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Efficacy and Safety of Stem Cell Therapy in Diabetic Retinopathy: A Scoping Review

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ABSTRACT

Background: Diabetic Retinopathy (DR) is a microvascular disorder that arises due to chronic hyperglycemia, which, if left untreated, would ultimately cause loss of vision. Although there are some established treatments for DR, those treatments failed to show a capability to induce cellular regeneration. Stem cells are unspecialized cells of the human body that would be able to differentiate and have the ability to self-regeneration and recently emerged as a potential treatment for DR. ***Aim:*** The aim of this review is to evaluate the ability of stem cells as a treatment for DR by promoting cellular regeneration and evaluate the safety of stem cell treatment. Method: We identified relevant articles from three established databases and did an advanced search using a combination of Medical SubHeading Terms (MeSH Terms) keywords and boolean operators such as: ("Diabetic Retinopathy'' [MeSH Terms]) AND stem cells [MeSH Terms]". ***Result:*** In this scoping review, the authors identified thirteen studies that meet the inclusion criteria. Of the twelve pre-clinical studies, eleven studies evaluated cellular regeneration, and five studies evaluated neurotrophic factors. Only two studies reported side effects of stem cell therapy in pre-clinical studies. Only one clinical study was identified that evaluated the cellular regeneration of stem cell therapy in DR. ***Conclusion:*** Several types of stem cells have been researched as a new therapeutic modality for Diabetic Retinopathy. Most studies showed successful application as noted on its ability to promote and preserve cell regeneration as well as increase neurotrophic factors of the retina with no serious adverse effects are reported.

Keywords: stem cell; Diabetic Retinopathy; therapy; cellular regeneration; safety

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by high blood sugar levels or hyperglycemia caused by failure of insulin secretion, insulin resistance in cells, or both [1], [2]. As of 2022, it is estimated that more than 536 million people, or about 1 in 10 people worldwide, have diabetes. More worrying is that this number is expected to rise. By 2045, following current trends, it is projected that there will be no less than 783 million people worldwide who have diabetes. This finding, together with more than 960 billion USD that was expedited globally, strongly suggests that diabetes is a massive and increasing burden worldwide [3]. Diabetes does not only cause an increasing burden but also elicits the emergence of various diseases as a complication of chronic hyperglycemia state, both in the level of organ and tissue. One of the most common complications arising from diabetes is diabetic retinopathy [2], [4], [5].

Diabetic Retinopathy (DR) is a leading global cause of blindness in the shape of a microvascular disorder that arises due to chronic hyperglycemia caused by diabetes [5]. Hyperglycemia induces the activation of some alternative pathways of glucose metabolism, which then produce byproducts such as sorbitol and increases the level of cytokine and reactive oxygen species (ROS). Sorbitol and ROS buildup in the retina would significantly damage the cells. [4]–[6] At the same time, the increased cytokine level would lead to microvascular alteration and abnormal inflammation in the retina. While the prognosis of DR heavily relies upon several factors like glycemic control and comorbidities, untreated DR would eventually progress and lead to blurred and distorted vision as well as partial and even total vision loss [4], [6], [7].

Several established treatments used for DR target different aspects of DR pathophysiology. As exaggerated inflammation is one of DR pathophysiology, anti-inflammatory drugs, both intravitreal steroid and NSAID, are commonly used, although mainly as a second-line therapy due to the nature of its side effects [4]. At the same time, anti-VEGF drugs are developing to be the primary first-line therapy by altering VEGF signaling, financial strain, and complicated doses hindered its commercial usage [8]. Other therapeutic agents, as well as traditional laser photocoagulation treatment, also provide some alternative treatments for DR [4], [7]. However, the inability of any treatment to induce regeneration of retinal cells means there still is a pressing need to discover other angles of potential treatment. Recently, stem cell treatment is emerging as a potential therapeutic and management method for DR.

