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Exosomal Biomarkers and Extracellular Vesicles in Diabetic Retinopathy: Emerging Mechanisms, Diagnostic Signatures and Therapeutic Frontiers

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Abstract

Diabetic retinopathy is a progressive complication of diabetes, a form of microvascular and neurodegenerative microvascular and neurodegenerative impairment that progresses to visual impairment and is a leading avoidable etiology of blindness in the world. The recent studies have highlighted the critical role of exosomes and extracellular vesicles in clarifying the pathophysiological mechanisms behind it, equipping the diagnostic modalities, and promoting therapeutic development that is relevant to diabetic retinopathy. Previously, these nanosized vesicles include a heterogeneous collection of molecular constituents, including microRNAs, proteins, lipids and metabolites and are utilized as active mediators of intercellular communication in the diabetic retina. Endothelial dysfunction, loss of the blood retinal barrier, oxidative stress, chronic inflammation, apoptosis of pericytes, and altered angiogenesis have all been implicated in the involvement of extracellular vesicles in the initial neuronal pathology and the subsequent vascular pathology. Observable exosomal signatures quantifiable in the plasma and vitreous fluid have a promising potential of being minimally invasive biomarkers by which early detection, disease progression, and prognostication can be performed. It is worth noting that exosomal miRNAs that mediate angiogenic and inflammatory pathways have a high diagnostic specificity. Exosomes made of mesenchymal stem cells have shown strong anti-inflammatory, anti-oxidative and neuroprotective effects therapeutically, making them a safe, cell-free, regenerative approach with a low immunogenicity. Further innovations in extracellular vesicle isolation methods, full molecular profiling and the nanotechnology-based platforms of delivery are also enhancing their translational capability. Nevertheless, even in the face of ongoing issues of

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standardization and clinical validation, exosome studies provide new mechanistic understanding and open new opportunities of specific diagnostics and therapeutic methods of diabetic retinopathy.

Keywords: Exosomes, Diabetic Retinopathy, miRNAs, Biomarkers, Angiogenesis, Inflammation.

1. Introduction

Diabetic retinopathy (DR) is a major microvascular complication of diabetes mellitus and one of the commonest avoidable causes of blindness in the world today. The pathogenesis of it is associated with oxidative stress caused by chronic hyperglycemia, inflammatory cascades, endothelial dysfunction, and neurodegenerative processes [1]. The traditional diagnostic methods are mostly based on the use of fundus photography that can detect the morphological changes already when the retinal injury is severe. Similarly, current treatment interventions such as intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, laser photocoagulation, and systemic corticosteroids, are mostly utilized at advanced disease stages, and not to prevent the onset of disease [2]. Recent studies show that exosomes and extracellular vesicles (EVs) could provide important information regarding the pathology of the retina in the early stages and offer a prospect of therapeutic intervention. Therefore, this chapter analyzes the immature diagnostic and intervention capabilities of EVs in the framework of DR management [3].

1.1 Overview of Diabetic Retinopathy

Diabetic retinopathy (DR) is a major microvascular and neurodegenerative diabetes mellitus sequela, with it being one of the important preventable etiologies of blindness. The sustained hyperglycemia leads to the development of oxidative stress, inflammatory cascades and dysfunction of endothelial cell and this in totality causes progressive damage to the retinal microvasculature [4]. DR normally starts as non-proliferative diabetic retinopathy (NPDR), which is a stage of retinopathy that is produced by the formation of microaneurysms, capillary occlusion, and pericyte loss. The situation can progress to proliferative diabetic retinopathy (PDR) with pathological neovascularization and high chances of hemorrhage or retinal detachment [5]. DME is a disease that can occur at any stage of the disease and is one of the major causes of central visual loss. Early neurodegenerative alterations, such as Muller cells, retinal ganglion cells, and photoreceptors are also substantively involved in the disease progression. DR is often asymptomatic at its initial phases thus making its early diagnosis difficult [6]. The increasing prevalence of diabetes in the global population leads to the fact that the multifactorial pathophysiology of DR would be the key to the development of more effective approaches to its diagnosis and treatment [7].

1.2 Limitations of Current Diagnostic and Therapeutic Approaches

There are significant limitations to the existing diagnostics and treatment methods of diabetic retinopathy (DR). Structural perturbations are only detected in a manner of conventional imaging modalities such as fundus photography,

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optical coherence tomography (OCT), and fluorescein angiography, after much damage has been done to the retina. Therefore, they cannot detect preliminary molecular changes, nor do they accurately predict developing stages, which pose a risk to the sight [8]. The primary interventions that have continued to be applied in the therapeutic sphere are intravitreal anti-vascular endothelial growth factor (VEGF) agents and corticosteroids. These modalities however require frequent play, are very expensive and have resulted in disparate responses in patients [9]. The adverse incidents include increased intraocular pressure, cataract genesis and infrequently, complications associated with the procedure. Although laser photocoagulation may stop the development of advanced disease, its destructive effect can damage peripheral vision [10].

