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Chapter

# Reduction of Myopia Burden and Progression

*Sangeethabalasri Pugazhendhi, Balamurali Ambati and Allan A. Hunter*



## Abstract

Myopia is a significant worldwide public health concern, and its prevalence is drastically increasing in recent years. It was once viewed as a benign refractive error, but is now one of the leading causes of blindness and is associated with numerous ocular diseases, which makes it crucial to develop viable treatment options to adequately correct the refractive error and to halt the disease progression. The treatment of myopia can be classified into three groups: optical, pharmacological, and surgical management, which are aimed at adjusting to the refractive error and reducing the axial elongation. The conventional treatment modalities for myopia, such as single vision glasses, correct the refractive error and improve visual quality of life, but do not affect myopia progression or axial elongation. The newer and various myopic interventions including spectacle corrections, contact lens corrections, pharmacological treatments and surgical corrections, hold great potential for adequate disease control to improve the quality of life, reduce myopia burden, and preserve the ocular health.

**Keywords:** myopia, refractive error, axial elongation, single vision lenses, multifocal lenses, rigid gas permeable contact lenses, soft bifocal contact lens, orthokeratology, atropine, pirenzepine, anti-hypoxic drugs



## 1. Introduction

Myopia is a refractive condition of the eye that has globally affected 1.89 billion people worldwide, and projected to affect 2.56 billion people by the year 2020 [1]. Over the past few decades, the prevalence of myopia in Asia has increased dramatically affecting as much as 80–90% of the pediatric Asian population, and 25–50% of the American and European population [2].

Refractive development in early ocular growth is an intricate and continuous process. At birth, there is a high prevalence of large refractive errors in newborn infants due to mismatch between the axial length and the focal length of its optics [3–5]. As the newborn matures, the eye develops in size and refracting power in a rapid fashion to attain an ideal refractive state in early childhood. This physiological process is known as emmetropization [5–7]. Coordination between axial length and optical components will allow for the images of distal objects to focus on the retina, rather than in front or behind it [5]. Interruption of this homeostatic process of ocular growth results in the development of refractive error. The disorder manifests in early childhood and progresses at an average of 0.5D every year until stabilizing during adolescence [8–10].

It was once considered a mere refractive error, but myopia is now often associated with a multitude of ocular diseases such as retinal detachment, glaucoma, cataract and chorioretinal abnormalities [11]. Therefore, in recent years, the focus of myopia research has been on halting the progression to decrease the risk of associated future ocular diseases.

This chapter focuses on the mechanics of the various treatment methods including optical, pharmacological and surgical strategies, for precise control of myopia. The goal of such treatment methods is to reduce both personal and societal burden, as well as prevent disease progression such as worsening refractions, axial length and overall ocular health.

## 2. Treatment of myopia

### 2.1 Optical management

#### *2.1.1 Spectacle correction*

While potential optical strategies are investigated for adequate myopia control, the visual outcomes of Single Vision Lenses (SVLs) are used as control for efficacy comparison. Single vision lenses (SVLs) have universally been utilized by ophthalmologists and optometrists for correction of refractive error. With periodic monitoring, the spectacle prescription is often adjusted to correct the increasing refractive error. The growth of the eye is regulated by visual signals, which are manipulated and controlled by the power of the spectacle lens [5]. By regulating the refractive error of the cornea and the axial length of the eye, SVLs emulate the eye's innate process of emmetropization by allowing the eye to focus the rays on the retina [5, 12].

While visual outcomes are improved, SVLs do not interrupt the myopia progression or axial length elongation. Though clinically insignificant, evidence from animal studies suggest compensatory eye growth in spectacle induced emmetropization [13, 14]. Since SVLs alter the refractive error but does not reduce progression or axial elongation, studies have investigated on alternate optical correction methods, such as under-correction of refractive error.

Animal studies have postulated that under-correction of the refractive error reduces the mean change in refractive error, in comparison to fully-corrected SVLs. Hence, some clinicians advocate for under-corrected SVLs in an attempt to reduce the axial growth and prevent further myopia progression. It is theorized that modest under-correction of SVLs by 0.5–0.75D reduces the accommodative stimulus and consequently the blur drive for near work accommodation [15, 16]. However, studies have demonstrated contradicting results.