Stem cells are unspecialized cells of the human body that would be able to differentiate and have the ability to self-regeneration [9]. The cells are retrieved from various sources, made in various ways, and have different grades of potency. Some examples are mesenchymal stem cells (MSC), a pluripotent stem cell that could differentiate into many tissues, while induced Pluripotent Stem Cells (iPSC) are adult somatic stem cells that are reprogrammed back into pluripotency. Stem cells usage for therapeutic measures in DR has a game-changing potential to not only limit the damage to the retina but also induce regeneration of the cells, something that current commercial drugs failed to do [10], [11]. However, the pathological nature of DR proved to be a hindrance to the ability of stem cells to regenerate adequately compared to in vitro situations. At the same time, inducing regeneration could trigger an unnecessary immune response in the individual with an already exaggerated immune response in DR [12], [13]. Both of these situations reflect a necessary and pressing need to evaluate the efficacy and safety of stem cells application. Thus this paper aims to review data among available literature to review the efficacy and safety of stem cell utilization as Diabetic Retinopathy therapy.

METHOD

Search Strategy

A literature search was done on three well-known and well-established databases: PubMed, Scopus, and ScienceDirect. Studies screened are within ten years of publication with the advanced search done using a combination of Medical SubHeading Terms (MeSH Terms) keywords and boolean operators such as: ("Diabetic Retinopathy" [MeSH Terms]) AND stem cells [MeSH Terms]". Further adjustments are made based on each database.

Eligibility Criteria

The study selection inclusion and exclusion criteria were determined in accordance with Participants- Intervention-Comparison- Outcome-Study Design (PICOS) scheme as seen on the following Table 1.

Data Extraction and Analysis

This scoping review is conducted following the Preferred Reporting Items for Systematic Review and Meta- Analysis extension for Scoping Review (PRISMA-ScR). The study selection process includes title screening, abstract screening, and full-text screening. Study information (author, year, country), intervention characteristic, duration of the study, subject characteristic, types of diabetic retinopathy, types of stem cell intervention, and outcome of cellular regeneration and neural trophic factors after intervention were all extracted. All reviewers worked independently to extract data by filling out an extraction data table. If any conflicts were found, discussions with the other reviewers were conducted.

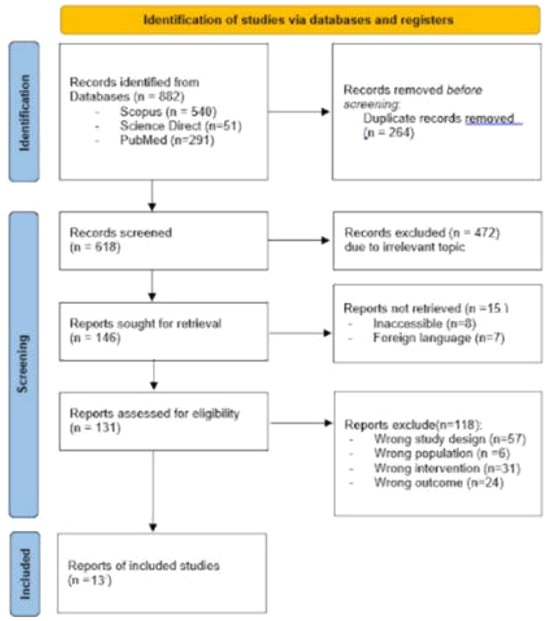

FIGURE 1: Study Selection According To Prisma-SCR

RESULT

Study Selection

Search results of published studies from PubMed, Science Direct, and Scopus databases from 2012 to 2022 were a total of 882 articles. The authors used an automation tool to remove 264 duplicate articles. Then, the authors assess the titles and abstracts of 618 articles. About 472 articles were excluded due to irrelevant titles and abstracts. The full text was retrieved from 146. However, eight articles were inaccessible, and seven articles were written in foreign languages. Then, the authors assessed the report for eligibility; 57 articles had the wrong study design, 6 articles had the wrong population, 31 articles had the wrong intervention, 24 articles had the wrong outcome. The final study selection resulted in 13 articles included in our study. Further details on the literature elimination process are visualized in accordance with the PRISMAScR flowchart, as seen in Figure 1.

Study Characteristics and Results

The elaborated study characteristics and results can be seen in Table 2. In this scoping review, there are a total of thirteen studies that meet the inclusion and exclusion criteria. Twelve studies discuss pre-clinical studies and there is one clinical study.

TABLE 1: Inclusion and Exclusion Criteria for Study Selection According to PICOS.

Parameters	Eligibility Criteria	
	Inclusion Criteria	**Exclusion Criteria**
Population	Diabetic retinopathy	Other types of retinopathy
Intervention	Stem cells for therapeuticmeasures	Stem cell for preventive measures,stem cell for other disease
Comparison	Blank control group, other groupstreated with different stem cells	-
Outcome	Cellular regeneration and neuraltrophic factors	Other effects of stem cells
Study design	Clinical study and Preclinicalresearches/ animal studies	Narrative/traditional reviews, systematic reviews and meta-analysis

TABLE 2: Study Characteristics and Results.

