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RESEARCH ARTICLE

PATHOLOGICAL MYOPIA– LONG-TERM THINKING FOR A SHORT-SIGHTED WORLD

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ABSTRACT

Background- Globally, pathologic myopia is a leading cause of visual impairment. Pathologic myopia is characterized by the presence of typical fundus changes (posterior staphyloma or myopic maculopathy). Many eye and vision professionals have been alerted to the global incidence of pathological myopia and are taking steps to stop its progression. **Methods**- This systematic review article is carried out after comprehensive analysis .Analysis is carried out following a thorough search of academic and guideline database for a period of one month.Once all searches were combined, observations were noted down in one month. **Results** - Evidence have shown that a proactive reshaping of the eyeball is the core point of myopia developing process, which particularly includes the weakening, thinning, and expanding of the sclera. As a result, it is thought that the sclera is a prime target for therapeutic modification to stop the progression of myopia. Hypoplasia and loss of RPE are characteristics seen during the progression of myopic maculopathy.The preliminary work has shown a promising way in stem cell-based therapy of patients with myopic maculopathy. Therefore, it is possible to achieve the ambitious goal by stem cell-based therapy. **Conclusion**- In this paper, we postulate that through shaping the eyeball and inhibiting abnormal scleral remodelling, scleral collagen cross-linking, or SXL, has enormous potential for stabilizing the myopic process.Also, replacing atrophic RPE cells with healthy ones through transplantation of RPE cells appears to be a better method of improving the visual outcomes of pathological myopia patients.

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INTRODUCTION

Myopic refractive error is one of the leading causes of vision loss worldwide.(1) Pathologic myopia is characterized by the presence of typical fundus changes (posterior staphyloma or myopic maculopathy). Many eye and vision professionals have been alerted to the global incidence of pathological myopia and are taking steps to stop its progression. Pathological myopia is often associated with scleral thinning.(2) The progression of myopia depends on the biochemical and biomechanical properties of the sclera.(1) Pathological thinning of the sclera is associated with a decrease in the diameter of collagen fibers, defective collagen fibrillogenesis, and collagen cross-linking.(2) If these scleral changes become the main target of manipulation, the progression of myopia can be controlled.(1). Reversing these abnormalities may make the sclera tougher and might serve as a treatment option for myopic progression.(2) Therefore, it is the need of the hour to find a therapy to strengthen scleral biomechanism to slow the progression of myopia and benefit millions of individuals (3). We discussed the current evidence-based applications of scleral collagen cross-linking (SXL) using different interventions.

In addition, we discussed an in vivo technique to evaluate the scleral biomechanical property and outcome after SXL in the human eye. RPE cell transplantation appears to be a better way to improve visual outcomes in myopic patients by replacing atrophic RPE cells with healthy ones. Compared with traditional surgerythe combination with iPSC-RPE transplantation would bring more advantages**.**

METHODS

We conducted a systematic search of all published articles related to pathologicalmyopia, by searching the online databases, including PubMed, Embase, and Google Scholar. The search terms contained ("myopia", "Pathological myopia "or "high myopia" or "new interventions" or "scleral crosslinking" or "stem cell based therapy"). Published studies were included including prospective observational studies conducted on humans and reported the new interventions used for treating the pathological myopia and preventing its complications. Only full-text studies published in English were included. Unpublished studies and meeting abstracts were not included due to uncertainly of methodological quality.

A total of 84 articles were identified in the initial search, After excluding duplicates papers and those that did not meet the inclusion criteria, a total of 36 full-text articles were subsequently screened. Analysis carried out following a thorough search of academic and guideline database for a period of one month. Once all searches were combined, observations were noted down in one month. In a nutshell, this review was based on 36 core papers that explainnew interventions used for treating the pathological myopia and preventing its complications.

