhibitors, angiogenesis stimulators, stem cells, and various natural-based products [23]. However, these interventions are predominantly supportive rather than curative, as they have certain limitations and frequently yield unsatisfactory outcomes. Although the mechanisms of wound healing have been partially elucidated, a need for further research is still present, as well as the improvement of existing therapeutics and the development of new approaches.

Diabetic cardiomyopathy is a common complication of both T1D and T2D that can lead to heart failure. Although it is defined as the occurrence of heart dysfunction without concurrent cardiovascular conditions, such as coronary artery disease, hypertension, significant valvular disease, or congenital heart disease, the lack of a universally recognized definition of diabetic cardiomyopathy poses a challenge in the research of its epidemiology, pathophysiology, clinical features, and outcomes [26]. The primary metabolic disturbances contributing to cardiac dysfunction in T2D encompass a reduction in mitochondrial glucose oxidation mediated by insulin due to IR [27]. IR also leads to an increase in fatty acid uptake by cardiomyocytes, which in turn impairs mitochondrial fatty acid β-oxidation, resulting in mitochondrial dysfunction and accumulation of toxic lipid metabolites within the myocardium [27]. The most commonly used therapy for diabetic cardiomyopathy is mainly based on the control of glucose levels and reduction of cardiotoxicity, together with lifestyle changes [26]. However, although these strategies are effective in alleviating the symptoms of diabetic cardiomyopathy to a certain extent, effective strategies for the prevention and treatment remain elusive. This indicates the need for further research that will clarify the pathophysiology of this disease in more detail and lead to the development of more effective therapy with fewer or no side effects.

As a systemic disease, T2D can lead to neurological complications, most notably cognitive impairment, which is classified by severity into cognitive decline, mild cognitive impairment, and dementia. Dementia is increasingly recognized as one of the complications of T2D and a clear link between T2D and an elevated risk of developing various types of dementia, including Alzheimer's disease and vascular dementia, was shown [28]. Moreover, beyond the influence of aging, diabetes contributes to the onset of dementia even in the early phase of diabetes [29].

The risk of developing diabetes-related dementia is influenced by several factors, but predominantly hyperglycemia, IR, and vascular damage, which can impair brain function and promote neurodegenerative changes [29, 30]. Moreover, a link between markers of glucose deregulation and both cognitive performance and neuroimaging findings was shown [31]. However, although some of the medications used to treat T2D have been associated with a lower risk of developing diabetes-related dementia, others showed limited effects [32, 33]. Consequently, further investigation remains necessary to deepen our understanding. Additionally, although not every person with diabetes will develop dementia, the condition is now considered a confirmed risk factor, and managing blood sugar levels, cardiovascular health, and lifestyle factors can help reduce this risk.

Extracellular vesicles (EVs) are lipid bilayer-delimited particles released by all cell types that cannot replicate on their own [34]. They consist of a diverse group of particles that differ in size, biological roles, and origin. According to the latest Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches guidelines, EVs can be broadly classified into two main populations based on their biogenesis: exosomes, small EVs originating from the endosomal system, and ectosomes and microvesicles, originating from the plasma membrane [34]. Nevertheless, ongoing research continues to yield new insights, and the classification of EVs has recently expanded to include additional subpopulations, such as: apoptotic bodies (released by apoptotic cells), mitovesicles (originating from mitochondria), migrasomes (formed during cell migration), oncosomes (microvesicles that contain oncogenic cargo), megavesicles (atypically large vesicles), and exophers (involved in cellular homeostasis) [35, 36]. To accurately identify the specific type of extracellular vesicles being discussed, it is essential to consider their biogenesis, particle size, and

distinct molecular biomarkers – all of which are clearly outlined in the MISEV2023.

Although initially considered cellular waste, EVs are now recognized as crucial regulators of cellular homeostasis due to their rich cargo of various macromolecules such as lipids, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and a wide range of proteins [37]. More significantly, EVs play a central role in intercellular molecular communication, contributing not only to the maintenance of homeostasis but also to the onset of various pathological conditions [38]. EVs are released by a variety of cells into the extracellular space and are present in several biological fluids, including saliva, bronchioalveolar lavage, mucus secretions, plasma, cerebrospinal fluid, amniotic fluid, breast milk, malignant ascites, and urine [36]. Taken together, these facts support the use of EVs as promising prognostic, diagnostic, and predictive biomarkers, as well as next-generation therapeutic strategies in the diagnosis, monitoring, but also in treatment of various diseases.

The most studied role of EVs in physiological and pathophysiological processes is the role of exosomes. These vesicles are shown to be involved in the regulation of reproduction and embryonic development [39], modulation of the immune system [40], angiogenesis [41], and promotion of matrix remodeling [42], but importantly also in the development and progression of numerous diseases, such as cardiovascular and metabolic diseases, neurodegeneration, as well as cancer [38].

Exosomes originate from multivesicular bodies (MVBs) of endosomes by a process that involves double invagination of the endosomal membrane and the production of intracellular MVBs that house intraluminal vesicles which are released into the extracellular space as exosomes in all cells in the body [38]. The formation of exosomes is regulated by the endosomal sorting complex required for transport (ESCRT) proteins which, together with its accessory proteins (Alix, TSG101, heat shock proteins (HSP) 70 and 90), tetraspanin family members (CD9, CD81, CD63), actin, integrins, and flotillins, may be commonly found in all exosomes as their markers regardless of the type of cell from which they originate [43]. However, other proteins, such as major histocompatibility complex class I and II proteins, are specific to the type of cell from which exosomes originate. Besides proteins, exosome membranes are composed of simple and complex lipids, such as phosphatidylserine, ceramides, sphingomyelin, cholesterol, arachidonic acid and other fatty acids, prostaglandins, and leukotrienes, which play roles in cargo sorting, secretion, structure, and signaling [43]. Additionally, exosomes contain a complex mixture of nucleic acids, including DNA, messenger RNA (mRNA), and non-coding RNA (ncRNA) species, among which microRNAs (miRNAs) are particularly abundant. Other RNA species present in exosomes include ribosomal RNA (rRNA), long non-coding RNA (lncRNA), transfer RNA (tRNA), circular RNA (circRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), and piwi-interacting RNA (piRNA) [44].

Once secreted by parental cells, exosomes act either locally or enter circulation, causing distal systemic effects. Exosomes mediate cell-to-cell communication through several mechanisms [43–45]. On the one hand, the recipient cells may internalize exosomes through direct binding to surface receptors, which triggers internal signaling pathways. Alternatively, exosomes may fuse with the cell membrane or be internalized through mechanisms such as endocytosis, phagocytosis, or pinocytosis, thereby delivering their contents into the cytoplasm. Consequently, exosome-mediated cell-to-cell communication occurs through direct surface-bound ligands, transfer of activated receptors to recipient cells, and epigenetic reprogramming of recipient cells through the delivery of functional biomolecules [43].

Analytical and translational limitations of exosomal MiRNAs application

Notwithstanding the rapidly expanding interest in exosomal miRNAs as diagnostic and therapeutic entities, their translational advancement is somewhat limited by unresolved analytical and manufacturing challenges intrinsic to extracellular vesicle biology. The absence of universally accepted standards for pre-analytical handling, exosome isolation, and downstream miRNA profiling still remains a major obstacle in the diagnostic domain. Currently employed isolation approaches—including ultracentrifugation, size-exclusion chromatography, precipitation-based methods, and immunoaffinity capture—provide vesicle populations that differ substantially in purity, yield, and molecular composition, thereby introducing systematic bias and impairing cross-study reproducibility [46]. Moreover, the lack of consensus regarding endogenous or exogenous normalization controls for exosomal miRNA quantification further complicates analytical validation and hampers the establishment of clinically robust reference ranges [47]. On the therapeutic front, while exosomes offer inherent advantages as biologically compatible nanocarriers, their large-scale production and quality control remain technically demanding. Scalable manufacturing under Good Manufacturing Practice conditions requires precise control over source cell identity, culture conditions, vesicle heterogeneity, and cargo consistency, all of which critically influence biological activity [48]. In addition, achieving efficient and tissue-specific delivery of exosome-encapsulated miRNAs remains an unresolved challenge, as systemically administered exosomes exhibit rapid clearance and preferential accumulation in reticuloendothelial

organs, limiting bioavailability at target sites [49]. Finally, although exosomes are often considered intrinsically safe, emerging evidence suggests that their immunomodulatory properties, long-term biodistribution, and potential off-target effects warrant careful evaluation, particularly in the context of repeated or chronic administration [50]. Collectively, these analytical, manufacturing, and safety-related constraints highlight the need for harmonized methodological frameworks, rigorous validation strategies, and comprehensive safety profiling to fully exploit the clinical potential of exosomal miRNA-based therapies.

