NARRATIVE REVIEW

The potential of stem cell therapy to tackle visual impairment

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Abstract

Visual impairment adversely impacts quality of life and affects more than 295 million individuals globally. Currently, there is no cure or tissue regenerative approaches in clinical practice for vision loss caused by corneal disease, glaucoma, cataracts, macular degeneration, diabetic retinopathy, and inherited retinal disease. Stem cells-based therapeutic approaches to diseases causing moderate to severe visual impairment have shown encouraging outcomes in animal models and in vitro studies. The goal of this narrative review is to describe and evaluate the potential of stem cell-based treatment, and their advantages and safety concerns in treating conditions causing vision loss.

Key words: Vision, Retinal, Macular, Cataract, Glaucoma, Corneal, Stem Cells, hereditary, pluripotential

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Introduction

Stem cells have the potential to transform treatment for varied conditions including ophthalmic diseases. Globally, nearly 43.3 million individuals suffer from blindness (i.e., no light perception with a prevalence of 5·49 per 1000) and 295 million individuals experience moderate to severe visual impairment (prevalence of 32·7cases per 1000)1. It is estimated that by 2050, individuals affected by blindness may reach 61 million globally with 474 million people enduring moderate to severe visual impairment[1].

Moderate to severe visual impairment is reported to be higher in Lower Middle-Income Countries (LMIC) and regions i.e., South Asia, Oceania, and Southeast Asia, with South Asia, (which includes Pakistan), reported to have the highest prevalence i.e., 229 per 10001 and a higher prevalence of blindness - above 30 cases per 1000 vs less than 5 cases per 1000 people in higher income regions (HICs) (North America, Asia Pacific, and Australasia). In LMICs compared to high-income countries, visual impairment is largely due to cataracts, refractive errors, and trachoma [2], although other diseases such as diabetic retinopathy and glaucoma are also emerging as major issues. According to the IDF Diabetes Atlas, 80 % of diabetics belong to LMICs[3] and one in three diabetics experiences diabetic retinopathy (DR)[4]. A significant rise in the prevalence of glaucoma has been recorded to be 150% over a period of 30 years (1990 to 2020) in causing moderate to severe visual impairment.[5] While the prevalence of blindness and visual impairment in HICs is significantly lower compared to LMICs, glaucoma and age-related macular degeneration (AMD) account for the main causes of blindness and uncorrected refractive errors are the leading cause of moderate to severe visual impairment in HICs.[5]

In Pakistan a study demonstrated that approximately 21.78 million individuals have been affected by Blindness and Visual impairment collectively.[6] Blindness had a prevalence of 1.12 million accounting for a 5% burden and cataracts were the leading cause of blindness followed by corneal diseases[7]. In individuals aged 60 years and above, cataracts, refractive disorders, glaucoma, and ARMD were among the prominent causes for visual impairment; since 2017, diabetic retinopathy (DR) has also featured as one of the major causes of visual impairment in Pakistan[6].

Rationale

The eye has become a key focus for stem cell transplantation therapy due to the increasing prevalence of incurable eye diseases, surgical accessibility, the ability to use a healthier fellow eye as a control, and the capacity to visualize and evaluate developments after transplantation with sophisticated structural and functional testing (e.g., microperimetry, multifocal electroretinography and optical coherence tomography).

In this narrative review, we highlight the leading causes of blindness and visual impairment globally, summarize advances and potential benefits of stem cell therapy,

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along with their limitations and safety concerns.

Methods

We undertook a narrative review, and a literature search was conducted over 2 months starting in September 2022. A comprehensive search was done on PubMed using the search string pertaining to "eye diseases" AND "stem cells" and 4,296 articles were retrieved (details of the search string is included in the appendix). Of these 4,296 articles, 735 were selected based on the following criteria:

A) Articles published in 1990 and onwards.

B) Open access

C) Availability in English language only and,

D) Focusing eye diseases on humans and its relative stem cell therapy approach

After considering the abstracts of the 735 articles, we chose three review articles by Miotti et al[8]., Blenkinsop et al[9]. and Stern et al.[10] as they provided a holistic approach for eye diseases and their potential stem cell solutions. These articles were critically analyzed. Based on these reviews and the burden of ocular disease, the articles were organized based on prevalence of disease as well as anatomical location of disease. We then provided an overview of current treatment modalities and their limitations and reviewed the potential of stem cell therapy in the treatment of such diseases. The latter was done by discussing previous and current breakthroughs in stem cell research. Relevant references in the review articles were also examined and included when appropriate. In our article two distinct terms are used related to vision i.e., "blindness" and "Visual impairment"[11]. Blindness includes individuals who completely lack the ability to perceive light. The term 'Visual impairment' includes individuals whose diminished vision impedes their ability to carry out daily tasks including driving, reading, and watching and the severity of visual impairment ranges from mild to severe according to the WHO ICD 11 criteria for visual impairment based on an individual's visual acuity[12].