RESULTS

Scleral Cross Linking (SXL): The human sclera makes up about 85% of the outer tunic of the eyeball and is made of dense collagen fibers embedded in a stromal matrix.(4) The majority of collagen is type 1.(2,4,5) The term "extracellular matrix" (ECM) mainly includes sulfated proteoglycans (PG), glycosaminoglycans (GAG), elastin fibers, cells, and nonfibrillar collagens.(4 ,5) PG, mainly decorin (74%) and biglucan (20%), form important bridging structures between fibrils and integrin, which mediate cell-collagen adhesion.(5).Collagen determines the stiffness of the sclera.(4) The role of scleral fibroblasts located between the lamina is to control the synthesis and circulation of the ECM.(5) The collagen fibers of the sclera have different diameters and different spacing, making them opaque.(4) The fibers of the outer layer of the sclera are the thickest and the inner stromal layer is the thinnest.(5) Fiber diameter and interfibrillar and intrafibrillar crosslinking primarily govern scleral stiffness.(2,6) The shape and size of the eye depends on the sclera.(7) Any changes in the microstructure and mechanical properties of the sclera can affect eye development and myopia (4).

A common mechanism behind the different cross-linking methods is to increase the stiffness of the sclera.(8, 9) The stiffness of the sclera largely depends on the inter- and intra-fibrillar cross-linking and the diameter of the collagen fibers. (2 ,6) All methods change the biomechanical properties of the sclera, making the sclera stiff.(7) These biomechanical changes are achieved by the formation of new chemical bonds (covalent bonds) between molecules of different fibers and within molecules of the same fiber and reducing the space between fibers.(5) (Figure 1). Different methods use different stimuli to induce a new bond; for example, endogenous uses an enzymatic or non-enzymatic pathway, and exogenous uses light (radiation), a chemical, or both. Once cross-linking is achieved, the sclera becomes difficult to resist stretching from progressive myopia.

METHODS FOR SXL

UV-A/Riboflavin: Photochemical cross-linking can be induced by a combination of UV-A light and the photosensitizer riboflavin.(1) It has been used for SXL in the human sclera and found to change its strength.(2,10) The light method has the advantage of being localized to the region of interest without damaging other regions.(11) The disadvantage is that we have to access the region of interest through the peritomy at the limbusand then invert the eyeball using straight traction sutures to expose the areas of irradiation.(10) 0.1% riboflavin and 20% dextran are used as photosensitizers.(10)

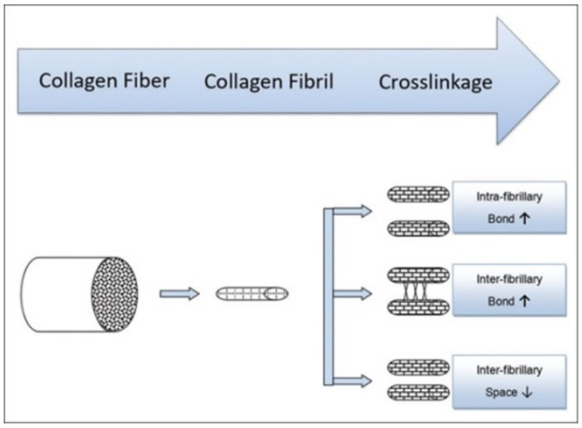

Figure 1. Mechanism of scleral cross linkage

The total duration of the procedure is 1 hour; during the first 30 minutes, we dripped the photosensitizing solution once per minute into the irradiation zone, then during the next 30 minutes we irradiated with UVA radiation (365 nm) and dripped the solution.(10) UV-A with photosensitizing solution produces singlet oxygen and is moderately cytotoxic.(9) The photosensitizer absorbs light energy and changes from the ground state to a short-lived singlet state and then relaxes to the triplet state.(12) The triplet state is followed by two types of reactions, called type I and type II.(12,13) Both reactions are distinguished by the absence or presence of singlet oxygen.(14,15) In the type I mechanism, triplets are formed; Medium radicals that react with collagen to form a crosslink (oxygen-independent).(12,16) Type II mechanism triples produce singlet oxygen that reacts with collagen to form a crosslink (oxygen-dependent).(12,16) Severe UV-A -radiation during crosslinking is cytotoxic to the sclera.(1) Another approach is transpupillary UV-A irradiation, but this is also toxic to the retina and exceeds the maximum safe limit for the cornea.(17) Another difficulty is that it is a complex invasive procedure involving a posterior approach and a large irradiation area, which makes the procedure more difficult to repeat.(1) SXL can cause glaucomatous damage due to impairment of axonal transport when applied close to the papillary region.(9) An in vivo pilot study confirmed the feasibility and safety of SXL in blind eyes, but we need more research, especially in human vision. (10) A protocol for administration to the human sclera, as with the cornea, is necessary to study dose effects and dose toxicity.