Exosomes and type 2 diabetes

Numerous studies have been conducted to elucidate the significance and role of exosomes in the pathophysiology of T2D [51]. Additionally, it has been shown that they have promising potential to be used in the clinical diagnosis and treatment of T2D [52]. Given the established role of exosomes in the development of T2D and its related complications, this review aims to present current insights into how exosomes contribute to the onset and progression of T2D, as well as explore their potential therapeutic advantages in managing the disease and its major complications.

Exosomes in the development of type 2 diabetes

As previously mentioned, T2D is caused by the development of defective insulin secretion by pancreatic β-cells and IR, which is strongly related to the development of chronic low-grade inflammation in obesity. Lately, a large body of evidence has highlighted the involvement of exosomes and their cargo in both processes. However, although the relationship between exosomes and T2D has received extensive attention, the role of exosomes in the development, as well as treatment of T2D and related complications, is still an inexhaustible source of research.

Starting from the basics, T2D is triggered by IR which is strongly related to the development of chronic low-grade inflammation within obesity [53, 54].

Adipose tissue functions as an actively secreting endocrine organ that releases diverse adipokines, pro- and anti-inflammatory interleukins, and growth factors. That secretion is significantly altered in obesity in such a way that the aforementioned mediators promote the development of inflammation, leading to the IR [55]. More recently, it has been found that, in addition to soluble mediators, adipose tissue secretes exosomes as well, and that exosomes isolated from the plasma of obese mice induce glucose intolerance and dyslipidemia when administered into control mice over a four-week period [56]. Moreover, quantitative and qualitative differences in exosomes related to obesity have been reported and emerging evidence suggests that exosomes and the content they carry significantly contribute not just to the onset and progression of obesity, but also to the obesity-related metabolic disorders, such as T2D [57]. Although the contribution of proteins derived from adipose tissue exosomes or exosome-like vesicles, such as sonic hedgehog (SHH) protein or tumor necrosis factor-α (TNF-α) and interleukin (IL)−6, respectively, to IR has been demonstrated [58, 59], the exosomal miRNAs are the content of exosomes, whose role in mediating adipose tissue inflammation and the accompanying IR that contribute to the development of T2D has been mostly described in the literature so far (Fig. 1).

Low-grade chronic inflammation in obesity is largely driven by exosomes released from adipocytes and macrophages within adipose tissue. Generally, these EVs promote the differentiation of macrophages, which in turn disrupt insulin signaling within human adipocytes, thus perpetuating a detrimental inflammatory cycle [60]. In this process, the role of adipocyte-derived exosomal miRNAs is of great importance since these biomolecules are significantly involved in the polarization of macrophages and modulation of related signaling pathways involved in the induction and promotion of inflammation [61]. The most extensively studied miRNA in this context is miR-155 whose increased expression in adipocyte-derived exosomes has been linked to the polarization of macrophages into the M1 phenotype through the inhibition of suppressor of cytokine signaling (*SOCS*) 1 gene [62].

This effect is accompanied by the activation of proinflammatory signal transducer and activator of transcription (STAT) 1 and suppression of the anti-inflammatory STAT6 signaling pathways and can be reversed by the inhibition of miR-155 [62, 63]. In addition to this, upregulation of adipocyte-derived exosomal miR-34a, miR-130b, or miR-1224 may intensify inflammation through the suppression of Krüppel-like factor 4 (KLF4), peroxisome proliferator-activated receptor (PPAR-γ), or Wnt/β-catenin signaling pathways, events that consequently inactivate anti-inflammatory M2 macrophages [64–66].

As previously discussed, alongside inflammation, IR represents a major contributor to the pathogenesis of T2D and is significantly driven by exosomal miRNAs originating from adipose tissue [53, 67]. For instance, elevated levels of exosomal miR-155 derived from adipose tissue macrophages modulate insulin signaling by inhibiting PPAR-γ and glucose transporter type 4 (GLUT4) in adipocite and muscle cells, while in primary hepatocytes it enhances insulin-induced suppression of hepatic glucose output [68]. Furthermore, exosomal miRNAs miR-222, miR-27a, and miR-802-5p, released by adipocytes, have been identified as contributors to IR by modulating critical regulatory factors, including insulin receptor substrate-1, PPAR-γ, and HSP60 [69]. Additionally, hepatocyte uptake of adipocyte-derived exosomes containing

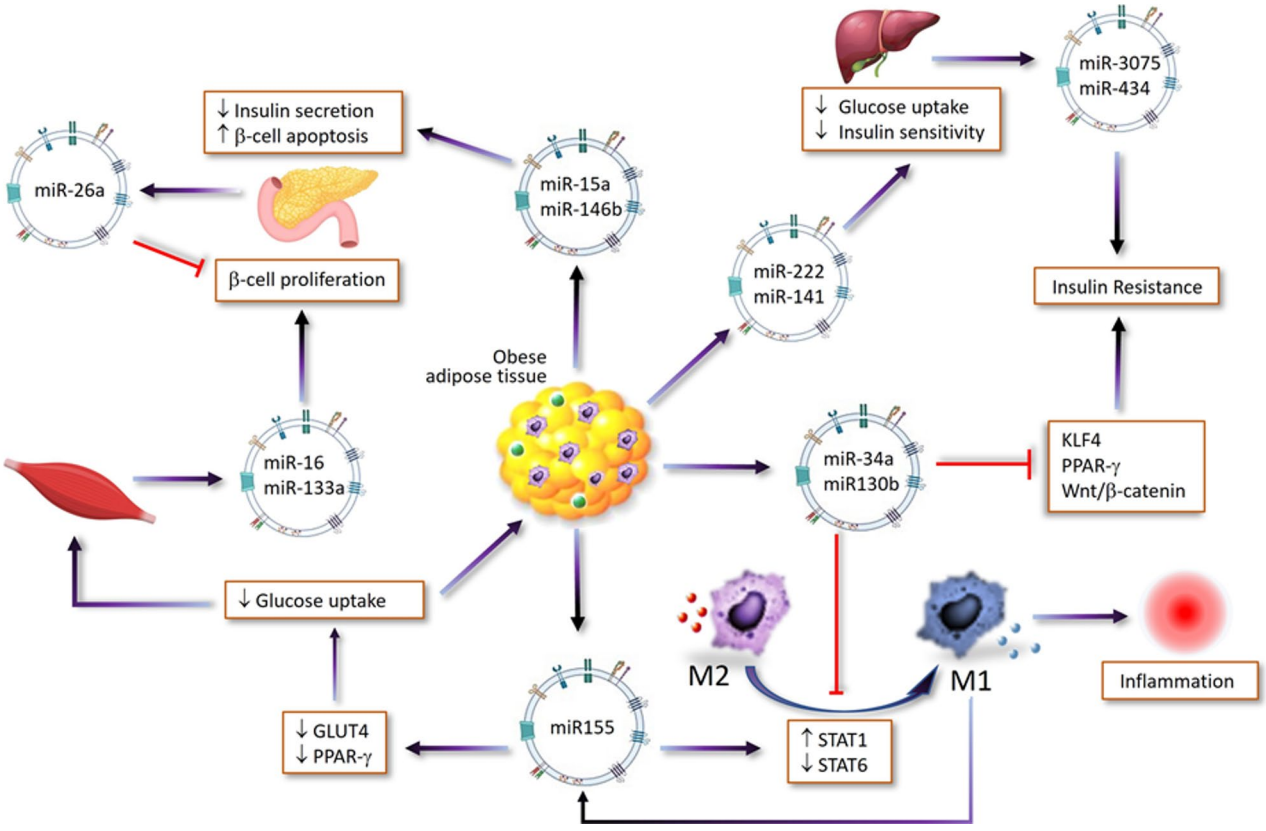

Fig. 1 Exosomes as mediators of metabolic changes and the development of T2D. Glucose transporter type 4 (GLUT4), peroxisome proliferator-activated receptor (PPAR-γ), macrophages (M), signal transducer and activator of transcription (STAT), Krüppel-like factor 4 (KLF4)

less miR-141-3p in obese mice resulted in inhibition of insulin sensitivity and glucose uptake by hepatocytes which can be reversed by overexpression of miR-141-3p [70]. Notably, during the early stages of obesity, hepatocytes release exosomes rich in the insulin-sensitizing miR-3075 as a compensatory mechanism in response to excess calorie intake [71]. However, in prolonged obesity, the production of these miR-3075-containing exosomes declines, and hepatocytes begin to secrete exosomes loaded with miRNAs that contribute to IR and glucose intolerance, such as miR-434-3p, by promoting a proinflammatory shift in adipose tissue macrophages.