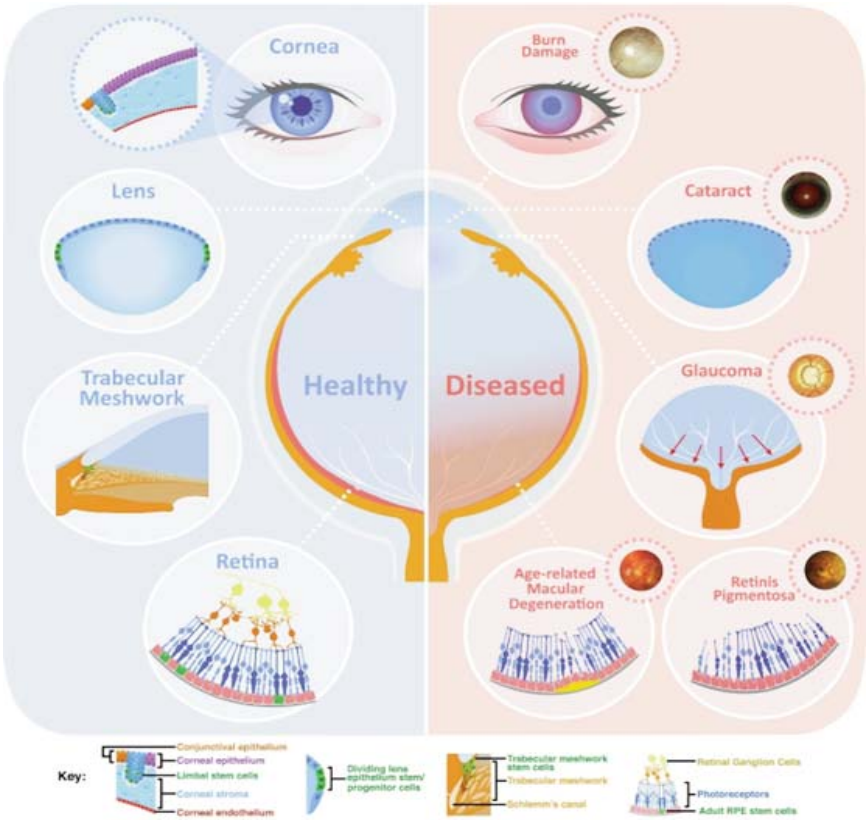

Figure-1: Ocular Stem Cells in Health and Disease. Schematic showing the location of corneal limbal, lens, trabecular meshwork (TM), and RPE stem cells and depicting ocular disorders that are being targeted by regenerative therapies. Reproduced from Stern et al.[10].

Stem Cells for the Treatment of Visual Impairment

The cornea, the trabecular meshwork, the lens, and the retina (neuronal and RPE), have become the primary sites targeted for stem cell therapy according to Figure 1[10]. Below we describe what regenerative medicine can offer to tackle the leading causes of blindness and visual impairment.

Stem cells used as potential therapy

Stem cells are unspecialized cells that are present during the embryonic, foetal, and adult phases of life. Stem cells have the potential to form into any state of a specialized cell and thus serve as the foundation for various tissues and organs. Most importantly, stem cells have the unique properties of self-renewal (the ability to multiply widely), and potency (the ability to differentiate into numerous cell types)[13].

Pluripotent cells and adult stem cells (unipotent stem cells) are potential sources for clinical research surrounding visual impairment and are described hereunder.