Author,Year	Study Characteristics				Study Outcome		
	Participants	Sample size	Stem Cell Types	Intervention	Cellular regeneration	Neurotrophic factors	Side effects
Pre-clinical studies							
Chakravarthy *et al.*, 2016 [14]	STZ-induced diabetic mice	n/a	BMMSC	Retroorbital injection of 2×10^6 cells	Significant increase in CAC release	-	-
Ebrahim et al., 2022 [15]	STZ-induced diabetic mice	81	BMMSC	Intravitreal injection of MSC-exosomes in a single dose of 0.5 m (100µg protein/ml)	Improved retinal thickness seen under microscope, Showed relatively normal retinal appearance	-	-
Ezquer etal., 2016 [16]	STZ-induced diabetic mice	n/a	Adipose-derivedMSC	a single intravitreal doseof 2 x 10^5 adipose-derived MSC	The MSCs remained in the eye but did not differentiate into neural or perivascular	A significant increase in mRNAof neurotrophic factors, namely NGF, bFGF, and GDNF.	The administration does not induce a provasculogenic microenvironment in the retina
Fu *et al.*, 2022 [17]	STZ-induced diabeticmice	20	hucMSC	Intravitreal injection of 4µL hucMSC-derived exosomes solution	The MSCs group showed higher number of Retinal Ganglion Cells	-	-
Kim et al., 2016 [18]	STZ-induced diabeticmice	80	hESC-derived PVPCs	50,000 to 100,000 hESC-PVPCs in 2 µl vehicle (Dulbecco's PBS containing 0.5% BSA&2mM of EDTA) were injected into vitreous	Improved damaged retinal vasculature	-	-
Kong et al., 2015 [19]	STZ-induced diabeticmice	36	hucMSC	Intravitreal injection ofdifferent concentrationof hUCMSC	-	Upregulated NGF protein expression	No disadvantages were identified and no side-effects or rejection phenomena were observedduring the study
Li et al., 2021[20]	STZ-induced diabeticmice	32	HucMSC derived exosomes	(1) 50 µg hucMSC exosomes suspended in µL PBS, (2) 50 µg miR-173p agomir-transfected hucMSC exosomes suspended in 5 µL PBS, (3) 50 µg miR-17-3p antagomir-transfected hucMSC exosomes suspended in 5 µL PBS. All interventions were injections done to the intravitreal body.	Lightens the pathological changes of the retinal tissue seen under microscope	Significant increasein Glutamin Synthetase level	-

Author,Year	Study Characteristics				Study Outcome		
	Participants	Sample size	Stem Cell Types	Intervention	Cellular regeneration	Neurotrophic factors	Side effects
Pre-clinical studies							
Rong et al., 2018 [21]	STZ-induced diabeticmice	22	BMSC CD133+	Intravitreal administration of EGFP- labeled CD133+ cells (1×10^5 in 1 µl) in the right eye, whereas PBS; 1 µl was administered tothe left eye.	The $CD133^+$ migrated into inner retina and showed ability to differentiate into neuronal cells, like retinal	The $CD133^+$ cellsexpressed BDNF	-
Sacaki etal., 2021 [22]	STZ-induced diabeticmice	18	hNPC	intravitreal injection ofhNPCs (1×10^6 cell/µL)	Repaired and regenerated cells, proved by increased thickness of neuroretinal layers, higher ERG oscillary potentials amplitude,	-	-
Xu et al., 2021 [23]	STZ-induced diabeticmice	15	hucMSC	intravitreal injections (once every week for 4 weeks) of different concentrations of hUCMSC-sEVs (10, 20, and 40 µg/mL)	Increased miR-18B level which alleviates apoptotic activity	-	-
Yazdanyaret al., 2020 [24]	STZ-induced diabeticmice	20	BMSCCD34+	Intravitreal injection of1 µL solution per eye ofeither EGFP-labeled human CD34 + BMSCs (50,000 cells)	Homing and integration of the stem cell to the retinal surface, preservationof retinal vasculature	-	-
Zhang etal., 2017 [25]	STZ-induced diabeticmice	42	HucMSC-derivedNSC	Intravitreal injection of 0.2×10^6 cells in 2 µL solution	Attenuated vascular dysfunction, preserved retinal vasculature	Increased BDNF level	-
Clinical studies							
Gu et al., 2018[26]	Human aged 18-70 years, with type 2 diabetes,at least one eye with visual impairment	7	ABMSC	One intravenous infusion of ABMSCs of which the total number for each patient was 3 x 10^6/kg, sequentially infused within 30 minutes	Increased visual acuity, increased BCVA, improved retinal thickness	-	No severe adverse events reported. One of 17 patients showed an increase in creatine kinase without any significant clinical symptom