Exosomes and the cargo they carry also influence the homeostasis of pancreatic β-cells, whose impairment of function is also a significant characteristic of T2D. For example, it has been shown that β-cell proliferation and survival are under the control of miR-132 which is shown to be reduced in adipose tissue and serum of individuals with obesity [72, 73]. In addition, miR-26a derived from β-cells exosomes is involved in the regulation of β-cells homeostasis through the inhibition of β-cell hyperplasia induced by obesity [74]. Moreover, this miRNA alleviates obesity-induced IR and hyperinsulinemia in β-cells but also enhances peripheral insulin sensitivity. miR-16 delivered by the exosomes derived from skeletal muscle cells contributes to the proliferation of β-cells by specifically targeting patched homolog 1 (*Ptch1*) gene associated with pancreatic development [75]. Furthermore, Cui et al. identified miR146b and miR-15a as exosomal miRNAs originating from dysfunctional adipose tissue with increased levels in circulation that suppress glucose-induced pancreatic insulin secretion [76]. However, although there are significant indications of the impact of adipose tissue-derived exosomal miRNA on the function of pancreatic β-cells, further investigations are needed.

Clinical potential of exosomes in diagnostics and treatment of type 2 diabetes

As previously outlined, exosomes have emerged as crucial contributors to the development of various diseases, demonstrating significant promise in both diagnostic and therapeutic applications. While extensively studied in oncology, their application extends to the realm of T2D diagnostics and treatment [69, 77, 78]. With the ability to carry biomolecules and genetic material, exosomes offer promising avenues for understanding disease mechanisms and developing targeted interventions. As research continues to unveil their diverse roles, exosomes stand poised as valuable tools in the quest for improved healthcare outcomes.

Exosomal MiRNAs as diagnostic biomarkers of type 2 diabetes

Numerous studies have highlighted variations in exosome levels between healthy individuals and those with T2D [77, 78]. Certain exosomes exhibit promising potential as clinical markers, particularly in preclinical diagnostics and monitoring of both the disease and its associated complications as potential indicators of T2D progression and prognosis. Although exosomal proteins such as SHH, TNF-α, and IL-6 have been identified as regulators of inflammation and IR contributing to the development of T2D [58, 59], current research has largely focused on miRNAs. These miRNAs not only play a role in the pathogenesis of T2D but also hold promise as potential diagnostic biomarkers. Accordingly, a direct or inverse correlation with T2D has already been shown for numerous exosomal miRNAs (Table 2), mostly detectable in serum or plasma samples [51].

A study by Kamalden et al. revealed that miR-15a, originating from pancreatic β-cells exosomes, is detectable in the blood plasma of individuals with T2D, and its elevated levels correlate with greater disease severity and can be transported to the retina where it contributes to the pathogenesis of T2D-associated retinopathy [79]. However, the study is limited by the use of insulinoma cell lines instead of primary β-cells, a relatively small cohort size, and methodological constraints related to exosome isolation, as well as by the lack of in vivo pharmacological validation of miR-15a as a therapeutic target. Moreover, earlier research reported that elevated miR-15a expression promotes intracellular accumulation of insulin by suppressing uncoupling protein-2 (UCP-2), suggesting a possible mechanism through which exosomal miR-15a may act in T2D [80]. Fu et al. reported elevated circulating miR-375-3p level in in vivo mouse model of streptozotocin-induced diabetes as well as in early-stage T2D patients, thus highlighting its potential utility as a biomarker of the early development of T2D [81]. However, the study has several limitations. The purity of the isolated exosomes was not verified, leaving uncertainty as to whether the analyzed miRNA originated solely from exosomes or was partly associated with other circulating complexes. In addition, limited blood volume per mouse required pooling serum from three to four animals to obtain a single sample, thereby reducing the ability to assess individual variability. Notably, previous studies have shown that miR-375-3p suppresses glucose-stimulated insulin secretion by targeting MTPN/PDK1 [82, 83]. Furthermore, miR-375 has been identified as a circulating marker of β-cell death [84] as it is highly enriched in β-cells and crucial for preserving normal β-cell function and mass [85]. Katayama et al. showed that circulating exosomal miR-20b-5p is elevated in T2D [86], and this was also confirmed later by other investigators [87]. However, the authors emphasized that, although the study participants were matched by age and body mass index, several individuals with T2D were on antidiabetic treatment and were taking more medications overall. As a result, it cannot be ruled out that these pharmacotherapies contributed to the observed exosomal miRNA profile. Furthermore, a study with a limited number of participants showed a downregulation of miR-551b-3p in human serum exosomes of obese subjects as well as a significant increase of the same serum exosomal miRNA in patients with obesity and T2D compared to patients with obesity without T2D, thus suggesting that miR-551b-3p can be viewed as a potential biomarker of T2D development in obesity [88]. Xu et al. showed that miR-26a is downregulated in serum exosomes associated with obesity in both humans and mice, as well as in pancreatic islets in a mouse model of obesity [74]. In humans, reduced circulating miR-26a levels were correlated with obesity and IR, but these data are associative, limiting causal interpretation. At a mechanistic level, miR-26a is involved in the modulation of insulin sensitivity [89]. Another study by Wang et al. addressed the potential of miR-146b as a diagnostic biomarker for T2D risk in adults with obesity [90], showing an increased level of exosomal miR-146b in the plasma of subjects with new-onset T2D, as well as in the plasma of db/db mice, which mimics human T2D associated with obesity. The authors

Table 2 Exosomal MiRNAs as potential diagnostic and prognostic markers in T2D

Exosomal miR	Expression in T2D	Origin	Potential mechanism of action
miR-15a	Increased	β-cells (pancreas)	Enhances glucose-stimulated insulin production by inhibiting UCP-2 expression
miR-375-3p	Increased	β-cells (pancreas)	Suppresses glucose-stimulated insulin secretion by targeting MTPN/PDK1 expression; biomarker of β-cell function
miR-20b-5p	Increased	Unknown	Impairs insulin signaling and suppresses genes in pathways related to immune function (AKTIP and STAT3)
miR-551b-3p	Increased	Unknown	Unknown
miR-26a	Decreased	β-cells (pancreas)	Regulates insulin sensitivity
miR-146b	Increased	β-cells (pancreas)	Regulates inflammatory processes by attenuating NF-κB-mediated cytokine signaling; targets the *Btg2* gene, protects β-cells from apoptosis and facilitates proliferation

also highlighted the need for longitudinal studies to better assess the diagnostic value of this miRNA.

microRNA (miR), uncoupling protein-2 (UCP-2), 3-phosphoinositide-dependent protein kinase 1 (PDK1), AKT interacting protein (AKTIP), signal transducer and activator of transcription 3 (STAT3), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), B-cell translocation gene 2 (*Btg2*).

Overall, while exosomal miRNAs show promise as diagnostic biomarkers for T2D, existing studies are limited by small sample sizes and uncertainty regarding exosome origin, underscoring the need for more comprehensive and well-designed research. However, it is important to underscore a key advantage of these studies, i.e., the use of serum or plasma samples as a source of circulating exosome-derived miRNAs. This approach offers an easily accessible biomaterial for analysis, often referred to as a non-invasive liquid biopsy.

Therapeutic potential of exosomal MiRNAs in type 2 diabetes

The field of research into the use of exosomes as therapeutics has experienced significant development in recent years. Due to their stability, ability to cross biological barriers, low immunogenicity and toxicity, as well as their biocompatibility and biodegradability, exosomes hold strong therapeutic potential to be used as both therapeutic targets and drug delivery vehicles capable of transporting biologically active molecules to specific sites [91]. In this context and intending to overcome current treatments that often come with various side effects [92], exosomes have been considered as a promising new option for more effective T2D management. Recent studies have highlighted the positive impact of exosomal contents in addressing metabolic disorders, including T2D (Table 3).

Table 3 Exosomal cargo with a potential therapeutic role in T2D

Exosomal cargo	Expression in T2D	The potential role in the treatment of T2D
aP2	Increased	Diminished secretion of aP2 from adipocytes improves regulation of systemic metabolism
Neutral ceramidase	Unknown	Overexpression of neutral ceramidase protects β-cells from lipotoxicity-induced apoptosis
miR-26a	Decreased	Increased expression of miR-26a modulates insulin secretion and β-cell replication and regulates peripheral insulin sensitivity - alleviation of obesity-induced IR and hyperinsulinemia
miR-146b	Increased	Overexpression of miR-146b target *Btg2* abolishes miR146b-induced apoptosis and restores suppressed proliferation of β-cells
miR-16	Increased	Transfer of miR-16 to the pancreas downregulates *Ptch1* in β-cells, followed by an increase in β-cells' proliferation
miR-130a-3p	Decreased	Overexpression of miR-130a-3p suppresses adipogenesis and regulates glucose/lipid metabolism in adipose tissues

The therapeutic efficacy of exosomes in T2D is predominantly attributed to their miRNA cargo, with protein components also contributing to their bioactivity. For example, targeted reduction of the release of adipocyte-derived exosomal adipocyte protein 2 (aP2), also known as adipocyte fatty acid-binding protein 4, may represent a novel opportunity in the treatment of metabolic diseases, including T2D [92]. aP2 is a lipid-binding protein, highly secreted from adipocytes during lipolysis, which has been shown to act as an adipokine that promotes hepatic glucose production and IR. Tang and colleagues showed the protective role of β-cells released neutral ceramidase packed in exosomes, which protects β-cells from lipotoxicity-induced apoptosis, like the one observed in T2D pathology [93]. The authors further demonstrated the role of neutral ceramidase in the sphingolipid-mediated signaling pathway, thus indicating that exogenous neutral ceramidase could be a potential therapy for T2D.