Pluripotent stem cells (PSCs)

Pluripotent stem cells (PSCs) can self-renew indefinitely in culture while maintaining the ability to become almost any cell type from all three embryonic germ layers (ectoderm, mesoderm, and endoderm) and thus have been considered a viable resource for stem cell therapy in visual impairment[14–18]. The derivation of induced pluripotent stem cells (iPSCs), which are genetically reprogrammed somatic cells when exposed to Yamanaka factors (Sox2, klf4, cMyc & Oct3/4), has revolutionized the field of regenerative medicine. Generation of patient-derived iPSCs (PD-iPSCs) serves as an invaluable reservoir of PSCs with extensive potential similar to that of embryonic stem cells. Upon differentiation in vitro, PD-iPSCs recapitulate the pathobiology of conditions and can serve as an important source for studying cellular expression and morphological changes during the course of the disease, thus facilitating early diagnosis. Additionally, they can be used as models to study drug response and hence can provide information regarding application of existing and potential therapeutic options.s.[19]

Adult stem cells

Adult stem cells are a population of endogenous multipotent stem cells and serve as an internal repair system that generates replacements for cells that are lost through normal tear, injury, or disease if prompted or induced by the body. Examples include stromal bone-marrow stem cells, human adipose-derived stem cells and most recently discovered, dental pulp stem cells[20]. In a resting physiological state, adult stem cells may remain quiescent (non-dividing) for long periods of time until they are activated by a normal need for more cells to maintain and repair tissues. Three types of adult stem cells have been found in the eye: Retinal Pigment Epithelial Stem Cells (RPESCs), Limbal Stem cells (LSCs)[8]:

1. Salero et al. identified and reviewed a subpopulation of RPE (Retinal Pigment epithelium) cells which under certain circumstances harbour the capacity for self-renewal and repair. For example, human RPE has been shown to proliferate in certain pathological conditions e.g. Proliferative Vitreo-retinopathy (PVR)), and such RPE cells in vitro can be activated to form RPESCs [21].

2. Schermer at al. in their experiment with keratin protein markers identified a stem cell population at the limbus of the eye, termed LSCs, with strong regenerative capacity[22.]

3. Xu et al. isolated progenitor cells from ciliary bodies of mammals and concluded that these progenitor cells have proliferative potential and expressed specific markers for retinal pigmented cells[23]. Similar observations were also reported by Cicero et al [24]. The results of Ballios et al. indicated that retinal stem cells reside in Ciliary body and be induced to form photoreceptor cells[25].

In the eye, stem cells can be introduced topically (such method is generally used in ocular surface diseases including corneal ailments and dry eye syndrome), by injection into various spaces/tissue planes as well as via transplantation [8]. In addition, it may be possible to induce dormant stem cells that are already present in the eye. Battu et al. in their review[26] described three ways to introduce stem cells into the eye i.e., subretinal, intravitreal, or suprachoroidal injection.

Stem cells in treating corneal diseases

The cornea is a clear, refractive tissue that makes up one-sixth of the eye's anterior region. It acts as a physiological barrier and focuses on the light reaching the eye. Reduced vision is caused by corneal pathologies which can be acquired or inherited. Current regimens to treat corneal diseases via stem cells include the use of LSCs, a population of adult stem cells that continually replace the epithelial layer of cornea present at the junction of sclera and cornea[27]. Diseases that destroy LSCs such as Steven-Johnson Syndrome, Limbal stem cell deficiency, or loss of LSCs due to chemical burns or trauma can be treated by Limbal stem cell transplantation (LSCT)[28] in combination with preserved Amniotic Membrane[29] proven successful in treating refractory ocular surface diseases in humans[30]. Moreover, transplantation of stromal Mesenchymal Stem Cells (MSC) derived from corneal stroma[31] has resulted in corneal clarity in an animal study[32] and has prevented stromal scarring in mouse model[33].

The corneal stroma is the central layer of the cornea and subject to a variety of disorders. Keratoconus is a complex stromal disorder in which corneal thinning takes place and distortion of vision occurs. The prevalence among different regions and nations varies widely ranging from 6.8-2340 per 100,000[34] and in Pakistan, it is commonly seen in ophthalmology clinics which had an approximate prevalence of 8.1% amongst the general population[7]. Current treatment involves spectacle and contact lens correction as well as corneal cross linking to stabilize the condition if it is detected early. In more advanced cases, full thickness corneal transplantation is needed. Recently, corneal stromal cell therapy consisting of the intrastromal implantation with autologous adipose-derived adult stem cells (ADASCs), and decellularized or ADASC-re-cellularized human donor corneal laminas in advanced keratoconus have yielded promising results[35].