1.3 Rationale for Exploring Exosomes and Extracellular Vesicles

Exosomes and extracellular vesicles (EVs) are one of the emerging directions of innovating the study of diabetic retinopathy (DR), as they are the central players in intercellular communication. These nanosized vesicles help to transport miRNAs, proteins and lipids, which regulate inflammation, angiogenesis, oxidative stress and neuronal survival, processes, which cannot be ignored in the pathogenesis of DR [11]. It is important to note that exosomal cargo perturbations occur at an early disease stage, which makes them attractive minimally invasive disease indicators to detect the disease early and track disease progression. Plasma and vitreous exosomal signatures are highly promising when it comes to early retinal-stress identification before structural changes will occur [12]. Exosomes produced by mesenchymal stem cells have anti-inflammatory, anti-angiogenic and neuroprotective effects, and as a cell free option are therefore safer than the standard stem-cell therapy. Their stability, immunogenicity and ability to possess therapeutic molecules makes them more translational. With the technologies of EV isolation and profiling constantly being improved, exosomes are the potential source of accurate diagnostics and direct therapeutics in the presence of diabetic retinopathy [13].

1. Biology of Extracellular Vesicles and Exosomes

Extracellular vesicles (EVs) represent nanoscale, membrane-closed structures released by virtually all cell types and thus, they are central to intercellular communication. Different bioactive molecules such as miRNAs, proteins, lipids, and metabolites are transported in these vesicles and regulate physiological and pathological activities [14]. Exosomes are one of the various subtypes of EVs that have received special interest because of their clear cellular biogenesis mechanisms and because of their ability to mirror the physiological conditions of their cellular formation [15]. EVs play a role in diabetic retinopathy inflammation, angiogenesis, vascular dysfunction, and neurodegeneration through the mediation of pathogenic signal transfers between retinal cells. Their intrinsic stability in the biological fluids and the profiles of disease-specific cargo of them make them excellent biomarkers and therapeutic agents. Therefore, a complete picture on the biology of

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EV is necessary to the development of diagnostic and therapeutic interventions [16].

2.1 Classification of EVs (Exosomes, Microvesicles, Apoptotic Bodies)

Extracellular vesicles (EVs) are a heterogeneous group of membrane-enclosed particles, which can be simply divided into exosomes, microvesicles, and apoptotic bodies, according to size, biogenesis, and molecular composition variations [17]. Exosomes are endosomal system derived structures, 30-150nm in diameter, which are released when multivesicular bodies fuse with the plasma membrane; they deliver selectively packaged nucleic acids and proteins [15]. The outward budding of the plasma membrane results in microvesicles of between 100 and 1000 nm and has a varied cargo depending on cellular stress, inflammation, or metabolic dysfunction. During apoptosis, apoptotic bodies are produced, and these bodies may include organelles, nuclear fragments, and cytosolic material, as well as have a diameter of 500 to 5000 nm [18]. Whereas the size range of these vesicular subtypes can overlap, different functional specificity is conferred by the difference in their origin and cargo composition. This classification is vital to research the role of vesicle-mediated communication in diabetic retinopathy because each of the subtypes of EV plays a distinct role in vascular damage, inflammation, and neuro-damage [19].

2.2 Biogenesis and Release Mechanisms

Extracellular vesicles (EVs) biogenesis is a coordinated process that defines the structural attributes of EVs and the biological role of the vesicles. Exosomes are created by inward budding of endosomal membranes to produce intraluminal vesicles that are formed in multivesicular bodies mediated either by ESCRT-dependent or ceramide-mediated mechanisms **(Figure 1)** [15]. These multivesicular bodies are then directed into lysosomal degradation or merged to the plasma membrane in order to induce exosome liberation. Microvesicle formation, in its turn, consists of outward budding and fission of the plasma membrane, controlled by influx of calcium, remodeling of actin-myosin cytoskeleton, and small GTPases like ARF6 and RhoA [20]. During programmed cell death, apoptotic bodies are generated with the involvement of caspases which induce blebbing and fragmentation of membranes. Stressors such as hyperglycemia, oxidative damage and inflammation have been identified to increase EV secretion and cargo composition. These processes in diabetic retinopathy have been shown to speed up pathological signaling, and so EV biogenesis lies at the center of disease processes and emerges as a therapeutic intervention option [21].

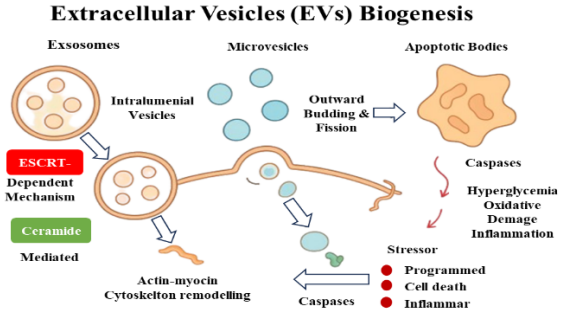

Figure 1: *Overview of extracellular vesicle (EV) biogenesis highlighting exosome formation, microvesicle*

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budding, and apoptotic body generation.Mechanisms involve ESCRT pathways, ceramide signaling, cytoskeletal remodeling, and caspase-mediated cell stress responses.

2.3 Molecular Cargo: miRNAs, Proteins, Lipids, and Metabolites

Extracellular vesicles (EVs) have dynamic molecular cargo which determines the physiological/pathological condition of their parent cells and contributes significantly to diabetic retinopathy. EVs enrich microRNAs, which are part of the miR-21, miR-126 and miR-200 families and regulate the processes of angiogenesis, vascular permeability, inflammatory processes and oxidative stress [22]. Their cargo protein includes tetra-panins, cytokines, growth factors and heat-shock proteins which are involved in endothelial signaling and neuroinflammatory mechanisms. Ceramides, phosphatidylserine and sphingomyelin are lipids that play a role in the stability of the vesicles and mediate metabolic or inflammatory reactions [23] Metabolites of distorted glucose and lipid metabolism characterizing diabetes are also present in EVs. Such a complicated cargo enables EVs to alter pathological signals between retinal cells, which subsequently affects neovascularization, vascular leakage, and neurons damage. Cargo profiling has shown good biomarkers and therapeutic targets to diabetic retinopathy [24].