Note: **ABMSC:** Autologous Bone Marrow Stem Cell; **BCVA:**best corrected visual acuity; **bFGF:** basic Fibroblast Growth Factor; **BMMSC:** Bone Marrow Mesenchymal Stem Cell; **BSA:** bovine serum albumin; **CAC:** Circulating Angiogenic Cell; **EDTA:** Ethylenediaminetetraacetic acid;**EGFP:** Enhanced Green Fluoroscent Protein; **ERG:** Electroretinography; **GDNF:** Glial Cell Derived Neurotrophic Factor; **hNPC;** human Neural Progenitor Cell; **hUCMSC:** human Umbilical Cord Mesenchymal Stem Cell; **mRNA:** messenger RNA; **NGF:** Nerve Growth Factor;**MSC:** Mesenchymal Stem Cell; **OCT:** Optical Coherence Tomography; **PVPC:** Perivascular Progenitor Cell; **PBS:** phosphate-buffered saline; **STZ:** Streptosozin.

Pre-clinical studies samples in the included studies were STZ-induced mice to represent the diabetic mice, with sample sizes varying from 15 to 80 mice. Of the twelve pre-clinical studies, the types of intervention given were primarily mesenchymal stem cells with the types as BMMSC, adipose-derived MSC, hucMSC, hESC- derived, hUCMSC, hUCMSC-derived exosomes, BMSC CD133+, BMSC CD34+, hUCMSC-derived NSC.

However, two studies used PVPCs and hNPCs as the intervention for stem cell therapy. Interventions were given to intravitreal injection in the orbita. Of the twelve pre-clinical studies, eleven studies evaluated cellular regeneration and five studies evaluated the neurotrophic factors. Only two studies reported side effects of stem cell therapy in pre-clinical studies. Only one clinical study of stem cell therapy for DR with interventions using ABMSC given as one intravenous infusion to diabetic retinopathy patients. Increased visual acuity, increased BCVA, and improved retinal thickness were reported, with no reported severe adverse events.

DISCUSSION

Diabetic Retinopathy & Pitfalls in Current Treatment

Diabetic retinopathy is the most frequently occurring complication of diabetes mellitus and remains a leading cause of vision loss globally. Diabetic retinopathy can be classified into two stages: non-proliferative and proliferative. Early stages of DR are a non-proliferative stage where visible signs of microvascular abnormalities and retinal hemorrhages are seen. Proliferative DR occurs with further retinal ischemia and is characterized by the growth of new blood vessels on the retina's surface or the optic disc. Diabetic macular edema (DME) can occur as these abnormal vessels are vulnerable and thus could result in vitreous hemorrhage, subsequent fibrosis, and tractional retinal detachment [27]. Its etiology and pathology have been extensively studied for half a century, yet there are disappointingly few therapeutic options.

Primary interventions, such as intensive glycemic and blood pressure control, can reduce the incidence of DR, while secondary interventions may prevent further progression of DR and vision loss [6]. Although some new treatments have been introduced for secondary interventions, such as intravitreal vascular endothelial growth factor inhibitors and new steroids, up to 50% of patients fail to respond [4], [8]. Furthermore, for people with proliferative diabetic retinopathy (PDR), laser photocoagulation remains a mainstay therapy, even though it is an inherently destructive procedure [4], [7].