However, as in diagnostics, the greatest therapeutic potential in T2D lies in exosome-derived miRNAs. Studies published to date suggest that these miRNAs may contribute to the treatment of experimental T2D by modulating molecular pathways related to obesity-driven inflammation, glucose and lipid metabolism, IR, hyperinsulinemia, and the maintenance of pancreatic β-cell homeostasis. Previously mentioned study by Xu et al., which reported a reduction of serum exosomal miR-26a that inversely correlated with clinical features of T2D, additionally showed for the first time that β-cell–derived exosomal miR-26a modulates insulin secretion and β-cell replication in an autocrine manner, but also regulates peripheral insulin sensitivity in a paracrine manner [74], although the detailed mechanisms of exosome uptake, delivery, and functional impact in vivo remain incompletely characterized. Additionally, only a subset of miR-26a downstream targets was validated, and these appear insufficient to fully explain the robust metabolic phenotype, indicating that additional targets are likely to remain unidentified. The authors also suggested the mechanism by which exosomal miR-26a alleviates obesity-induced IR and hyperinsulinemia, thus providing new opportunities for the treatment of T2D. Overall, the use of genetically engineered mouse models may not fully recapitulate physiological regulation in humans, and the complex molecular composition of exosomes makes it difficult to attribute systemic effects solely to miR-26a without dissecting contributions from other exosomal components.

A study by Wang et al. showed a biomarker potential of miR-146b in the diagnosis of T2D, but they also provided a new insight into the molecular mechanism by which miR-146b, originating from β-cells, targets B cell translocation gene 2 (*Btg2*) and is involved in the negative regulation of β-cell number and function [90]. Additionally, the authors showed that overexpression of *Btg2* reversed miR-146b-induced apoptosis and suppressed the proliferation of β-cells. Jalabert and colleagues showed overexpression of miR-16 in exosome-like vesicles isolated from diet-induced insulin-resistant muscle, and that the transfer of this miRNA to the pancreas downregulates *Ptch1* gene in β-cells [94]. As *Ptch1* is suggested to have a role in the development of the pancreas as a receptor involved in the SHH pathway, the authors concluded that miR-16-mediated reduction of *Ptch1* led to an increase in β-cells proliferation. However, key limitations of the study include the inability to specifically isolate skeletal-muscle–derived EVs, uncertainty in EV biodistribution in vivo, as well as the fact that many mechanistic insights were derived from in vitro models and a high-palmitate diet mouse model, which may not fully reflect human physiology. Therefore, further studies, including physiologically relevant in vivo models capable of selectively labeling skeletal-muscle EVs are necessary to validate the proposed muscle–pancreas communication axis. Furthermore, Wu and colleagues investigated the crosstalk between liver and adipose tissues mediated by exosomal miR-130a-3p [95]. The authors demonstrated a mechanistic background of the hepatic exosome-derived miR-130a-3p suppression of adipogenesis and regulation of glucose/lipid metabolism in adipose tissues, thus elucidating a new mechanism of T2D targeted therapy.

microRNA (miR), adipocyte protein 2 (aP2), B cell translocation gene 2 (*Btg2*), patched homolog 1 (Ptch1).

Although the application of exosomes in the treatment of T2D remains in its infancy and is primarily supported by emerging scientific research, their use in the treatment of T2D-related complications has been more extensively investigated.

Exosomes as diagnostic and therapeutic tools in chronic type 2 diabetes-related complications

Exosomal cargo, especially miRNA, has been described as a key modulator of various biological processes, including the regulation of cellular signaling pathways in the development of T2D-related complications (Fig. 2). Altered circulating miRNA profiles may serve as early indicators of disease, potentially enabling diagnosis before the onset of clinical symptoms and thereby enhancing the management of T2D and its related disorders.

In addition to the previously described roles of exosomes and their cargo in the diagnosis and/or therapy of T2D, studies have identified exosomes as possible

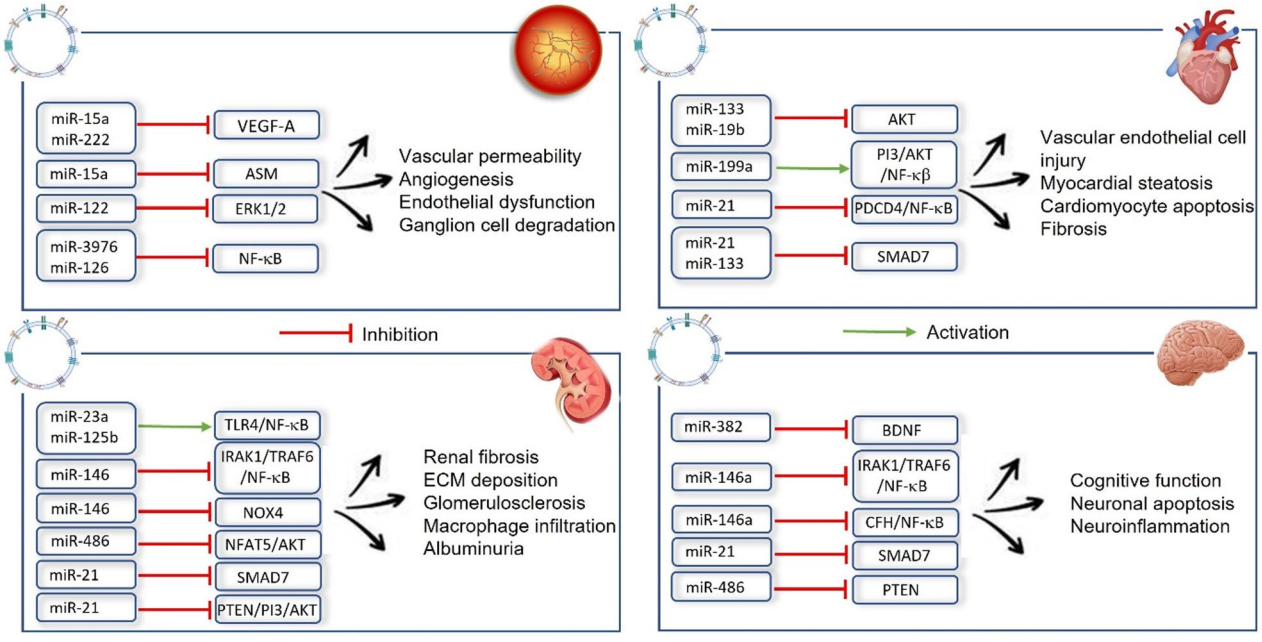

Fig. 2 Putative molecular targets and signaling pathways of exosomal miRNAs in the development of complications related to T2D. Vascular endothelial growth factor A (VEGF-A), acid sphingomyelinase (ASM), extracellular regulated protein kinases 1/2 (ERK1/2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Toll-like receptor 4 (TLR4), protein kinase B (AKT), phosphatidylinositol 3-kinase (PI3K), phosphatase and tensin homolog (PTEN), nuclear factor of activated T cells-5 (NFAT-5), complement factor H (CFH), nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4), IL-1 receptor-associated kinase 1 (IRAK1), TNF receptor-associated factor 6 (TRAF6), mothers against decapentaplegic homolog 7 (SMAD7), brain-derived neurotrophic factor (BDNF), transforming growth factor-beta (TGF-β), programmed cell death protein 4 (PDCD4), extracellular matrix (ECM)