Table-1: Summary of stem cell advancements for intra- ocular Lenses

Study	Population	Phase/type of Study	Stem Cells used	Outcome
Murphy et al. [14]	Rat	Clinical Research	induced Pluripotent Stem Cells (iPSCs)	Successful demonstration of the production of light-focusing human micro-lenses
Lin H et al.[50]	Rabbits, macaques, and human infants	Randomized, controlled clinical trial	Lens Epithelial Cells (LECs)	A minimally invasive surgical procedure that allowed the removal of cataracts, yet preserved lens epithelial cells, which later led to regeneration of the intra-ocular lens and after a period of eight months, the lens had achieved physiological thickness, and improved visual acuity
Masoud Maleki[52]	Human Wharton Jelly in animal models i.e., Rabbits, Rats etc.	Hypothetical Study	human Wharton's Jelly Stem Cells (hWJSCs)	It is hypothesized that after removal of cloudy lens, hWJSCs are injected into the lens capsular bag and the stem cells will grow into lens fiber cells.

The corneal endothelium is the single, innermost layer of the cornea that is responsible, in large part, for managing the hydration of the corneal stroma. Corneal Endothelial Cell (CEC) disorders which include Fuchs dystrophy and bullous keratopathy cause blurriness and visual impairment in patients[27]. Amano et al and Yokoo et al. in their respective studies have discovered a dormant population of endothelial progenitor cells in the eye[36,37] stimulated via ROCK inhibitor Y-27632. These cells can be activated and can help recover vision loss caused by CEC disorders[38]. However, a study that involved the transplant of corneal endothelium to improve the CEC population along with a ROCK inhibitor demonstrated an increase in CEC density post-transplant in patients with resultant bullous keratopathy[39]. In addition, studies have shown that corneal endothelial cells required for transplant can be derived from stromal MSC present in the eye [40,41], PSCs[42] and human embryonic stem cells (hESCs).[43,44] Zhao et al. differentiated PSCs to Eye Field stem Cells (EFSCs) which were next differentiated to Neural Crest Stem Cells (NCSCs), and then finally CECs. Song et al.[43] identified typical cellular markers from hESCs derived CECs which shared similar molecular markers when compared with human CECs (adult and fetal) thus paving a way for quality verification of CEC derivatives from hESCs. In addition, McCabe et al.[44] demonstrated a 96% similarity in their derivation of CEC from hESCs and concluded that hESC derived CEC were morphologically similar and genetically identical to adult corneal endothelial cells and offers a viable stem cell-based alternative to a donor corneal endothelial transplant.

Stem cells in treating Glaucoma

As mentioned earlier, glaucoma is a leading cause of blindness worldwide. It is an optic neuropathy marked by the gradual destruction of retinal ganglion cells (RGCs). Ganglion cells are central nervous system neurons with cell bodies in the inner retina and axons in the optic nerve. The primary risk factor associated with the pathogenesis of glaucoma is high intra-ocular pressure (IOP, related to damage to the aqueous outflow system) which causes mechanical strain and stress on the optic nerve as well as vascular compromise. If not treated, glaucoma can lead to irreversible loss of vision. Current treatment employs methods of lowering IOP with medication, laser, or surgery. This assists in preventing or slowing loss of vision but is not a cure for the disease.

The trabecular meshwork (TM), an avascular structure between the cornea and iris that regulates the outflow of aqueous humor[45]. With progressive age or acquired dysfunction via genetic and other factors, TM cells lose their physiologic function and are unable to play an effective role in drainage of aqueous humor. This causes a buildup of fluid in the eye and raises IOP to pathological levels. Regenerative studies have focused largely on how to recover the function of TM cells. Ding et. al in 2014 in their study reported the successful induction of iPSCs into cells resembling the structure and function of TM cells in mice and were confident that human iPSCs may also be induced to form TM cells that could be used for autologous transplantation to treat various glaucoma[15]. Abu-Hassan et. al also identified that iPSCs-derived TM cell transplantation could potentially restore TM function and lower IOP[18]. A review by Behtaj et. al however suggested a different approach with transplantation of Retinal Ganglion Cells (RGCs). This is because degeneration of such cells is also a hallmark of glaucoma, and these cells are incapable of self-renewal; transplantation of RGCs with stem cells has the potential to restore sight[46].