2.4 Methods for Isolation and Characterization of EVs

Isolation and characterization of extracellular vesicles (EVs) is done using various methods of analysis. The most popular and commonly used method is the use of a differential ultracentrifugation where EVs can be separated based on their size and density; density-gradient centrifugation can also enhance the purity of prepared vesicles. Size-exclusion chromatography is soft, reproducible, and, in contrast, polymer-based precipitation allows the quick recovery, but it is not as specific to EVs [25]. ELVs can be captured with rapidity and high sensitivity by using advanced microfluidics, which makes them an appropriate choice in clinical diagnostics. To characterize the nanoparticles used, nanoparticle tracking, dynamic light scattering, and electron microscopy are applied in determining vesicle size and morphology; whereas Western blotting, flow cytometry, and ELISA are used to identify the EV-specific protein markers of CD63, CD81, CD9, and Annexin V [26]. The combination of different isolation and characterization techniques is necessary to reliably profile the vesicle subtypes, which is a precondition to validate biomarkers and to develop EV-based diagnostic and therapeutic approaches in diabetic [25].

3. Pathogenic Roles of Exosomes in Diabetic Retinopathy

The role of exosomes in pathogenetic processes of diabetic retinopathy (DR) suggests that the exosomes serve as the mediators of molecular signaling that coordinates the inflammatory reactions, vascular dysfunction, and neurodegeneration [27]. Higher glycaemia, oxidative stress, and metabolic dysregulation alter the compositional profile of exosomal

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cargo of retinal endothelial cells, pericytes, Muller glia, microglia, and retinal pigment epithelium (RPE). These extracellular vesicles carry pathologic microRNAs, pro-inflammatory cytokines, angiogenic

proteins and lipid mediators hence exacerbating retinal injury [22]. Exosomes mediate blood-retinal barrier rupture, neovascularization, microvascular unsteadiness, and at the same time induce neuronal apoptosis and glial activation (**Figure 2)**. The ability of the exosomes to propagate disease-related messages through the retinal layers forms the fundament of its significance as the key contributors to the development of DR. The study of these pathogenic interactions can provide essential information about the first molecular processes in DR and place exosomes as the would-be biomarkers and targets of therapeutic intervention [28].

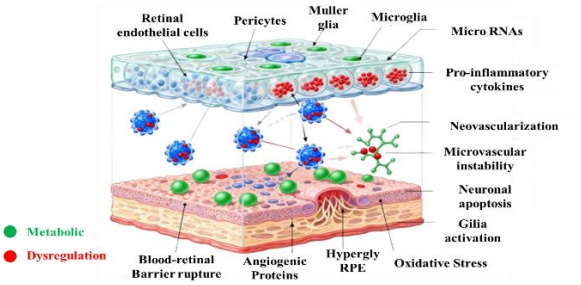

Figure 2: *This schematic illustrates exosome-mediated intercellular communication driving diabetic retinopathy progression. Exosomal microRNAs, cytokines, and metabolic dysregulation disrupt endothelial cells, pericytes, Müller glia, and microglia. These signals promote oxidative stress, angiogenic protein release, blood–retinal barrier breakdown, and microvascular instability. Consequently, hyperglycemic RPE dysfunction leads to neovascularization, glial activation, and neuronal apoptosis.*

3.1. EV-Mediated Intercellular Communication in the Retina

The extracellular vesicles (EVs) are essential intercellular communication mediators in the retina, but they are highly dysregulated in the emergence of diabetic retinopathy (DR). Hypoglycemic events, oxidative stress and chronic inflammatory states all provoke an excessive EVs release in retinal pigment epithelial (RPE) cells, endothelial cells, Muller glia, microglia and pericytes. These EVs mediate the microRNA, proteins and lipids that regulate the integrity of the vascular system, inflammatory pathways and neuronal functions [11]. The EVs cargo of diabetic milieu is skewed toward pro-inflammatory and pro-angiogenic mediators, therefore, interfering with normal retinal homeostasis. EVs produced by endothelial cells can stimulate microglial cells, whereas EVs produced by RPE cells can strengthen adhesion of leukocytes, as well as weakening the blood-retina barrier. This ensuing change in EV messaging creates a pathogenic positive-

feedback response which accelerates vascular leakage, capillary dropout, and neurodegeneration [29]. The explanation of the molecular changes of EV-based communication provides the key information on early DR biomarkers and preconditions therapeutic interventions intended to restore normal cellular contacts of the retina [30].