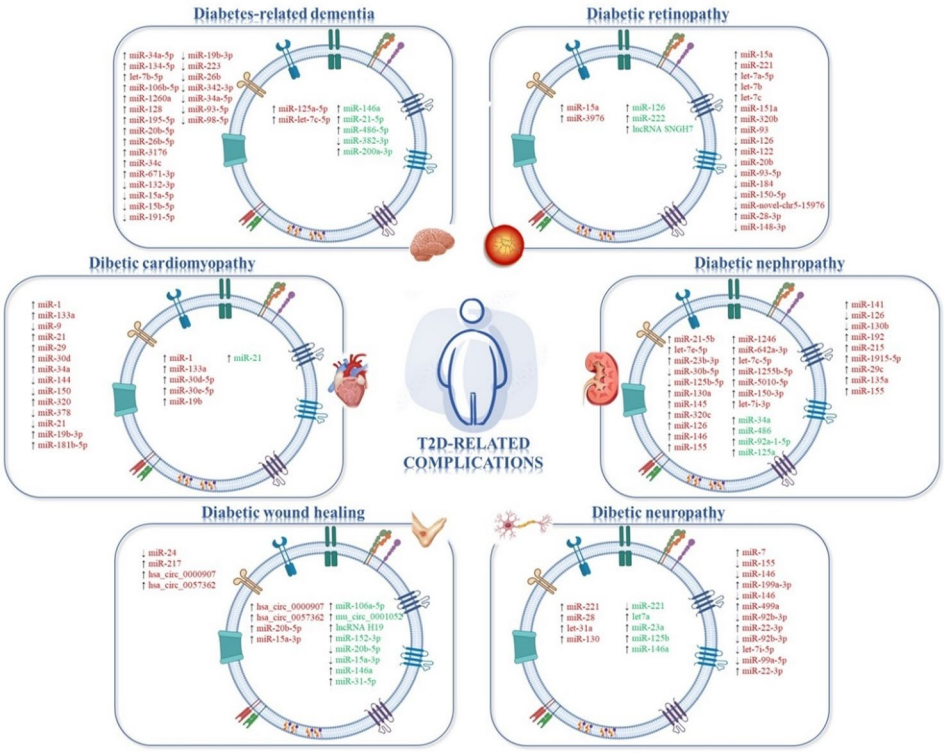

Fig. 3 A potential role of exosomal and non-exosomal miRNAs in the diagnosis and treatment of T2D-related complications. ↑ upregulation, ↓ downregulation, biomarker, therapy

biomarkers, as well as therapeutics in T2D-related complications. Exosomal miRNAs exhibiting such potential have been selectively identified and concisely described within the scope of this review (Fig. 3).

Exosomal miRNAs can be used as markers of diabetic retinopathy development and severity. Although limited by observational design and small sample size, which restrict definitive conclusions, a study by Sangalli et al. demonstrated an increase in free and EV incorporated circulating miR-15a in subjects with T2D [96],. In line with this, earlier research showed that, in response to high-glucose conditions, pancreatic β-cells release exosomal miR-15a, which can be transported to the retina and contribute to T2D-induced retinopathy [79]. Moreover, the extent of this elevation was observed to correspond to the severity of diabetic retinopathy. Yang et al. showed that serum-derived exosomal miR-3976 has the potential to serve as a biomarker for the early stages of diabetic retinopathy through the regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-associated mechanisms [97]. Additionally, the authors also demonstrated that suitable contents of miRNA-3976 promoted proliferation and reduced apoptosis of retinal ganglion cells damaged in retinopathy. Although significant, this research requires further validation since it is based on a small sample size and in vitro analysis, as well as a more detailed investigation of underlying mechanisms. However, significant circulatory miRNAs have been shown to correlate, either positively or negatively, with the development of T2D-related retinopathy, although their exclusive exosomal origin has not been demonstrated [98–100], or their expression is changed in T2D but without a significant change in diabetic retinopathy, as in the case of miR-155. Lower plasma levels of this miRNA were demonstrated in T2D patients compared to healthy controls without significant variations regarding the presence or severity of diabetic retinopathy, but this result must be taken with caution since it is a case-control study, which prevents establishing a causal relationship between plasma miR-155 levels and the development of diabetic retinopathy or T2D [101].

In the context of diabetic retinopathy management, recent significant research efforts have been directed toward the investigation of stem cell-derived exosomes which retain the therapeutic properties of stem cell regenerative therapy while reducing immunogenic responses [102]. So far, the therapeutic potential of exosomal miRNAs has been shown for miR-126 which, transferred by mesenchymal stem cells-derived exosomes, suppressed the hyperglycemia-induced inflammation and retinal endothelial dysfunction in diabetic retinopathy by targeting high mobility group box 1 and inactivating NF-κB p65 [103]. Although the results of this

study are consistent with the beneficial effects of miR-126 either in diabetes or diabetic retinopathy reviewed by Zhao et al. [104], the research has several limitations. The study relies on high-glucose–treated human retinal endothelial cells and streptozotocin-induced diabetic rats, which do not fully represent the chronic, progressive, and multifactorial pathology of human diabetic retinopathy that restricts direct clinical applicability. Furthermore, the study shows that exosomes derived from human mesenchymal stem cells are effective in rats, cross-species interactions may differ significantly from human physiology. Immunogenicity and biodistribution in humans are therefore uncertain. Moreover, the study does not provide comprehensive details on exosome characterization parameters, leaving issues of reproducibility and therapeutic standardization unresolved. Furthermore, the important role of exosomal miR-222 in retinal tissue repair was demonstrated for the first time [105]. Levels of miR-222 were significantly reduced in the retinal tissue of streptozotocin-induced diabetes, with severe retinal damage and extensive hemorrhage in different layers of the retina. Exosomal-mediated transfer of miR-222 increased the expression level of miR-222 in retinal tissue, thus affecting the regeneration of the tissue. However, the animal model used in the study only partially mimics the chronic, multifactorial course of human diabetic retinopathy, so species differences in retinal physiology, immune response, and glucose metabolism may limit the direct applicability of the results to humans. Cao et al. explored the potential role of exosomal lncRNA SNHG7 in diabetic retinopathy development by isolating exosomes from mesenchymal stem cells [106]. They exposed human retinal microvascular endothelial cells to high glucose levels, observing endothelial damage and endothelial-mesenchymal transition, along with reduced lncRNA SNHG7 levels and increased miR-34a-5p expression. Treating human retinal microvascular endothelial cells with exosomes containing overexpressed lncRNA SNHG7 significantly decreased endothelial-mesenchymal transition and tube formation by suppressing miR-34a-5p. These findings underscore the potential therapeutic value of exosomal lncRNA SNHG7 in alleviating diabetic retinopathy.

So far, several exosomal proteins present in urine exosomes emerged as potential non-invasive biological markers for diabetic nephropathy: Wilms tumor-1 protein, which can be used as a marker of early diabetic kidney injury; α–1-microglobulin/bikunin precursor, lysine-specific methyltransferase 2 C (MLL3), and the voltage-dependent anion channel 1, which can be used for a prediction of early abnormalities of diabetic nephropathy; leucine aminopeptidase and dipeptidyl peptidase 4 (DPP4), which are associated with biological parameters closely associated with the severity of diabetic nephropathy [107, 108]. Likewise, exosomal miRNAs have been shown to be promising biomarkers for the early diagnosis of diabetic nephropathy [107]. However, most data on miRNA expressions associated with diabetic nephropathy should be interpreted with caution due to inconsistent reproducibility of findings related to small sample sizes, heterogeneity of patients' clinical characteristics, variability in sample collection and experimental procedures, significantly limited characterization of exosomes, as well as the heterogeneity of the disease and previously applied therapies. For example, an upregulation in exosomal miR-21-5p, let-7e-5p, and miR-23b-3p was detected in urinary samples from patients with diabetic nephropathy, while the expression of miR-30b-5p and miR-125b-5p was significantly decreased [109]. An abundance of miR-130a and miR-145 packed in urine exosomes released from glomerular mesangial cells, whose expression positively correlated with glucose concentration, was also shown in urine patients with diabetic nephropathy [110]. Furthermore, increased expression of miR-320c, which may impact transforming growth factor-beta (TGF-β) signaling by targeting thrombospondin-1, was observed in the urine exosomes of T2D patients with diabetic nephropathy compared to those without, and this result was confirmed in two independent cohort studies, although both included a small sample size [111]. In a study by Gonzales-Palomo et al. authors investigated the profile expression of urine exosomal miRNAs in healthy subjects and T2D patients with and without albuminuria, identifying several miRNAs as a biomarker of early kidney damage [112]. The results showed that exosomal miR-126 was significantly increased in the T2D patients, while the expression of miR-146 was significantly increased in T2D patients without albuminuria compared with healthy subjects and the T2D with albuminuria group. Notably, an increase in miR-155 expression was observed in T2D patients compared with healthy subjects consistent with findings showing its absence reduces the risk of hyperglycemia-induced nephropathy [113]. In addition to urine exosomal miRNA, an upregulation of exosomal miR-1246, miR-642a-3p, let-7c-5p, miR-1255b-5p, miR-5010-5p, miR-150-3p, and let-7i-3p in the serum of diabetic patients with nephropathy compared to healthy volunteers was detected, although authors highlighted the limitations of the study, such as small number of participants, differences in demographic and clinical characteristics between groups, lack of standardized exosome isolation methods, need for validation with complementary techniques, limitations of the statistical normalization approach, lack of functional validation of identified miRNAs and uncertain cellular origin of circulating exosomes [114]. In addition to significant changes in the expression of exosomal miRNAs, studies have also

shown changes in the expression profile of free non-exosomal miRNAs present in serum, plasma, or urine that may also serve as biomarkers for nephropathy associated with T2D [115, 116]. For example, it was shown that the level of circulating miR-155 was significantly increased in patients with diabetic nephropathy compared to the control subjects [117]. However, the most relevant limitation of studies involving free circulating miRNAs is the unknown origin that complicates biological interpretation and reduces specificity for tissue or disease.