Stem Cells

With the increasing incidence of DM, several approaches to clinically deal with this disease have been reviewed. One of these new methods is the application of stem cell therapy to improve diabetic complications, especially in DR. In cell therapy, stem cells can be employed as substitutes to replace injured cells or reproduce tissues [28]. A stem cell is recognized as a vital source cell in regenerative medicine due to its capacity for self-renewal and multidirectional differentiation. A variety of stem cells, including bone marrow mesenchymal stem cells (BM-MSC), adipose stem cells (ASC), and induced pluripotent stem cells (iPSC), have been considered in diabetic retinopathy. ASC and BM-MSC have been shown to bear promise in regenerating and recovering the retina once it has been damaged [29]. Stem cells have also been reported to be a valuable source of paracrine factors that can protect retinal ganglion cells (RGCs) and aid in regenerating the optic nerve in some degenerative eye diseases. Increasingly, stem cells display a therapeutic value in ameliorating many refractory diseases by replacing injured cells and secreting growth factors through the secretion of neuroprotective and anti-inflammatory factors [30].

Efficacy of Stem Cells in Preclinical and Clinical Research

The two most recent studies regarding the topic were pre-clinical studies conducted by injecting streptozozin to induce diabetes in mice. Ebrahim et al in 2022 then conducted this in vivo study by intravitreally injecting BMMSC-exosomes in a single dose of 0.5 m (100 µg protein/ml) [15]. Likewise, Fu et al in 2022 conducted the study by injecting exosomes intravitreally, although they used 4 µL of hUCMSC-derived exosomes instead of BMMSC-derived [17]. Albeit different types of stem cells were used, both studies showed that the group that was given stem cells had thicker retinal layers under a microscope with HE staining compared to the control group. At the same time, Ebrahim et al further reported that the participant group had relatively normal retinal appearance under fundus examination and OCT [15]. These findings are in line with the other studies using various types of stem cells, which reported that mice treated with stem cells, compared to the control group, showed milder pathological changes, mainly shown as preservation of normal retinal thickness and normal retinal vasculature. A clinical prospective cohort study conducted by Gu et al in 2018 also reported that, compared to DR patients that received conventional treatment, patients treated with stem cells had relatively normal retinal function and structure, proved by the patients' better visual acuity and improvement of retinal thickness [26]. As retinal layer degeneration and abnormal vasculature are two of the most common pathophysiological phenomenons in DR, all these findings show promises that stem cell treatment could, at the very least, alleviate the pathological conditions that arise in diabetic patients.

Not only did the study find relatively normal retinal structure, but Fu et al study also found that the mice treated with stem cells had a higher count of Retinal Ganglion Cells than the control group [17]. This finding is in line with studies conducted by Rong et al in 2018 and Yazdanyar et al in 2020. The studies intravitreally injected BMSC CD133+ and BMSC CD34+, respectively, reported that the bone marrow stem cells could differentiate into neuronal cells and further homing and integrating into the retinal surface [21], [24]. Chakravarthy et al in 2016 approached things a bit differently, and instead of doing injection intravitreal, they injected BMMSC in the retroorbital area and later found that the mice injected with stem cells had a significantly higher CAC, one type of progenitor cell, numbers than the control group [14]. These findings, together with stem cell ability to alleviate apoptosis activity as shown by Xu et al study in 2021, showed promises that stem cells would be able to repair damaged retinal tissue by regenerating damaged cells or promoting progenitor cells activity while also impeding further damage; something that conventional therapy is yet to be able to do [23].

Stem cell ability to repair retinal tissue is also supported by the findings of its correlation with neurotrophic levels. Zhang et al in 2017 conducted an animal study by injecting 0.2 × 106 hUCMSC-derived Neural Stem Cells in 2 µL solution intravitreally into STZ-induced diabetic mice and found a significant increase of BDNF, a protein that has an important role in neurogenesis, especially in neuronal differentiation, in the treated mice [25]. Expression of BDNF is also found in the injection of BMSC CD133+. Besides BDNF, other studies found various types of neurotrophic factors. Kong et al in 2015 reported an upregulation of NGF, a protein that has shown neuroprotective and neural growth function, in the mice that are treated with hUCMSC [19].

Similar findings were reported by Ezquer et al in 2016 while Li et al in 2021 found the upregulation of Glutamine Synthetase, an enzyme whose decrease correlates closely with diabetes, which can be additional supporting findings about how stem cells could ameliorate DR through its neurotrophic-promoting activity [16], [20].

Differences between interventions and methods among studies included in this review are incomparable. Furthermore, albeit promises shown in many pre-clinical studies regarding the efficacy of stem cells treatment, it is also worth noting that there are very limited published human clinical studies. Thus, the author recommends the need to conduct more and further clinical studies to find how well animal studies results are translated into human patients.