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3.2. Exosomal miRNAs in Retinal Vascular Dysfunction

The exosomal microRNAs (miRNAs) are essential in ensuring the retinal vascular stability and any disruption in their expression is directly linked with the pathogenesis of diabetic retinopathy (DR) [31]. Hyperglycemic-related stimulations provoke the release of exosomes by retina cells that are loaded with miRNAs that can regulate endothelial activities, angiogenesis, and inflammatory processes. Others of these, miR-21, miR-27b, and miR-200b, are proangiogenic miRNAs, which stimulate the endothelial expansion and neovascularization. On the other hand, miRNAs like miR -126, miR -146a, and miR -29b are downregulated, which leads to defects in the integrity of the barrier and increases inflammation in the vascularity [32]. Customary exosomal miRNAs produced by pericytes It is typical that endothelial health is maintained by pericyte-produced exosomal miRNAs, but diabetes disturbs the molecular signature of these miRNAs and thus accelerates the loss of the pericytes and subsequent microvascular destabilization [33]. Exosomal miRNAs released by retinal pigment epithelial (RPE) cells also control the expression of vascular endothelial growth factor (VEGF) as well as the activation and inhibition of pathological angiogenic signaling cascades. Since the exosomal miRNAs exist in both ocular and systemic fluids, they are a promising group of early biomarkers of DR. The development of engineered exosomes that entrap protective miRNAs could be one of the possible approaches to restore vascular integrity in diabetic retinal disease [34].

3.3. Protein and Lipid Cargo Contributing to Inflammation and Neurodegeneration

The exosome protein and lipid cargo of diabetic retinopathy (DR) has a significant role in the promotion of inflammation and neurodegeneration. Hyperglycemia changes the exosome structure, increasing the content of the vesicles with cytokines, chemokines, and proteins associated with oxidative stress, including TNF-a, IL-1b, VEGF, and MMP-9 [11]. These molecules stimulate microglia, enhance leukocyte adhesion and disrupt endothelial tight junctions leading to a break down of blood-retinal barrier. Exosomal lipids, such as ceramides, sphingomyelins, and oxidized phospholipids, also increase the extent of mitochondrial damage leading to apoptosis in retinal neurons [35]. The exosomes that contain ceramides are mostly associated with premature retinal ganglion cell damage and neural malfunction [36]. Microglial activation via lipid mediated mechanisms maintains chronic inflammation, which forms an unhealthy microenvironment, which hastens the vascular and neuronal damage. The anti-exosomal modification of cargo or the prevention of the release of pathogenic vesicles can be considered potential future approaches to restrain neuroinflammation and preserve retinal functions in diabetes [37].

3.4. Crosstalk Between Retinal Cells via EVs

Crosstalk between retinal cells facilitated by extracellular vesicle (EV) is critical in the process of neurovascular balance, and its breakdown is a major cause of diabetic retinopathy (DR). RPE-produced EVs balance endothelial survival and

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angiogenesis but in hyperglycemic conditions, the EVs cargo changes to favor VEGF, inflammatory mediators and harmful miRNAs, thus resulting in the development of vascular dysfunction [38]. EVs that are released by endothelial cells relay stress signals to pericytes and microglia, disrupting the stability of pericytes and enhancing inflammation. EVs released by pericytes usually reinforce endothelial barrier integrity, but with diabetes, the cargo is changed, leading to the pericyte apoptosis and destabilization of the capillaries [39]. Microglial EVs control the health of neurons and vessels, yet, in DR proinflammatory cytokines and miRNAs are carried by the EVs that enhance neuroinflammation, and endothelial leakage. This is a complicated, multidimensional EV exchange which connects vascular traumas, inflammation, and neural degeneration. Re-establishing normal EV-based communication is a promising treatment approach to retinal protection, in terms of structure and function [40].

4. Exosomal Biomarkers in Diabetic Retinopathy

Exosomal biomarkers are a fairly emerging diagnostic format of diabetic retinopathy (DR), due to their natural stability, availability, and the ability to capture underlying retinal pathophysiology [11]. The isolated exosomes of plasma, vitreous or ocular tissues contain a set of miRNAs, proteins, lipids and metabolites which prove to be correlated with the severity of the disease. These vesicles are cellular stress, inflammation, angiogenesis, and neurodegeneration indicators, which are some of the most significant pathogenic pathways driving DR progression [22]. The cargo composition in them is rendered with changes in dynamism through the early, non-proliferative, and proliferative phases, as a result of which it allows distinguishing clinical subtypes. Most importantly, exosomal signatures can be easily detected, making them better than traditional fundus imaging in screening at the earliest stage [41]. Multi-omic exosomal integrations have a high potential to be utilized in the prediction algorithms, risk stratification customization, and longitudinal disease surveillance in diabetic cohorts [42].

4.1. Plasma-Derived Exosome Signatures

The exosomes obtained in plasma offer an easy, non-invasive tool of the detection of circulating biomarkers that relate to diabetic retinopathy. The changes in their miRNA and protein cargo are evidence of systemic metabolic stress, endothelial stress, oxidative imbalance, and microvascular damage typical of the disease [43]. Dysregulated miRNAs have been reported to include miR 21,

miR126, miR200b, VEGF signaling and inflammatory and extra cellular matrix remodeling protein markers. These are some of the signatures that correlate with the disease stage and can be differentiated as mild non-proliferative diabetic retinopathy, advanced non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy [44]. Moreover, plasma exosome profiles may have prognostic information because it predicts those who are at risk of developing rapidly. This is because their stability in circulation and

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compatibility with high-throughput analyses is high, making them a good candidate in the screening and longitudinal monitoring of diabetic populations [45].