UV-B/Riboflavin: The main limitations of UV-A are retinal toxicity and lower scleral penetration.(8) Other light sources such as UV-B (445 nm) have been proposed to avoid these disadvantages and improve efficiency.(11) UV-B (blue) light is another absorption peak for riboflavin.(8) SXL with UV-B/riboflavin in human cadaver and pig eyes has been reported to control the pathological process of myopia.(13) The longer the wavelength (UV-B), the less potential for biological damage.(8) The crosslinking procedure is the same as for UV-A/riboflavin.(1) Riboflavin/blue light SXL has the advantage of stiffening the sclera with minimal retinal damage.(8) Conversely, high intensity UV-B damages scleral cells, the ECM, cellular infiltration in the outer scleral layer, and increased metabolism in the inner scleral layer, leading to scarring.(1) Blue light with riboflavin cross-links in human and pig eyes has been found to play a role in controlling the progression of myopia, but further research is needed.(13)

Rose Bengal (RB)/green light irradiation (RGX): Another SXL method was proposed using photosensitizer rose (RB) and green light (532 nm) as an existing tip to induce cross-linking.(18) The photochemical role of RB in the cornea has already been demonstrated and found to be as effective as riboflavin/UV crosslinking.(19-21) RB penetrates less into the surrounding tissue and is less toxic to keratocytes than riboflavin/UV. -A.(19) The proposed mechanism is singlet oxygen and electron transfer.(9) Porcine (pig) and rabbit-eye RGX significantly stiffens the sclera, making it a possibility in the treatment of myopia progression.(18,20) Another study also reported that rabbit-eye RDX is effective in posterior scleral stiffening.(21) RGX is more effective at lower concentrations and shorter light exposures compared to riboflavin/UVA.(19) These results suggest the efficacy of RGX-induced scleral stiffening and provide a basis for further in vivo studies.(21) . Although the pig sclera is closer to the human sclera, we need more research to determine the long-term effects of RGX use.(8).

Methylene blue + Red light: Methylene blue (MB) is a well-known photosensitizer.(16) It has been used in humans as a treatment for malaria and methemoglobinemia.(22) MB is excited by red light at 660 nm, and this property makes it another suitable option for cross-linking.(16) The cross-linking effect of MB is the production of singlet oxygen by type II mechanism.(22) Studies have shown that MB increases collagen stability in rat tail tendons and pig heart muscle tissue.(22) It has been used in animal studies to treat myopia and glaucoma.(16) Further studies are needed to determine its efficacy and safety as a cross-linking agent in collagen-rich tissue such as the sclera.(22)