Exosomal miRNAs also provided new directions in the treatment of T2D-related nephropathy. Zheng et al. observed a high expression of miR-34a in kidney exosomes of a mouse model of diabetic nephropathy, which negatively regulated *PARGC1A* and rescued macrophage polarization and renal tubular cell fibrosis [118]. Although these findings are promising, they were obtained in an animal model, and validation in human diabetic nephropathy is required, given the complexity of the disease.

Significant short-term therapeutic potential in the treatment of diabetic nephropathy has been shown for miR-486, miR-125a, and miR-92a-1-5p in animal models, although research related to exosome transfer or their biodistribution is lacking, which would significantly increase the relevance of the results. Enhanced expression of miR-486 in adipocyte-derived stem cells secreted exosomes ameliorated diabetic nephropathy through the inhibition of SMAD1/mammalian target of rapamycin signaling pathway in podocytes [119]. Podocyte damage is one of the major clinical features of diabetic nephropathy and can be used as a clinical predictor in the evolution of the disease. Furthermore, adipose-derived mesenchymal stem cells-derived exosomes carrying miR-125a, which binds to histone deacetylase 1 and consequently inhibits endothelin-1, inhibited diabetic nephropathy progression and alleviated the symptoms [120]. Proximal tubular epithelial cells-derived exosomal miR-92a-1-5p worsened diabetic nephropathy in in vivo and in vitro models [121]. However, the inhibition of miR-92a-1-5p rescued nephropathic features, thus indicating this miRNA could be used as a therapeutic agent for diabetic kidney disease.

Research on the diagnostic use of exosomal miRNA in diabetic neuropathy is still scarce, with most existing studies concentrating more broadly on circulating non-exosomal miRNAs [122, 123]. An elevation of exosome-free miR-7 was reported in the serum of T2D individuals as well as in those with T2D-related microvascular complications, including diabetic neuropathy [124]. However, although this indicated the biomarker potential of miR-7 for the early identification of diabetic neuropathy, it remains unclear whether miR-7 is specifically associated with diabetic neuropathy or overlaps with other microvascular complications related to T2D, such as retinopathy or nephropathy. Furthermore, circulating levels of miR-155 and miR-146a were significantly reduced in T2D patients, with a more pronounced decrease in those with diabetic peripheral neuropathy compared to T2D alone [125]. However, the single-center design of the study and small sample size may limit the generalizability of the findings, highlighting the need for larger multicenter studies and better DPN staging. Authors also emphasized that they could not establish causality or explain the reduced expression of miR-155 and miR-146a in diabetic peripheral neuropathy, underscoring the need for further mechanistic studies to assess their potential as therapeutic targets. miR-221 was identified as another potential biomarker specifically of diabetic peripheral neuropathy by demonstrating overexpression of serum exosomal miR-221 in an in vivo model of streptozotocin-induced diabetic peripheral neuropathy [126]. Additionally, the therapeutic potential of miR-221 was highlighted, since it was shown that miR-221 inhibition reduced pain and decreased expression of inflammatory factors by targeting SOCS3. Significantly, a study by Jia et al. demonstrated the role of exosomes in the specific diagnosis of diabetic peripheral neuropathy as a subtype. Although the study focuses primarily on Schwann cell–derived exosomes and dorsal root ganglia neurons, even though diabetic peripheral neuropathy involves multiple cell types whose contributions were not investigated, the results showed that high glucose-treated Schwann cells produce exosomes enriched for miR-28, miR-31a, and miR-130 that contribute to the early onset and progression of diabetic peripheral neuropathy [127]. However, regardless of the relevant results obtained in vitro and in vivo, further research on human samples are needed to confirm the applicability of the obtained results. A novel therapeutic approach for diabetic peripheral neuropathy involving exosomes derived from mesenchymal stromal cells has been proposed [128]. When administered to mice with the condition, this treatment reduced neurovascular impairment and axonal demyelination, leading to improved neurological outcomes. In doing so, the authors emphasize the administration of a specific number of exosomes into the animals, as well as tracking the distribution of exosomes precisely to the sciatic nerve and footpad tissue, highlighting the relevance of this finding. Additional miRNA sequence and bioinformatic analysis revealed that mesenchymal stromal cells-derived exosomes are enriched in miRNAs, such as let-7a, miR-23a, and miR-125b, among others, which targeted the Toll-like receptor (TLR) 4/NF-κB signaling pathway, thereby contributing to the inactivation of the proinflammatory signaling cascade involved in the pathogenesis of diabetic peripheral neuropathy. A subsequent study introduced a new therapeutic strategy, showing

that engineered exosomes enriched with miR-146a significantly enhanced the effectiveness of mesenchymal stromal cells in treating diabetic peripheral neuropathy [129]. Significant evidence of exosome markers, purity and delivery of a specific miRNA as cargo to the peripheral nervous system makes the results of this study more robust. However, the clinical translation of mesenchymal stromal cells-derived exosomes depends on overcoming challenges related to large-scale production, as well as ensuring consistent quality, reproducibility, and therapeutic potency - efforts that require substantial development.

To date, only a limited number of miRNAs, whether exosomal or non-exosomal, have been recognized for their potential as biomarkers in diagnosing diabetic foot ulcers. For example, decreased expression of plasma miR-24 and increased expression of serum miR-217 have been shown in patients with diabetic foot ulcer in single-center studies and more research is needed to confirm these, as well as the causal relationship between miRNAs and the pathogenesis of [130, 131]. The investigation of the expression profile of serum and exosomal circRNAs between patients with diabetic foot ulcer and normal human wounds suggested that serum and exosomal circRNAs hsa_circ_0000907 and hsa_circ_0057362 may serve as important markers in the early diagnosis of diabetic foot ulcer [132]. The therapeutic approach for foot ulcers has focused primarily on wound healing, but the current therapy is not sufficient [133]. Therefore, there is an urgent need for new effective therapies in which exosomes and their cargo have shown significant potential so far. It has been shown that exosomes derived from adipose stem cells promoted proliferation and angiogenesis in endothelial progenitor cells in a high glucose environment, as well as wound healing in a diabetic rat model of foot ulcer, and this protective effect of exosomes increased with the overexpression of nuclear factor-E2-related factor 2 [134]. However, experiments were conducted exclusively in a rat model of diabetic foot ulcers, which cannot fully reproduce the complexity of human diabetic wound pathology, potentially limiting the translational applicability of the findings. Additionally, the sample size and study duration were relatively limited, preventing assessment of long-term safety. Furthermore, exosome heterogeneity, purity, and stability were not explored in depth, leaving uncertainties regarding the consistency of the therapeutic product. Furthermore, exosomal mmu_circ_0001052 derived from adipose-derived stem cells was shown to ameliorate angiogenesis of wound healing by repressing miR-106a-5p and activating FGF4/p38MAPK pathway was proposed [135]. Li et al. described a mechanism by which lncRNA H19 overexpressed in exosomes derived from mesenchymal stem cells interacts with miR-152-3p, which further targets the PTEN-mediated PI3K/AKT signaling pathway, thus stimulating the wound healing process [136]. Based on the above, various exosomal cargoes identified as playing a role in detecting or promoting diabetic wound healing can serve either as biomarkers for diabetic foot ulcers or as therapeutic agents in their management. Unfortunately, a reliable prognostic biomarker capable of predicting adverse outcomes and identifying individuals at particularly high risk is still lacking. Such a marker would enable earlier diagnosis, warrant prompt intervention, and help prevent complications such as infections, ulcers, and ultimately, lower limb amputation. In most cases, exosomal miRNA cargo has been proposed both as a biomarker and a therapeutic agent. In line with this, Xiong et al. reported a significantly higher abundance of exosomal miR-20b-5p in the peripheral blood of patients with T2D compared to healthy controls [87]. Furthermore, authors showed that upregulation of miR-20b-5p delayed wound healing by inhibiting the Wnt9b/β-catenin signaling pathway, a process that was restored by the suppression of miR-20b-5p. These results not only indicated a biomarker potential of exosomal miR-20b-5p but also suggested a promising therapeutic approach to promote wound healing through the inhibition of this miRNA. The same group of researchers also showed that exosomes from diabetic peripheral blood are rich in miR-15a-3p compared to the control, whose inhibition accelerated diabetic wound repair by activating nicotinamide adenine dinucleotide phosphate oxidase (*NOX*) 5 [137]. However, when it comes specifically to therapy, it has been shown that exosomes in general have great potential in the treatment of diabetic wounds, where the effects of exosomes, mostly originating from stem cells, have been primarily investigated in the context of a so-called cell-free therapeutic strategy. Although limited by the investigation of the effect of human exosomes secreted by adipose-derived mesenchymal stem cells in a diabetic mouse model, several results unveiled that these exosomes facilitated diabetic wound healing through various mechanisms, including promoting re-epithelialization, stimulating cell proliferation, enhancing collagen synthesis, facilitating tissue remodeling, restoring skin barrier function, promoting angiogenesis, and suppressing apoptosis and inflammation. For example, Zhao et al. observed a significant acceleration of wound healing by exosomal promotion of collagen synthesis [138]. Exosomes derived from mesenchymal stem cells of adipose tissue improved wound healing by reducing senescence, which disrupts the integrity of the endothelial blood vessels characteristic of diabetes, rescuing angiogenesis, and improving migration and proliferation of senescent endothelial cells induced by oxidative stress and high glucose in vitro [139, 140]. Additionally, the following in vivo analysis supported these claims by confirming wound healing after