4.2. Vitreous Exosome Profiling

Vitreous exosome profiling provides a direct route of investigative approach to the microenvironmental changes of the retina in the course of diabetic retinopathy. Exosomal cargo of the vitreous, which has been shown to be anatomically adjacent to retinal tissue, has been found to reflect local cellular responses, including neovascularization, inflammation, neuronal damage, and neuronal disturbance of the blood-retinal barrier [46]. Proteomic and miRNA characterization continually show enrichment pro-angiogenic factors, cytokines and molecules related to oxidative stress during the proliferative phase of diabetic retinopathy. Pathogenic miRNAs, in particular, miR 21, miR 15a, and miR 31), are uniformly up-regulated, and neuroprotective miRNAs are correspondingly down-regulated [44]. Although the process of vitreous sampling is invasive, the unique specificity of exosomal content offers unmatched results regarding the pathogenic mechanisms in the molecular level. Such molecular signatures have potential to lead to the management of targeted therapeutic intervention, and potentially set standards of plasma-based diagnostic analyses [47].

4.3. miRNA Panels as Diagnostic and Prognostic Biomarkers

Exosomal miRNA panels have significant potential in terms of diagnostic, prognostic, and stage-specific bio-markers of diabetic retinopathy. MicroRNAs coordinate key signaling pathways, such as angiogenesis, inflammation, endothelial dysfunction, apoptosis, and neuronal damage, and hence their deregulation is directly relevant to the diabetic retinopathy pathophysiology [32]. MicroRNA-including panels, including miR-126, miR-200b, miR-21, miR-29b and miR-146a, can be used to differentiate early diabetic retinopathy with more advanced forms and predict those at a higher risk of developing diabetic retinopathy **(Table 1)** [44]. The natural stability of these microRNAs in exosomes protects them against degradation, which makes it possible to easily detect them in biological fluids, including plasma, serum, vitreous humor, or tears. The use of machine learning methods also increases the precision of multi-miRNA signatures, which leads to an improved level of diagnostic accuracy [48]. The clinical translation and the extensive adoption of screening protocols will not be possible without standardization of panel composition, normalization protocols and threshold values [49].

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Table 1: Summary of Exosomal miRNAs and Their Roles in Diabetic Retinopathy Placement

miRNA	Origin (Plasma / Vitreous / RPE / Endothelial Cells)	Target Genes / Pathways	Role in DR	Clinical Relevance	References
miR-21	Plasma, RPE cells	PTEN, TGF-β pathway	Pro-angiogenic, pro-fibrotic	Elevated in early DR; potential biomarker for progression	[50]
miR-146a	Plasma, vitreous	IRAK1, TRAF6 (NF-κB signaling)	Anti-inflammatory, protective	Reduced in DR; candidate for inflammation monitoring	[51]
miR-126	Endothelial cells, plasma	VEGF, PI3K/Akt	Maintains vascular integrity; anti-angiogenic	Downregulated in DR; strong biomarker for vascular injury	[52]
miR-15a/16	Plasma, endothelial cells	VEGF, BCL2	Anti-angiogenic, pro-apoptotic	Useful in distinguishing NPDR vs PDR	[22]
miR-200b	Vitreous, retina	VEGF, ZEB1	Anti-angiogenic	Correlates with neovascular severity	[53]
miR-29b	RPE cells	Collagen genes, ECM regulators	Anti-fibrotic, anti-inflammatory	Biomarker for retinal fibrosis progression	[54]

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miR-124	Microglia, neural retina	STAT3, MCP-1	Neuroprotective, anti-inflammatory	Promising marker for neurodegeneration in early DR	[55]
miR-320a	Plasma	IGF-1, HIF-1α	Anti-angiogenic	Associated with reduced neovascularization severity	[56]
miR-9	RPE, plasma	SIRT1, NF-ϰB	Modulates inflammation	Elevated in DR; potential prognostic marker	[57]

4.4. Exosomal Proteins Associated with DR Severity and Progression

Exosomal proteins are important in the regulation of retinal angiogenesis, inflammation and neurodegeneration and are informative biomarkers of the severity of diabetic retinopathy [43]. VEGF signalling proteins, TNF -a pathways, ICAM -1, matrix metalloproteinases, and oxidative-stress regulators are commonly enriched in exosomes of diabetic retinopathy [58]. High levels of angiogenic mediator are associated with proliferative disease and inflammatory and apoptosis-related proteins imply progressive microvascular damage. The identity of the source of pathogenic signalling is also assisted by retinal-cell-specific exosomal proteins, which differentiate between retinal pigment-epithelial, endothelial and Muller-cell vesicles [59]. The patterns of quantifiable expression of these proteins give an insight into the stage of the disease, the response to therapy

and prognosis. Proteomic data coupled with miRNA and metabolomic signatures can also improve the quality of diagnostic and could be used to measure individual treatment plans [60]

4.5. Potential for Early-Stage DR Detection Using Exosome-Based Biomarkers

Biomarkers that are exosome-based have provided a revolutionary avenue to the earlier detection of diabetic retinopathy, especially before the development of clinical signs or observable retinal alterations. Since exosomal cargo indicates non-obvious molecular pathophysiology changes, including oxidative stress, endothelial dysfunction, and low-grade inflammation, its presence can predict the presence of high-risk individuals years before the emergence of diabetic retinopathy [43]. Early microvascular leakage and neurodegeneration has been associated with specific miRNAs, proteins and lipid signatures. They are suitable as routine screening is due to their availability in forms of

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plasma or tear samples [61]. The early diagnosis provides the advantage of timely treatment thus better prognosis and minimized incidence to stages at which sight poses a risk. However, exosome-based assays have to be established by means of large scale validation, standardized protocols, and efficient diagnostic thresholds to be used in clinical practice [62].