Chemical SXL: SXL by using the light method is associated with phototoxicity to ocular tissue and is an invasive surgical procedure with slow recovery.(23) An alternative approach is the chemical or dark method.(1,23) The chemical cross-linking method involves artificially induced cross-linkage, avoiding light exposure.(1) The chemical method uses cross-linking reagents containing reactive groups (amino and thiol) that can form new covalent bonds to enhance the stability of sclera.(13) These chemical reagents are directly injected into the sub-Tenon space on the scleral surface.(1) Comparatively, chemical or dark SXL can improve the scleral stiffness more effectively than photochemical or light SXL.(13) Chemical methods can also be used in areas near photosensitive structures to avoid irradiation-related tissue toxicity.(9) The advantage is that it is less invasive than the light method as we do not need peritomy to expose the sclera for irradiation.(13) The disadvantage is chemical cross-linking reagents can easily diffuse to areas other than the cross-linking area.(13) Many chemical cross-linking agents are available, but only a few are found to be effective on SXL. Glyceraldehyde, genipin, aliphatic β-nitro alcohols, formaldehyde releasers, decoron, and transglutaminases have been reported in various studies in vitro or in vivo.(9,23) Glyceraldehyde, a chemical agent, has been used in the New Zealand rabbit eye through sub-Tenon's injection route, causing shorter axial length with no histological damage in the retina or choroid.(24) Another study in German rabbits showed that glyceraldehyde increased scleral stiffness with some inflammatory infiltration and moderate loss of keratocytes.(25) The mechanism of action for glyceraldehyde is through AGE, which increases scleral stiffness and simultaneously reduces the elasticity of lamina cribrosa, which may be a risk for glaucomatous optic nerve damage.(13) Similarly, another chemical agent, genipin, is used through the sub-Tenon route in tree shrew eyes, resulting in slowing axial elongation and myopia progression.(26) However, the reason behind these side effects could be different concentrations and different number of injections used.(26) Another study on guinea pigs reported that sub-Tenon's injection of genipin increased scleral hardness effectively and inhibited myopia development.(26) However, side effects of increased IOP, glaucomatous changes in the optic disc, and histological and molecular changes in the sclera were found, raising safety concerns.(26) Formaldehyde-releasing agents (FARs, which include nitro alcohols) are naturally cross-linking agents.(27) Hydroxymethyl glycinate (SMG), a formaldehyde releaser, has been used through the posterior sub-Tenon route in rabbit eyes in vivo.(27) The compound has a minimal toxic effect on ocular tissue, and the axial length is limited to 10%–20% after a 5–6-week follow-up.(27) Transglutaminases are a type of natural enzyme, and microbial transglutaminases are known as enzyme-mediated cross-linking agents.(7) Microbial transglutaminases have been used in rabbit eyes in vivo for cross-linking purposes and have been found to stiffen the sclera and are safe for the retina.(7) Another option is carbohydrate-based collagen cross-linking agents. Monosaccharide ribose is a naturally occurring substance with good penetration to the sclera and less toxic to sclera.(23) The sub-Tenon injections of ribose in the white rabbit eye were found to strengthen the sclera through nonenzymatic glycation.(23) The disadvantage is diffusion across the adjacent structures, low cytotoxic, subconjunctival fibrosis, and retinal toxicity.(23,11) Various chemical SXL studies have laid the foundation for identifying a suitable drug and deciding an ideal dose, injection site, and frequency to improve their penetrability and bioavailability and to reduce their systemic absorption and side effects.

Low-level laser therapy: Low-level laser therapy (LLLT) or photobiomodulation has been used in SXL for progressive myopia.(23) LLLT differs from UV or green light in that it uses red and near-infrared light with wavelengths between 600 and 1100 nm.(3) The longer the wavelength, the better the penetration and less chance of biological damage.(8) LLLT transforms light energy into metabolic energy to change the biological functions of cells.(23) Oxidative stress, inflammation and apoptosis play central roles in the regulation of myopia.(3) Red light and infrared light are safe for direct eye contact and do not pose a thermal hazard to the retina.(14) Low-level laser therapy reduces inflammation and swelling, improves tissue microcirculation, and treats neurological disorders.(3) The main light receptor in the red and near-infrared regions is mitochondrial cytochrome oxidase, which is involved in neuronal and free radical metabolism, the process of apoptosis, and glutamate regulation.(23) This low-level treatment stimulates the target tissue without changing the temperature of the surrounding tissues.(3) A human trial of 74 children treated with LLLT reported a delay in the progression of myopia, and a significant association between changes in axial length and subfoveal choroidal thickness (SFChT) was observed at six months of follow-up.(3) Choroidal thinning has been shown to be associated with the onset of myopia, faster axial elongation, and the onset of myopic macular degeneration.(28)

A study of 120 myopic children showed promising efficacy and safety of repetitive low-level red light (RLRL) therapy (650 nm) in controlling the progression of myopia.(28) Another study of 62 myopic children reported that RLRL (650 nm) was more effective than low-dose atropine eye drops in controlling axial elongation and myopic progression over 12 months.(15) A meta-analytic review concluded that RLRL was effective in slowing myopia progression and axial lengthening, but recommended larger RCTs with 2-year follow-up.(14).