administration of adipose tissue-derived mesenchymal stem cell exosomes in a mouse model of diabetic wound healing. These findings suggested a potential mechanism by which exosomes derived from adipose tissue mesenchymal stem cells may rejuvenate senescent endothelial cells, primarily through miR-146a-driven inhibition of Src phosphorylation. A study by Bian et al. found that decidua-derived mesenchymal stem cell small extracellular vesicles, characterized as exosomes, protect human dermal fibroblasts exposed to high glucose levels that accelerate their senescence, and consequently impair normal wound healing, in which fibroblasts play a crucial role [141]. The authors also proposed a mechanism for this action that includes suppression of the receptor for advanced glycation end products pathway and activation of the SMAD pathway. Additionally, they showed that topical administration of vesicles notably expedited wound closure in a mouse experimental model of diabetes, underscoring the potential of decidua-derived mesenchymal stem cell small extracellular vesicles as a promising therapeutic avenue for promoting diabetic wound healing.

The therapeutic potential of exosomes derived from human urine stem cells in treating diabetic wounds has been validated through both in vitro studies and in vivo models [142]. The healing mechanism involves enhanced re-epithelialization, increased collagen deposition, and improved vascularization, primarily driven by the transfer of the exosomal protein deleted in malignant brain tumors 1, which is highly expressed. However, the healing effect does not necessarily have to be triggered solely by urinary stem cells' exosomes but also mediated by the activation of keratinocytes and fibroblasts, which requires further investigation, as well as the mechanisms by which the exosomes are internalized by recipient cells. Nonetheless, the use of exosomes and miRNAs in diabetic wound healing has advanced significantly, representing a more refined and effective therapeutic strategy. For example, Huang et al. devised a method involving engineered exosomes to target wound recovery [143]. Initially, they analyzed miRNA expression in diabetic chronic wounds using patient samples. Upon discovering a notable decrease in miR-31-5p levels in such wounds, they demonstrated that miR-31-5p expression in vitro facilitated fibrogenesis, epithelialization, and angiogenesis. Subsequently, they engineered miR-31-5p carrying exosomes and administered them to diabetic rats. Animals exhibited accelerated wound healing compared to control groups, one treated with non-engineered exosomes and the other receiving no exosomes. Although the study showed beneficial effects of engineered exosomes in diabetic wound healing, the authors emphasized certain limitations, such as limited clinical translation of the study due to the use of cell lines instead of stem cells for exosomes production and potential tumorigenesis of exosomes related to the short-term observation. Since it has been shown that miRNAs are significantly involved in the pathogenesis of diabetic cardiomyopathy, it can be assumed that they may be harnessed as either biomarkers of the disease or novel therapeutic strategies in treating diabetic cardiomyopathy [144]. Moreover, several published studies have already shown a significant biomarker potential of either exosomal or non-exosomal miRNAs. De Gonzalo-Calvo et al. conducted the assessment of miRNA biomarkers in humans for diabetic cardiomyopathy, aiming to evaluate their practical clinical utility. Interestingly, in vitro, in vivo, and patient-based studies revealed a positive correlation between circulatory miR-1 and miR-133a and myocardial steatosis, a hallmark of diabetic cardiomyopathy, indicating promising prospects for the clinical application of these miRNAs as biomarkers [145]. The study's relevance to broader populations is limited because it involved only male participants, and excluding T2D patients with ischemia or other significant comorbidities further narrows the applicability of the results. Moreover, since circulating miR-1 and miR-133a are associated with necrotic and ischemic processes and may also be released in response to various cardiac stressors beyond lipid accumulation, the specificity of these biomarkers may be reduced. Veitch and colleagues identified exosomal miR-30d-5p and miR-30e-5p as potential serum markers of coronary microvascular endothelial cell dysfunction preceding T2D-associated diastolic dysfunction [146]. Moreover, besides demonstrating a correlation between the upregulation of miR-30d-5p and miR-30e-5p and cardiac microvascular endothelial dysfunction, authors also showed that the miR-30 family regulates exogenous fatty acid β-oxidation in cultured endothelial cells and increases oxidative stress, lipid peroxidation and endothelial dysfunction, but also that inhibition of the miR-30 family in vivo reduces markers of oxidative stress and DNA damage/senescence in the microvascular endothelium of diabetic mice. Importantly, endothelial biology was examined primarily using human umbilical vein endothelial cells, which may not fully represent cardiac microvascular endothelial cells, highlighting the need for vascular-bed–specific validation. Additionally, the role of exosomal miR-30d-5p and miR-30e-5p in intercellular communication remains unexplored, leaving gaps in understanding how these miRNAs function systemically. Moreover, the work focused on early-stage T2D in young db/db mice, so it remains unclear whether longer-term miR-30 inhibition would improve later manifestations. Finally, the translational relevance of these findings is uncertain because it has not yet been determined whether the identified miRNAs can serve as early biomarkers of coronary microvascular or diastolic dysfunction in human T2D

patients. Several other studies have indicated the role of circulatory miRNAs in the diagnosis of diabetic cardiomyopathy, but without a clear definition of their exosome origin. For instance, plasma levels of miR-21 were found to be significantly lower in T2D patients with diabetic cardiomyopathy compared to those without, indicating its potential as a biomarker [147]. In addition, it was demonstrated that cardiac progenitor cell-derived exosomal miR-21 can protect cardiomyocytes from apoptosis induced by oxidative stress by downregulating the expression of programmed cell death protein 4 (PDCD4) [148]. Therefore, this study may indicate an exosomal origin of plasma miR-21, demonstrating its potential protective role in the development of cardiomyopathy related to T2D. This opens up the possibility of new research on the transfer of miRNAs through exosomes, which ultimately affects the preservation of the integrity of miRNAs outside the cell. Another study suggested circulatory miR-19b-3p and miR-181b-5p as potential biomarkers for diabetic cardiomyopathy [149]. The authors demonstrated that plasma levels of the identified miRNAs were associated with a degree of cardiac dysfunction during the development of diabetic cardiomyopathy, suggesting that these miRNAs may contribute to myocardial pathogenesis during diabetes. However, the exosomal origin of both miR-19b-3p and miR-181b-5p still needs to be determined concerning the development of diabetic cardiomyopathy. In line with this, a review by Reiss highlighted several roles of exosomal miR-19b in intracellular cardiac communication that emphasize the negative impact of miR-19b in the context of various cardiac pathologies [150]. In contrast, miR-181b, in a cluster with miR-181a, is abundantly expressed in cardiac tissue and overexpression of this cluster has been shown to exert a cardioprotective [151].

Exosomal, as well as non-exosomal miRNAs are also emerging as important players in both the development and potential treatment of T2D-related dementia. So far, several exosomal miRNAs have been identified as biomarkers or targets for potential therapeutic use in the treatment of T2D-related dementia. For example, serum exosomal miR-125a-5p, originating from adipose tissue, has been identified as a potential causal biomarker for cognitive decline in individuals with T2D, but a longer follow-up is needed to determine whether changes in this biomarker can predict future progression to Alzheimer's disease [152]. Additionally, elevated levels of plasma exosomal miR-let-7c-5p in T2D patients with mild cognitive impairment suggest a role in disease progression, possibly through the downregulation of IL-10 in plasma, although this may not [153]. In line with this, exosomes were isolated collectively from plasma rather than from specific central nervous system-related cell types which may have provided more targeted insights into neuroinflammatory pathways. The study also lacks well-designed cohort data needed to clarify the causal relationships between IL-10 or miR-let-7c-5p and diabetes-related cognitive decline, and further basic research is required to elucidate the mechanistic interplay between these molecules. Ran et al. highlighted the therapeutic potential of exosomes derived from mesenchymal stem cells and their content, emphasizing their beneficial effects through anti-inflammatory and antioxidant mechanisms, as well as their ability to enhance brain function [154]. For instance, miR-146a, derived from bone marrow mesenchymal stem cells, was shown to exhibit anti-inflammatory properties by downregulating the expression of IL-1 receptor-associated kinase 1 (IRAK1), NF-κB, and TNF-α, thereby helping to prevent cognitive impairment associated with diabetes [155]. Additionally, exosomes derived from bone marrow mesenchymal stem cells have been shown to alleviate cognitive deficits induced by diabetes and promote the repair of damaged neurons and astrocytes in diabetic mice, suggesting their potential as a therapeutic approach for diabetes-related cognitive impairment [156]. Elucidating the precise mechanisms underlying the process described in previously mentioned studies could have significant implications for the development of targeted and more effective therapeutic strategies for diabetic cognitive impairment in humans. Furthermore, a transfer of exosomal miR-21-5p and miR-486-5p by induced pluripotent stem cell-derived mesenchymal stem cells promoted neurogenesis and restored cognitive function in mice with postoperative cognitive dysfunction associated with diabetes [157]. While this study indicates a novel cell-free therapeutic approach for diabetic patients with postoperative cognitive dysfunction, it lacks long-term evaluation of cognitive changes related to postoperative cognitive dysfunction that may develop over extended periods. Another study observed that elevated metastasis-associated lung adenocarcinoma transcript 1 levels in serum exosomes competitively inhibited the expression of miR-382-3p and enhanced the expression of brain-derived neurotrophic factor, leading to improved cognitive function in T2D mice following light-intensity exercise [158]. Although limited only to a mouse model, findings by Shima et al. suggested that an increase in exosomal miR-200a-3p originating from the gastrocnemius muscle may help improve memory deficits in T2D mice engaged in light-intensity exercise [159]. Further clinical trials and verification of clinical potential are needed.