5. Therapeutic Potential of Exosomes in Diabetic Retinopathy

Exosomes have significant therapeutic potential with regard to diabetic retinopathy as they have the inherent characteristics of bioactivity, biocompatibility, and the ability to transport functionality to retinal cells. They also regulate pathological angiogenesis, inflammation, oxidative stress, and neuronal degeneration and thus, they are flexible candidates to regenerative therapies. More specifically, tissue repair, vascular stability, and retinal homeostasis are promoted by exosomes of stem cells [63]. Their inherent capacity to penetrate in biologic barriers and reach particular cell types also makes them the best delivery systems of drugs, siRNAs or gene-editing factors. Unlike cell-based interventions, exosomes have lower immunogenicity and eliminate the dangers of (uncontrolled) proliferation. However, manufacturing, optimization of dose and safety evaluation issues still exist; however, initial preclinical results indicate a prospect of strong translatability [64].

5.1. Mesenchymal Stem Cell (MSC)-Derived Exosomes for Retinal Repair

Mesenchymal stem -cell-derived exosomes are now an attractive cell-free therapeutic agent in the treatment of diabetic retinopathy due to their regenerative, anti-inflammatory, and pro-survival capabilities [65]. The protective miRNAs, growth factors and proteins contained in these vesicles facilitate endothelial stabilization, reduce the effects of oxidative stress, and aid neuronal survival. They strengthen tight junction integrity and, in the process, confine bloodretinal barrier disturbance, and inhibit pathological angiogenesis [66]. In contrast to MSC transplantation, MSC -derived exosomes avoid issues of immune rejection, ectopic differentiation or tumorigenicity. As shown by preclinical studies, there are increased retinal activity, reduced vascular permeability and reduced inflammation with intravitreal or systemic delivery. Current studies are aimed at streamlining dosing schedules, routes of delivery, and mass manufacturing, and thus translating into pre-clinical trials to manage diabetic retinopathy **(Table 2)** [67].

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Table 2. Therapeutic Applications of MSC-Derived Exosomes in Diabetic Retinopathy

MSC Source	Key Exosomal Cargo (miRNAs / Proteins)	Mechanisms in DR	Preclinical Findings (In vitro / In vivo)	Translational Status	References
Bone Marrow–Derived MSCs (BM-MSCs)	miR-126, miR-21, PDGF, TSG-6	Anti-angiogenic, anti-inflammatory, vascular repair	Reduced VEGF expression; restored endothelial barrier; decreased retinal leakage in STZ models	Early preclinical; no clinical trials yet	[68]
Umbilical Cord–Derived MSCs (UC-MSCs)	miR-146a, miR-21-5p, TIMP-1, HGF	Suppresses NF-κB signaling; inhibits microglial activation; neuroprotection	Improved retinal thickness; reduced microglial inflammation; enhanced neuronal survival	Strong preclinical evidence; considered for future IND applications	[69]
Adipose-Derived MSCs (AD-MSCs)	miR-192, miR-222, VEGF-regulating proteins	Anti-fibrotic, anti-apoptotic, modulation of angiogenesis	Reduced oxidative stress; decreased endothelial apoptosis; improved RPE survival	Preclinical stage with promising regenerative potential	[70]
Dental Pulp MSCs (DP-MSCs)	miR-124, neurotrophic factors	Neuroprotective; reduces retinal inflammation	Enhanced survival of retinal ganglion cells; reduced TNF-α levels	Emerging research; early exploratory preclinical studies	[71]

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5.2. Anti-Inflammatory and Anti-Angiogenic Actions

Exosomes have strong anti-inflammatory and anti-angiogenic activities which can offset the fundamental pathogenic mechanisms underlying diabetic retinopathy. They inhibit inflammatory responses through the transfer of miRNAs like miR -146a, miR -21-5p, and miR -124 that inhibit NF-KB activation, cytokine release, and overactivation of the microglia. Their anti-angiogenic cargo (miR -15a, miR -20b and certain protein regulators) inhibits the expression of VEGF as well as endothelial proliferation, and as a result, neovascularization is restrained in proliferative diabetic retinopathy [72]. Mesenchymal stem cell, retinal progenitor cell exosomes, and vascular homeostasis can be restored simultaneously by downregulation of oxidative stress combined with the replenishment of mesenchymal stem cell and retinal progenitor cell exosomes. These two functions make exosomes highly potent therapeutic agents that can be used to treat both vascular and inflammatory aspects of diseases. In the future, they can be optimised to increase their accuracy and treatment longevity [73]

5.3. Exosomes as Drug Delivery Vehicles (Targeted Therapy)

Exosomes are gradually being identified as one of the most effective drug delivery vehicles in diabetic retinopathy treatment due to their inherent targeting property, biocompatibility and their ability to entrap a wide range of therapeutic molecules. They have the capability of transporting anti-VEGFs, corticosteroids, antioxidants, siRNAs or small-molecule inhibitors directly into tissues of the retina to improve the pharmacologic specificity of therapy as well as reduced systemic exposure [74]. They are endogenously presented on their membranes which allows them to be absorbed in a cell-specific manner, especially by endothelial cells, Muller cells and retinal pigment epithelium cells, some of the major participants in diabetic retinopathy pathogenesis [75]. Surface-modified engineered exosomes can be retinally targeted or loaded with gene-editing components like CRISPR components. Their stability and capacity to cross the biological barriers make them next-generation nanoscale carriers of personalized diabetic retinopathy care [76].