Stem cells in treating cataracts

A cataract is an opacity within the intraocular lens of the eye, which limits the amount of incoming light and results in diminished visual acuity. Cataracts are usually formed due to factors including but not limited to natural aging

process, steroid use, trauma, ultraviolet light exposure, congenital disease, etc.[47]. The current treatment for visually significant cataracts is surgery with removal of the opacified lens and replacement with a synthetic intraocular lens (typically acrylic or silicone material). Surgery is highly successful but carries with it the risk of serious complications including posterior capsular rupture[48], macular oedema, retinal detachment, choroidal haemorrhage, and endophthalmitis[49].

A study by Murphy et al. demonstrated the production of the human micro-lens in animals using iPSCs derived from lens epithelial cells[14]. In another study conducted on rabbits, macaques, and human infants suffering from cataracts, Lin et al. presented a minimally invasive surgical procedure that allowed the removal of cataracts, yet preserved lens epithelial cells, which later led to regeneration of the intra-ocular lens. After eight months, the lens had achieved physiological thickness, and improved visual acuity[50]. In addition, studies have been conducted with the use of Wharton's Jelly, through which stem cells are derived, and which has shown the potential to regenerate the intra-ocular lens[51,52].

Stem cells for treating retinal diseases

Age-related macular degeneration (AMD) is a prevalent, persistent, gradual degenerative disease of the macula and is a common cause of central vision loss. AMD affects elderly people[53], especially in high-income countries, and 90% are affected by the dry form of the disease which currently has no effective treatment whereas a smaller percentage have the wet form of the disease with development of choroidal neovascular membrane a period. In the wet form, anti-VEGF (vascular endothelial growth factor) injections are effective to improve vision as well as prevent further visual deterioration[54]. In Pakistan AMD accounts for 0.02 % prevalence among the general population.[6] Rods, which are activated in dim light, and cones, which are triggered in bright light (with specific wavelengths), are the two types of photoreceptor cells that make up the afferent portion of the retina's light-responsive system. The macula enables precise and accurate colour vision because the cones are clustered in this region[55]. Since photoreceptors are specialized neurons, they cannot regenerate after injury.

The main pathogenesis behind AMD is the degeneration of Retinal Pigment Epithelium (RPE) related to aging, smoking, ultraviolet light, and polygenic factors. This leads to death of photoreceptor cells as the function of RPE is to supply nutritional and physiological support for these cells. RPE replacement to recover vision loss has been hypothesized via transplanting iPSC induced RPE cells to the affected areas. Recent research in animals indicates that RPE cells produced from iPSCs of AMD patients are generally healthy when clinically evaluated in the laboratory[56], and such healthy RPE transplants are not anticipated to revert to a pathologic state right away. Approaches to stem cell therapy for dry-AMD are summarized in Table 2.

Table-2: Summary of cell therapy approaches for dry age-related macular degeneration (reproduced with permission from Ingrid et al).[57]

Sponsor	Product	Cell type	Delivery	Phase
Regenerative Patch Technologies	CPCB-RPE1	Human embryonic stem cell-derived RPE cells on a parylene membrane	Subretinal implantation	Phase 2a
NIH	iPSC-derived RPE/PLGA	Autologous iPSC-derived RPE on a biodegradable poly lactic-co-glycolic acid (PLGA) scaffold	Subretinal transplantation	Phase 1/2a
Astellas	ASP7317 (MA09-hRPE)	Human embryonic stem cell-derived RPE cells	Subretinal injection	Phase 1/2a
Lineage Cell Therapeutics	OpRegen	Human pluripotent stem cell-derived RPE cells	Subretinal injection	Phase 1/2a
Janssen Labs	CNTO-2476 (palucorcel)	Human umbilical tissue-derived cells (hUTCs) of mesenchymal origin	Subretinal administration using a microcatheter	Phase 2b
Luxa Biotechnology	RPESC-RPE-4W	Allogeneic RPE stem cell (RPESC)-derived RPE cells (RPESC-RPE) isolated from the RPE layer of human cadaveric eyes	Transplanted under the macular	Phase1/2a