SPECIFIC CELL THERAPY FOR MYOPIC MACULOPATHY

Cell therapy is a replacement therapy for dysfunctional tissues or cells that heal through cell regeneration(29). It is anew method of treating diseases that were previously thought to be incurable. Here we look at cells that are theoretically available for cell therapy in pathological myopia.

Autologous iPSC-RPE: Hypoplasia and RPE loss are hallmarks of myopic maculopathy progression. As with other forms of macular degeneration, the loss of RPE cells leads to photoreceptor apoptosis in pathology, increased matrix metalloproteinase-2 (MMP-2) activity (30), decreased proteoglycan turnover (30),and structural changes in collagen fibrils result in weak and tight sclera. RPE cell transplantation appears to be a better way to improve visual outcomes in myopic patients by replacing atrophic RPE cells with healthy ones. The efficacy and safety of GMP-grade human iPSC-RPE were demonstrated in preclinical studies by Zhang *et al*.(31). Here, transplanted cells were injected into the subretinal space. RPE transplantation requires a scaffold with excellent cytocompatibility and biocompatibility (32) Compared with traditional surgery, combining iPSC-RPE with transplantation would provide more advantages**.** One problem with RPE cell patch transplantation is the viability of the cell patch when choroidal perfusion is severely lacking in the atrophic choroid. Pang *et al*.(33)in 2015 recognized that myopic eyes with very thin **c**horoids ($\leq$ 20 μm) can still have BCVA $\geq$ 20/40. They proposed two explanations: (1) the fovea**,** with its very thin choroid, received its blood supply from larger open choroidal vessels located eccentrically to the subfoveal region; and (2) an atrophic retina with a thinner layer allows more oxygen to penetrate from the deep capillary plexus into the outer retina. Therefore, we have reason to believe that transplantation of RPE cell fragments into eyes with myopic macular holes is possible**.**

Fibroblasts/My ofibroblasts: The wall of the sclera, or eyeball**,** must have strength to protect the delicate intraocular structures andsome elasticity to buffer fluctuations in intraocular pressure. A decrease in the number of fibroblasts and the diameter of collagen fibrils can be observed in the posterior sclera of the myopic eye(30).In addition, fibrils with an unusual stellate cross-section enlarge the myopic sclera (30). It is known that anincrease of matrix metalloproteinase-2 (MMP-2) activity (30), a decrease of turnover rate of proteoglycan(30), and structural changes of collagen fibrils result in a weak and extensible sclera. The changed scleral biomechanics is thought to be responsible for the increasing AL and development of myopia.Myofibroblasts is a population of scleral cells derived from fibroblasts. Migration is stimulatedby mechanical stress through transforming growth factor β (TGF-β) and cellular fibronectin (30). Myofibroblasts are highly contractile cells that can express alpha-smooth muscle actin (α-SMA) to respond to scleral mechanical stress and limit the expansion of the surrounding matrix (30). Downregulation of TGF-βpromotes ECM remodelling during myopia development (30). TGF-β is importantin regulation of ECM turnover. Depletion of TGF-β would induce α-SMA expression and decreased cell-mediated contraction(30). TGF-β not only encourages myofibroblasts to synthesize α-SMA, but also promotestype I collagen production(30). Myofibroblasts contract stress fibers attached to the surrounding ECM and cause local contraction of the matrix. Myofibroblasts then deposit ECM to stabilize contraction(30). Shinohara *et al*.(34) found that transplantation of human dermal fibroblasts into the sclera is an effective way to reduceaxial tension in myopic malformation-deficient rats. Transplanted fibroblasts can synthesize new collagen fibrils with a bundle-like appearance and a striated pattern. Newly synthesized collagen fibrils can strengthen the sclera and slow axial elongation in myopic eyes. An immunosuppressant was used in this study due to heterotransplantation. As a new type of therapy, it is possible to use autologousiPSC fibroblasts or autologous iPSC myofibroblasts to treat the posterior sclera.Therefore, fibroblast or myofibroblast transplantation is a promising way to reduce the progression of myopia and prevent the development of myopic maculopathy in myopes.