5.4. Gene Editing and miRNA-Based Therapeutic Applications

As an approach to address diabetic retinopathy, exosomes are a promising platform to gene-editing and miRNA-based therapeutic approaches. They offer effective delivery of functional miRNAs or anti-miRNAs, and thus, regulate angiogenesis, inflammation, and neurodegeneration [77]. CRISPR/Cas9, siRNAs or antisense oligonucleotide loaded into engineered exosomes can be specifically targeted to pathogenic genes including VEGF, HIF -1a, TNF-a and other inflammatory cytokines. This is a strategy that avoids the restrictions of viral vectors; this includes immunogenicity and genome integration risks [78]. With the help of the natural tendencies of exosomes to the retinal cells, gene treatment could be delivered with improved safety and precision of localization. Despite the positive results of preclinical models, issues related to off-target editing, efficacy of delivery, and controlled release as well as any long-term outcomes require thorough research before translation into clinical research [79].

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5.5. Safety, Immunogenicity, and Clinical Translation Challenges

In spite of the promising therapeutic potential, exosome based interventions are faced with a considerable challenge in the areas of immunogenicity, safety and translational applicability. Standardization and reproducibility is complicated by the biological variability caused by sources of donor cells, isolation techniques and cargo composition [80]. Exosomes, though regarded as low-immunogenicity, can have immunogenicity reactions depending on their origin and dose. Mass production and the development of production lines that can be GMP-compliant are significant logistical problems [81]. The long-term safety profile in terms of repeated dose, biodistribution and the possible off-target effects is not sufficiently described. The regulatory frameworks on extracellular vesicle based therapeutics are in their infancy hence complicating design of clinical trials. The challenges listed above are solvable only by the harmonised protocols, tested potency assays, as well as the solid preclinical data; without these, it is impossible to introduce exosome therapies in the daily care of diabetic retinopathy [82].

6. Technological and Methodological Advances

Advances in technology have hastened the exosome studies in diabetic retinopathy, which afford the opportunity to take a closer look at cargo structure and functionality. The comprehensive profiling of exosomal miRNAs, proteins, lipids, and metabolites can be done with the help of high-throughput sequencing, single-vesicle analysis, and multi-omics platforms [83]. Nanotechnological diagnostic platforms are sensitive in terms of analysis and assist in the detection of exosomal biomarkers at the point-of-care. Pattern identification, the identification of biomarkers, and prediction of the disease in early stages can be done using machine-learned and AI-free analytics to detect these patterns [84]. Microfluidic technology has enhanced the isolation purity and scalability of extracellular vesicles (EV) and new imaging technologies have enabled the real-time visualization of vesicle biodistribution. Altogether, all these innovations support the idea that exosome-based diagnostics and therapeutics can have a tremendous translational potential and that EVs will be at the heart of the next generation of retinal disease treatment [85].

6.1. High-Throughput Sequencing for Exosomal Cargo Profiling

The exosome research has been transformed by the high-throughput sequencing technique that allows the use of unbiased, comprehensive profiling of vesicular miRNAs, mRNAs, lncRNAs, and small RNAs in relation to diabetic retinopathy [86]. The technology offers high accuracy and sensitivity in quantification of low-abundance molecules, as well as the discovery of regulatory RNAs that may play a role in angiogenesis, inflammation and neurodegeneration. Proteomics and metabolomics integration also add advantages in the comprehension of the complexity of exosomal cargo [87]. Multi-marker panels that are used to detect diabetic retinopathy disease at an early stage and differentiate its stages are also developed with the help of sequencing. Improved depth, accuracy and cost-efficiency make high-throughput sequencing a base tool used to discover biomarkers and to discover personalized medicine. Single-vesicle sequencing is becoming increasingly advanced, and it is likely

to yield new possibilities to identify the heterogeneity of EVs and the contributions of individual cells [88].

6.2. Nanotechnology and EV-Based Diagnostic Platforms

With nanotechnology, it has been possible to develop ultra sensitive, fast, and miniaturized exosome-based diagnostics in diabetic retinopathy. Nanoparticles like gold nanoparticles, quantum dots, magnetic beads, and graphene-based sensors enhance the detection signals enabling the detection of miRNAs or proteins of low concentration [89]. The microfluidic chip systems combine the isolation, enrichment, and analysis of exosomes in single devices that can be used at the point of care. Such technologies decrease the amount of the sample and enhance diagnostic quality. Nanotechnology in combination with biosensing modalities, like electrochemical, optical, or plasmonic, detection, has a significant clinical benefit. Such platforms can facilitate regular screening of diabetic patients, and thus they can be detected earlier and better stratified with the risk than the existing imaging techniques [90].

6.3. Machine Learning Approaches for Biomarker Identification

Machine learning (ML) is critical in handling the multidimensional data that is complex because of the exosomal studies. Using miRNA, protein, lipidomic, and clinical data can identify patterns of biomarkers, classify stages of disease, and predict its progression with the help of ML algorithms [91]. Random forests, neural networks, SVMs, and clustering models, are methods that enhance the accuracy of diagnoses and reveal the relationships that were not used in the exosomal cargo before. ML also facilitates the process of feature selection, which makes it possible to refine biomarker panels to be useful in clinical practice [92]. The integration of extracellular vesicle data sets with retinal images and clinical factors help achieve precision medicine in diabetic retinopathy with the help of ML frameworks. The next generation of the ML model can potentially allow real-time automated prediction of the risks of DR through non-invasive exosome assays [93].