Microvascular lesions caused by diabetes mellitus (DM) in diabetic retinopathy (DR) results in damage to the retina's vasculature, neurons, and glial cells.[58] Choroidal capillaries become occluded because of neutrophil and monocyte activation against endothelial cells, leading to progressive hypoxia and retinal ischaemia, and this trigger increased expression of pro-angiogenic factors including VEGF. Excessive sVEGF triggers inflammatory and angiogenic processes. Patients with uncontrolled diabetes eventually experience blood-retinal barrier instability, increased vaso-permeability, fluid buildup, and neovascularization. These conditions can progress to the diabetic macular oedema (DME) and proliferative DR.[59,60] Globally a significant increase in the prevalence of DR since 1990 has been recorded in the regions of South Asia, Sub Saharan Africa, and North America. South Asia has shown an increase of 123% of DR cases among diabetics over 30 years and a current prevalence of 1.28 per 1000 individuals5. Currently available treatments, including anti-VEGF injections (injected intravitreally), corticosteroids (injected intravitreally), vitreoretinal surgery and laser photocoagulation (creates pigment epithelial – retinal adhesions via laser application) targets the later stages of disease when extensive and sometimes irreversible injuries have already taken place. However, it is pertinent to understand that none of these treatments address early and reversible retinal changes in DR. Retinal laser as well as intravitreal anti-VGEF injections may be needed to achieve a therapeutic effect, and at times multiple injections may be necessary. This is costly and inconvenient to patients and diabetic macular oedema may persist after treatment. Moreover, laser photocoagulation and injections help prevent or impede further deterioration of vision, but progression can still take place.[61] At present, the best way to control the development of DR from its initial stages to a stage of severe visual impairment is to control the blood glucose level and control other risk factors for progression including hypertension, smoking and hypercholesterolaemia [62].

Lechner et. al proposed 3 major pathways for treating DR using stem cells[63]:

- Treating retinal vasculopathy,
- Treating retinal neuropathy,
- Replacing the RPE

For treating vasculopathy caused by loss of pericytes, stem cells can be acquired from MSCs, Bone Marrow (CD 34+), Endothelial colony forming cells (ECFCs), and Myeloid angiogenic cells (MACs). These stem cells demonstrated vascular repair of the damaged capillaries and supported growth in Rat/mice models[16,64–71] . Adipose Stem cells (ASCs) when injected into rats showed developing pericyte specific markers and capillary vascular regrowth and repair[72,73].

Neuropathy in DR involves neurodegeneration of the five types of neurons present in the retina[74]. The approach to stem cell therapy for neuropathy involves the generation and replacement of these neurons[75], photoreceptors and RGCs which are the most affected in DR. Retinal progenitor cells (RPCs) derived from foetal retinas, embryonic stem cells (ESCs), and iPSCs have the clinical potential for successful transplantation to restore the function of damaged neurons[76]. Studies conducted in mice demonstrated that human RPCs injected subretinally integrated effectively within the host retina, expressed visual pigments, and restored vision[76]. Moreover, there was no indication of rejection or uncontrolled cell proliferation. Research in non-human primates using subretinally administered hESC or hiPSC-derived photoreceptor precursors showed encouraging outcomes after photoreceptor elimination[17,77]. Donor cells had the ability to endure, develop into adult photoreceptors, interact synaptically with host bipolar cells, and facilitate structural repair.

Müller cells have also been identified with neuro-regenerative properties. in vitro Studies have demonstrated Müller cells isolated from mice and human retinas differentiating into neuronal progenitors and photoreceptors[78–80]. Müller cells were also able to differentiate into ganglion cells in a study where rats lacking in ganglion cells received intravitreal injections of Human Müller cell-derived ganglion cell precursors. Four weeks after transplantation, these cells adapted into the host retina confined to the RGC layer and demonstrated specific RGC markers[81].

Inherited retinal diseases (IRD) cause the outer retina and retinal pigment epithelium (RPE) to degenerate over time, eventually causing significant vision loss which includes Retinitis Pigmentosa (RP) and Stargardt disease (STGD). Globally, the prevalence of IRD is 1 out of 2000 individuals and has affected 2 million individuals worldwide[82]. In Pakistan, consanguineous marriages have led to an increased prevalence of IRDs.[83] Although prevalence studies are scarce, one study revealed that 1 out of 800 individuals have IRD with RP being most prevalent[83]. Such diseases may be treated with gene therapy, which introduces a functional copy of the defective gene into host cells to restore cellular function, or cell replacement therapy, which replaces the damaged/ non-functional cells with stem cells[26]. With the latter mode of treatment,

STGD may be treated by replacing the RPE derived via hESCs according to a study by Schwartz et. al[84]. In another study, three patients with STGD received hESC-derived RPE. Two patients reported improved visual acuity, however at different follow-up periods, and one patient developed rhegmatogenous retinal detachment[85]. IRD which causes loss of photoreceptors includes RP in which death of rod photoreceptors (that account for 90% of the population of photoreceptors) causes night blindness. Stem cell therapy targetting RP currently includes the replacement of photoreceptors derived from hESCs/iPSCs. These studies have been carried out in mice via the transplant of photoreceptors with stem cells[86,87] indicating the potential to treat RP in humans and restore vision.