Safety of Stem Cells in Preclinical and Clinical Research

There are a limited number of studies conducted that also reported the safety aspect of the treatment. Nevertheless, in this study, we reviewed two animal studies and one clinical trial study regarding the safety aspect of stem cell therapy. Ezquer et al in 2016 conducted a study by administering a single intravitreal dose of 2 x 105 adipose-derived MSC to STZ-induced diabetic mice. While the study found that the administration upregulated various neurotrophic factors, it is reported that it does not induce a provasculogenic microenvironment in the retina [16]. It is important to note that while the regenerative ability of stem cells is its main difference compared to conventional therapeutic strategies, overgrowth of vascularization is one of the main pathological phenomena that happens in DR and could lead to a dramatic decrease in visual acuity [4]. Therefore, the stem cell's ability to selectively upregulate neurotrophic factors without inducing over vascularization is a favorable critical safety consideration before administering the treatment on a wider scale.

Immunological rejection is one of the biggest challenges in the development of stem cell therapy. Even though many preventive measures have been developed and potential curative agents to alleviate the immune response have been made, transplantation rejection is still one of the causes of stem cell therapy failure in DR and other diseases. Kong et al in 2015 injected different concentrations of hUCSMC into different groups of STZ-induced diabetic mice and reported no rejection side effects observed in the mice. The study also noted no disadvantages being detected [19]. This pre-clinical finding is supported by a prospective study conducted by Gu et al in 2018. The study looked for the efficacy and safety aspects of stem cell treatment within human patients compared to patients treated with conventional treatment and found no adverse effects, such as malignancy or immunological rejection, reported during the follow-up. The study also assessed organ function by conducting various laboratory tests and reported that there were not any significant abnormalities seen in the laboratory result, with the exception of Creatine Kinase (CK) and creatinine levels [26].

While these studies provide promising results regarding the safety aspect of stem cell therapy, it is important to note that the number of studies is limited and therefore presents a pressing need to conduct more studies regarding the safety aspect of the treatment. Although it did not lead to a more severe adverse effect, a slight increase in CK and creatinine levels posed a caution to kidney function during stem cell treatment.

Applicability and Future Prospects

Currently, multiple ongoing clinical trials are aiming to test stem cell therapy for DR. Aside from one included study in our study, ongoing study NCT01736059 examines intravitreal injections of CD34+ BMMSCs for irreversible vision loss from retinal degenerative diseases or retinal vascular disease, including DR. Another clinical trial (NCT03403283) is underway to determine whether or not endothelial progenitor cells (EPC's) are defective in people with diabetes to understand the mechanisms of the disease further. A third clinical trial (NCT03403699) examines the abilities of iPSCs to generate endothelial cells and pericytes in areas with capillary degeneration seen in DR [29].

Strength and Limitations

There are several strengths in our review. Firstly, as far as our knowledge, there has never been a published study that tried to specifically review both cellular regeneration ability and the safety aspect of stem cell treatment in DR. Secondly, we limit the study to only include pre-clinical studies where the retinopathy is caused by chemical induced diabetes and exclude other methods to mimic DR in mice, such as ischemic-induced retinopathy, which not only improve the comparability between studies but also resemble the actual DR better. We also include both direct cellular regeneration and indirect cause of regeneration by an increased neurotrophic factor to fully uncover the potential of stem cells as a regeneration therapy for DR. However, there are also certain limitations to our study. Firstly, there are dissimilarities between studies regarding stem cell application methods and differences in methodology to find the outcome; both may affect the comparability between studies. We also did not conduct a thorough appraisal and assessment of each article, nor did we conduct a meta-analysis to quantify our findings.

CONCLUSIONS

Several types of stem cells have been researched as a new therapeutic modality for Diabetic Retinopathy. Most studies showed successful application, as noted on its ability to promote and preserve cell regeneration and increase neurotrophic factors of the retina, with no serious adverse effects reported. The limitations of this study lie in the scarcity of conducted clinical studies and studies that focus on the safety of stem cells. The authors recommend conducting more intensive research on the safety of stem cells and more studies in clinical settings to obtain as much evidence and information as possible.

DECLARATION

Disclosure

None.

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CONFLICT OF INTEREST

The authors declared that there was no conflict of interest in conducting this review

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