In addition to exosomal, there is a large number of studies on the role of non-exosomal miRNAs in the development of cognitive impairment and dementia associated with T2D, which can thus serve in the detection of the disease or its treatment. Liu et al. identified silent information regulator 1 and miR-34-5p as valuable biomarkers for the early detection of cognitive impairment

in T2D patients using peripheral blood mononuclear cells from patients with Alzheimer's disease and T2D patients with or without cognitive impairment [160]. Furthermore, the study by Sun et al. explored the impact of cognitive intervention and rehabilitation training on the expression of miR-134-5p, a miRNA associated with synaptic plasticity and cognitive function. The researchers determined that these non-pharmacological treatments decreased miR-134-5p levels and improved cognitive outcomes in elderly patients with T2D and mild cognitive impairment [161]. In the recent systematic review by Teixeira et al., the authors investigated circulating miRNAs expressed in both T2D and Alzheimer's disease and identified 21 dysregulated serum or plasma miRNAs, 10 upregulated and 11 downregulated [162]. Moreover, the authors investigated their target genes and related molecular pathways, offering insights into the common underlying mechanisms that help explain the link between T2D and Alzheimer's disease, along with identifying potential targets for therapy.

Conclusions and future perspectives

T2D is a widespread chronic condition with rising incidence. Although its mechanisms are not fully understood, T2D is primarily driven by IR, which reduces glucose uptake in the liver, muscle, and adipose tissue, leading to hyperglycemia. Poorly managed T2D can result in serious complications, including retinopathy, neuropathy, nephropathy, impaired wound healing, cardiomyopathy, and cognitive decline. EVs, especially exosomes, have recently emerged as crucial mediators of intercellular communication and are implicated in both normal physiology and the development of diseases, including T2D and its complications. As naturally occurring nanoparticles, exosomes are considered promising therapeutic agents and drug delivery vehicles due to their low immunogenicity, excellent biocompatibility, high structural stability, and favorable bioavailability [163]. Moreover, they are capable of targeting specific cell types by crossing natural physiological barriers, such as the blood-brain barrier. These advantages not only overcome the limitations of conventional delivery systems, such as viruses and liposomes, but also render exosomes superior to synthetic carriers and nanoparticles [164]. The lipid bilayer structure gives them an amphiphilic nature that enables them to encapsulate and transport both hydrophobic and hydrophilic compounds, while their intrinsic biomolecular components can act synergistically with encapsulated therapeutics, thereby enhancing their overall therapeutic efficacy [165]. With the ongoing progression of medical science and technological innovation, alongside deeper investigations and enhanced comprehension of exosome physiology and attributes, the potential for their integration into clinical practice is increasingly promising.

The diagnostic advantage of exosomes T2D and related complications lies in their remarkable stability within body fluids and the relatively low cost of isolation and detection. In this context, most studies have focused on exosomes obtained from serum, plasma, or urine, demonstrating that even variations in their quantity may serve as potential biomarkers for T2D or its related [52]. Moreover, the molecular content of circulating exosomes also changes, primarily reflecting alterations in protein and miRNAs expression. When it comes to therapy, studies have demonstrated that exosomes and their molecular cargo play a therapeutic role in T2D by modulating glucose metabolism and promoting β-cell regeneration. Additionally, they contribute to alleviating T2D-related complications by reducing inflammation, oxidative stress, and apoptosis, while enhancing angiogenesis and tissue repair [52, 166].

According to the available literature, there are currently no completed interventional clinical trials directly testing exosomal miRNA-based therapies in T2D patients, and most exosome-miRNA research remains preclinical or observational, with a major need for translation into a controlled trial [51]. Some trials investigate T2D therapies (e.g., glucagon-like protein (GLP)-1 receptor agonists), but no human trial has yet formally evaluated therapy-induced changes in exosomal miRNAs. A 2025 systematic review explicitly notes that no clinical studies have yet reported GLP-1 receptor agonist-related exosomal miRNA signatures, despite preclinical data [166]. Although not interventional, a recent large exosome-wide association study that identified several differentially expressed miRNAs in exosomes from patients with T2D, diabetic lower extremity arterial disease and diabetic foot, represents one of the most translational efforts to date, supporting progress toward clinical application [167]. Specifically, has-miR-409-3p distinguished T2D from lower extremity arterial disease, hsa-miR-543 differentiated T2D from diabetic foot, and hsa-miR-206 separated lower extremity arterial disease from diabetic foot. Mendelian randomization further suggested causal associations between exosomal miR-30b-3p and miR-30b-5p and both T2D and peripheral arterial disease. A review of *clinicaltrials.gov* identified three ongoing studies. These clinical trials are investigating exosomes either as complementary treatments alongside standard T2D therapies or exploring exosomal microRNAs as potential diagnostic indicators for diabetic nephropathy. Although notable progress has been made toward clinical translation in this field, several significant challenges remain. Most current evidences are derived from animal models, underscoring the urgent need for well-designed human trials. Standardization of exosome isolation, quantification, and characterization remains a major technical hurdle. Furthermore, large-scale, multi-ethnic clinical studies are

essential to validate exosomal miRNAs as reliable universal biomarkers. On the therapeutic side, engineering exosomes requires significant advances in target specificity, dosing strategies, safety assessment, and scalable production to ensure clinical applicability.

Despite their great promise in theranostics—combining diagnostic and therapeutic applications—many aspects of exosome biology and mechanism of action remain to be fully understood. Ongoing research may uncover innovative diagnostic tools and treatment strategies, potentially transforming the management of T2D and related complications, and ultimately improving patient outcomes.

Abbreviations

AKT	Protein kinase B
AKTIP	AKT interacting protein
aP2	Adipocyte protein 2
ASM	Acid sphingomyelinase
BDNF	Brain-derived neurotrophic factor
Btg2	B-cell translocation gene 2
CFH	Complement factor H
circRNA	Circular RNA
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DPP4	Dipeptidyl peptidase 4
ECM	Extracellular matrix
ERK1/2	Extracellular regulated protein kinases 1/2
EVs	Extracellular Vesicles
GLP-1	Glucagon-like peptide 1
GLUT4	Glucose transporter type 4
HDAC1	Histone deacetylase 1
HMGB1	High mobility group box 1
HSP	Heat shock protein
IL	Interleukin
IR	Insulin resistance
IRAK1	Interleukin-1 receptor-associated kinase 1
IRS-1	Insulin receptor substrate-1
KLF4	Krüppel-like factor 4
lncRNA	Long non-coding RNA
mRNA	Messenger RNA (mRNA)
miR	MicroRNA
miRNA	MicroRNA
MVBs	Multivesicular bodies
ncRNA	Non-coding RNA
NFAT-5	Nuclear factor of activated T cells-5
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
PDCD4	Programmed cell death protein 4
PDK1	3-phosphoinositide-dependent protein kinase 1
PI3K	Phosphatidylinositol 3-kinase
piRNA	Piwi-interacting RNA (piRNA)
PPAR-γ	Peroxisome proliferator-activated receptor
Ptch1	Patched homolog 1
PTEN	Phosphatase and tensin homolog
RNA	Ribonucleic acid
rRNA	Ribosomal RNA (rRNA)
SC	Subcutaneous
SHH	Sonic hedgehog
SMAD	Mothers against decapentaplegic homolog
snRNA	Small nuclear RNA
snoRNA	Small nucleolar RNA
SOCS	Suppressor of cytokine signaling
STAT	Signal transducer and activator of transcription
T2D	Type 2 diabetes
T1D	Type 1 diabetes
TGF-β	Transforming growth factor-beta
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-α
TRAF6	TNF receptor-associated factor 6
tRNA	Transfer RNA
UCP-2	Uncoupling protein-2
VEGF-A	Vascular endothelial growth factor A

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Data availability
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Declarations

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