Scleral stem/progenitor cells (SSPC): Scleral stem/progenitor cells (SSPC) have been isolated from mouse sclera (35). SSPCs express the stem cell genes ABCG2, Six2, Pax6 and Notch1 and are positive for mesenchymal markers including Sca-1, CD90.2,CD44, CD105 and CD73. In addition, SSPCs can differentiate into adipogenic, chondrogenic and neurogeniclineages (35).However, related studies are rare and studies describing SSPCs are still needed.

Limitation: SXL has limited effects on the human eye. Only a few studies (RLRL and LLLT) have been conducted on human eye sight, with small sample sizes and short follow-up. Photochemical CXL requires examination of the conjunctiva at the limbus for irradiation, and reproducibility is a common limitation of this procedure. Another difficulty is to reach the sclera posterior to the equator, which requires a complex invasive procedure. Chemical CXL is unpredictable because its field of action is unlimited after posterior sub-tenon injection. We need more SXL studies on the human eye with large samples and long-term follow-up to refine the process and eliminate shortcomings.

Although we see good prospects for stem cell-based treatment of myopic maculopathy, we have to consider several problems. When is the best therapeutic window? For myopic patients with diffuse or macular atrophy, iPSC-RPE subretinal transplantation is a good optionto reduce photoreceptor loss due to RPE loss. However, the best treatment window is difficultto explain. In patients with severe photoreceptor loss, a single RPE transplant does not help. Anothersituation is when there is diffuse atrophy that spares the fovea and the patient maintains good visual acuity.In this case, subretinal transplantation of iPSC-RPE poses a high risk to vision.Experienced surgeons are required during PPV surgery for iPSC-RPE subretinal transplantation.Subretinal injection of RPE cell suspension or placements of an RPE cell patch under the retina, especially in high myopic patients with thin retinas, are complex procedures. Surgeons must prevent the

transplanted cells from breaking into the glass or hold the patch of cells in place.

Future: Photochemical CXL (especially UV-A and UV-B irradiation) is toxic to the retina and cornea. This can be overcome by avoiding the transpupillary approach and focusing directly on local scleral irradiation with a minimally invasive procedure up to the ocular equator. Chemical CXL and LLLT are good alternatives to postequatorial SXL because they avoid complicated research procedures. We need to develop a method-strategy protocol and select photosensitizers based on their efficacy at physiological pH, temperature, permeability and cytotoxicity. Further studies are needed to conclude the dose-effect relationship and the dose-toxicity relationship in the human sclera. We also need to work on the quality of the equipment used to measure in vivo changes in eye tissue after cross-linking. In addition to myopia, SXL has also been used in patients with glaucoma around the optic disc to strengthen the Lamina cribrosa to prevent glaucoma progression. However, it can impair axonal transport and exacerbate glaucomatous damage to the optic nerve; In addition, for iPSC-RPE subretinal transplantation, special surgical instruments are required for example, a 25/41 G double-tube cannula is used to create a subretinal bubble (36) and a special instrument is required to deliver a subretinal cell patch.Therefore, further work on safety and efficacy is needed.(9)

CONCLUSION

The only way to improve the prognosis of patients with pathological myopia is to prevent the development of myopic maculopathy and timely control it. Anti-VEGF agents have partially preserved vision in patients with mCNV, but most patients with higher myopic maculopathy are at high risk of visual impairment. Animal studies have shown that the SXL method has the potential to control the progression of myopia; However, the safety of SXL requires further research. Because the work of SXL in the human eye is limited, we believe that continued research and development will eventually lead to a new method to manage the progression of myopia. Cell-based therapy has opened a new era in treatment.Stem cell-based therapy has been hailed as the future of medicine and has been highlighted as a cure for incurablediseases. Stem cell transplant therapy has made great strides in corneal and retinal degenerative diseases. It is hoped that the atrophic structures in myopic eyes can be replaced by stem cells and the tissue regenerated. Preliminary work has shown a promising approach in stem cell-based treatment of patients with myopic maculopathy. Therefore, an ambitious goal can be achieved with stem cell-basedtherapy.

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