7. Challenges, Limitations, and Future Directions

Although the use of exosomes in diabetic retinopathy is associated with rapid progress in exosome research, there are various challenges that hinder clinical translation. The inconsistency in the extracellular vesicle (EV) isolation protocols, characterization criteria, and quantification mechanisms prevents the reproducibility of various studies [94]. The biological heterogeneity, regulatory uncertainties as well as the need to perform robust validations on a large population still slow down clinical implementation. The solution to these gaps includes international standardization, scalable production method innovation, and multi-omic and AI-based tools integration in order to optimize biomarker panels [95]. The future perspectives include exosome therapeutics engineered, point-of-care diagnostics and risk profiling of individuals. Exosome-based interventions need to be examined in terms of their safety, durability and real-world performance over the long term [96].

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7.1. Standardization of EV Isolation and Characterization

One of the biggest technical challenges in exosomes is standardization of their isolation and characterization. Existing methods: ultracentrifugation, precipitation kits, size-exclusion chromatography and microfluidics are in great diversities in terms of yield, purity and reproducibility. This makes it difficult to have a global agreement of isolation protocols, which leads to different outcomes of biomarkers in studies. Similarly, standards of characterization of particle size, protein markers and cargo profiling need to be harmonized to permit facilitating cross-laboratory comparisons [97]. The creation of proven reference materials, optimization of quality-control indicators, and the introduction of such guidelines as MISEV are critical measures. With standardization, the clinical trial design process will be strengthened, better diagnosis will be made, and the construction of EV-based therapies to treat diabetic retinopathy will be expedited [98].

7.2. Barriers to Clinical Implementation of Exosome-Based Diagnostics

There are many challenges that hinder the clinical use of exosome-based diagnostics of diabetic retinopathy. Technical limitations, such as the isolation of high-purity exosomes, high price of high-tech sequencing and nanotechnology platforms and the variety of biomarkers signatures are barriers to frequent use [99]. Furthermore, regulatory principles of extracellular vesicle diagnostics are not well-established, thus making it difficult to get approval. Mega-validation studies that involve a wide population are yet to come and the best cutoff values of biomarker panels are not established [100]. Besides this, clinical practitioners need expert training and standard operations to integrate exosome assays into their daily practice. These barriers can only be overcome through the concerted efforts of the researchers, the regulatory authorities, and clinicians to develop dependable, scalable, and cost-effective diagnostic systems [101].

7.3. Potential Integration into Precision Medicine

The exosome-based diagnostics and therapy offer a significant potential to be integrated in the paradigm of precision-medicine of diabetic retinopathy. Exosomes can be used to provide the individual molecular signatures to guide early diagnosis, risk stratification, as well as to design custom therapeutic regimes [102]. Multi-omic exosomal pattern combined with state-of-the-art machine-learning analysis eases the forecasting of the disease evolution and treatment outcome. Genetically engineered exosomes can also be used therapeutically to deliver patient-specific molecular profiles of therapeutic microRNAs, pharmacologic or gene-editing payloads [103]. Their low invasiveness coupled with the fact that they are compatible with the blood or tear-derived sampling modalities make them susceptible to regular surveillance. The combination of exosome analytic and clinical imaging and metabolic data can make diabetic retinopathy care a personalized and proactive model [104].

7.4. Future Research Priorities

Future research in the area of exosomes in diabetic retinopathy is recommended to focus on highlighting the role of cell-specific extracellular vesicles, authenticate multi-omic biomarker signatures, and optimize delivery systems. Such studies will demand large-scale

longitudinal studies that will support the predictive ability of the candidate biomarkers in heterogeneous populations. Enhancing the retinal targeting, cargo specificity, and stability of exosomes Therapeutic loads is also a significant area of development. They should also be conducted in studies that cover safety, dose, biodistribution and long term effects to enable clinical translation. The combination of AI-based analytics, single-vescel technologies, and precision medicine solutions will help in streamlining the process of diagnostic and therapeutic modalities, which will eventually help to customize the management of diabetic retinopathy.

8. Conclusion

Exosomes and extracellular vesicles (EVs) are one of the fast-growing areas of understanding and treatment of diabetic retinopathy (DR). Their ability to carry biochemically active miRNAs, proteins and lipids makes them effective signifiers of retinal stress, inflammation, vascular dysfunction, and neurodegeneration. Exosomal signatures with plasma, vitreous and ocular cells are minimally invasive biomarkers that provide high diagnostic and prognostic accuracy and thus, with the opportunity to detect early-stage DR long before clinical symptomatology. Mesenchymal stem cell-exosomes are strong anti-inflammatory, anti-angiogenic and neuroprotective agents, and as such, exosomes may be important in cell-free regenerative therapy. The simultaneous development of sequencing, nanotechnology, and machine learning also enhance the characterization of EVs and their use in the clinic. However, there are still difficulties, such as standardization of the methods of isolation, the security of it, and transfer of the pre-clinical achievements in the human experiments. These gaps will be inevitable to the complete integration of the exosome-based diagnostics and therapeutics into precision medicine to DR.

Conflict of Interest

The authors have no conflict of interest

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Data Availability

All the data presented in this manuscript are original and have not been published elsewhere.

Authors' Contributions

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