Synergistic approaches of Stem cell therapy with biomedical engineering and nanotechnology

Advances in biomedical engineering and nanotechnology have facilitated introduction and application of potential materials and three-dimensional structures for cell therapy of the eye. There is potential to combine these approaches with stem cell therapy. Miotte et al.[8] have summarized such research in their article including the generation and differentiation of functional 3D retinal and corneal structures. They described the use of modified cultures in which stem cells can be differentiated in vitro, be observed for functionality, and then can be transplanted onto hosts once prepared.

Safety and ethical concerns

The clinical application of stem cell technology, particularly for degenerative disorders, is highly anticipated. However, some safety concerns exist. First and foremost, the methods of generating iPSCs can cause genomic instability to occur at any stage of iPSCs after induction or reprogramming and during development of these cells (during passaging) which can lead to a higher risk of teratomas and malignancy, and chromosomal aberration[88] . Moreover, stem cell treatment carries a risk of complications as reported by Kuriyan et. al where three patients suffered severe vision loss after intravitreal injections of Adipose-derived stem cells. The visual loss was caused by ocular hypertension, haemorrhagic retinopathy, vitreous haemorrhage, combined traction, and rhegmatogenous retinal detachment, or lens dislocation[89].

Ethical concerns regarding the use ESCs and UC-MSCs for regenerative therapy remain and are related to annihilation of human embryos for cell extraction. This is linked to abortion and maleficence because an embryo has the potential to become a human being. Hence there is a need to carefully consider policies related to areas such as consent, control, and justice[90].

The future promise of stem cell therapy

At present, stem cell therapy is very costly compared to conventional treatments for ocular pathologies. However, ongoing research including clinical trials, will pave the way for more cost-efficient technology and approaches. Many Educational institutions in the USA are engaged in research in the field of Ocular Regenerative medicine including Harvard University which has had success in employing embryonic-derived stem cells in the treatment of AMD, Glaucoma, and RP.[91]. John Hopkins Wilmer Eye Institute, The Center for Stem Cell Ocular Regenerative Medicine, (STORM) have successfully developed human retinas, ganglion cells from human stem cells and repaired damaged retinal vasculature in animal models and currently are working on the development of efficacious methods for vision restoration in diseases of glaucoma and the optic nerve[92]. Research institutes in China for example the Beijing Institute for ophthalmology are involved in extensive research from developing retinal organoids to complete retinal regeneration regimens[93], and The Kobe eye city hospital in Japan is currently using allogenic iPSCs derived retinal transplants in human retinal diseases i.e. Retinitis Pigmentosa, AMD[94]

Some Institutes and research centers in Pakistan are involved in stem cell research and are employing stem cell therapy for various diseases and disorders[95]. Currently, Shifa Rejuvenation Clinic in Islamabad offers a therapeutic stem cell approach in ocular diseases[96]. At the Aga Khan University, Karachi, Pakistan, the Center for Regenerative Medicine and Stem Cell Research (CRM) is currently employing the use of iPSCs-derived cerebral organoids to study early human brain development and neurodevelopmental disorders; tissue engineering approaches including 3D bioprinting of tissues are also being developed to facilitate research related to regenerative approaches. Even though current publications related to stem cell therapy from Pakistan remain substantially low[95], collaborations among institutions (nationally and internationally) for focused research can potentially accelerate stem cell therapy and provide restorative approaches in multiple diseases.

Conclusion

Blindness and visual impairment related to cataract, glaucoma, retinal and corneal diseases is projected to increase globally over the next 2-3 decades. Current

treatments can either halt and, in some cases, ameliorate the disease outcome, depending on stage of disease presentation and access to various treatment modalities. The field is rapidly evolving and application of stem cells from varied sources is under extensive research. Although no clinical treatments are approved yet, multiple trials are in progress to explore the potential benefits of using stem cells for treating blindness and vision loss.

The article previews approaches and challenges for translation of stem cell-based approaches into clinically approved personalized therapies. Although SC modeling approaches need improvements, they hold great potential and are essential for understanding the pathogenesis of disease and to improve the overall outcome and quality of life for patients affected.

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