The pilot randomized study performed by Chung et al. compared the effects of under correction versus full correction on Hong Kong Chinese children. The study demonstrated that myopia progression was slightly greater in patients with under-correction in comparison to full correction, with 0.5 and 0.35D, respectively [17]. Similar results were obtained by study conducted by Adler et al., which showed 0.66 versus 0.55D for patients with under-correction and full correction, respectively [18]. Both studies concluded that myopic defocus through under-correction slightly increased the rate of myopia progression. While SVLs attend to the refractive error and vision complaints of the child, it does not have a protective role on the health and growth of the eye.

As an alternative to SVLs, multifocal lenses have gained popularity for use in slowing or halting the progression of myopia and axial elongation of the eye. It

is believed that these lenses decrease the rate of myopia progression by reducing accommodation effort and hyperopic defocus. A relatively newer version of the multifocal lenses is Progressive Addition Lenses (PALs). The Correction of Myopia Evaluation Trial (COMET) study is the largest double randomized, double masked clinical trial that evaluates the effect of PALs versus SVLs on the progression of myopia in children. Although clinically insignificant, the study revealed decreased mean increase of myopia in children treated with PALs, compared to children with SVLs [13, 19].

A similar study conducted by Hasebe et al. investigated the effects of PALs versus SVLs on slowing the progression of myopia using a crossover design, which switches the spectacle type at the half of the study. At the end of this 3-year study period, progression was less in the group wearing PALs first than the group with SVLs first. The study concludes that early intervention with PALs is more effective that SVLs in controlling myopia, slowing progression and halting axial elongation of the eye [20]. Several other statistically significant, but clinically insignificant, studies have explored the use of PALs compared to SVLs for slowing the progression of myopia [21–23]. With more large population and long duration studies, the studies can achieve statistical and clinical significance in preventing myopia progression and axial elongation.

Myovision lenses appear similar to SVLs, but they are a newer design of spectacles that correct central and side vision that are experimented on many myopic Asian pediatric populations. The mechanism of these spectacles is to reduce the peripheral hyperopia and prevent myopia progression. These lenses resemble SVLs in appearance, are comfortable to wear and easy to adapt to the young population [24]. Similar studies with MyoVision lenses on Japanese children, which reveal an insignificant difference between the effect of MyoVision lenses and SVL wearers on spherical equivalent refraction and axial elongation of the eye [25].

At this early stage of exploration, the efficacy of MyoVision lenses are not yet fully understood or proven. With additional studies that can reduce peripheral hyperopic defocus more effectively, there is more potential for reduction of myopia progression and axial elongation.

### *2.1.2 Contact lens correction*

Majority of the myopic population advocate for contact lenses are from the adult population, as it produces cosmetic benefits in addition to functional improvement of the vision and their quality of life. However, contact lenses, such as rigid gas permeable contact lens, have also been utilized in the pediatric population to retard myopia progression and decrease axial elongation.

Rigid gas permeable contact lenses have been shown to retard myopia progression in studies such as, The Contact Lens and Myopia Progression (CLAMP), which explored the progression of myopia in rigid gas permeable contact lens wearers versus soft lens controls. The CLAMP study reported that in 2 years the myopia progression was less in rigid gas permeable wearers (−1.56 ± 0.95D) than in soft contact lens wearers (−2.19 ± 0.89D) [11, 26]. Numerous other studies have demonstrated that the provisional decrease in myopia progression in rigid gas permeable contact lens wearers in comparison to other treatment groups, was a consequence of flattening of the cornea, and not the axial length of the eye [26–28].

Soft bifocal contact lens has demonstrated slowing of myopia progression by reducing the accommodation effort and halting axial elongation [29]. These lenses are designed with power for distance in the center and additional power in the periphery, or inversely, which corrects central myopia and reduces relative peripheral hyperopia. A study conducted by Walline et al. compared the effects of soft

multifocal contact lenses with single vision lenses, and reported that the average myopic progression at 2 years was 0.41 ± 0.03D for the single-vision contact lens wearers and 0.29 ± 0.03D for the soft multifocal contact lens wearers [29]. While the study produced statistically significant results, it was clinically insignificant.

Using a contralateral eye study design, Anstice et al. demonstrated that the eye wearing soft bifocal contact lens have a slower axial elongation in comparison to the eye wearing soft single vision contact lens. However, this was not clinically significant [30].

There is much potential for soft bifocal contact lenses to reduce myopic progression and axial elongation, which can be achieved with future large-scale studies that explore the mechanism of myopic control through reduced accommodation effort and studies that compare the effectiveness of soft bifocal contact lens with other modes of optical control of myopia.

Orthokeratology is a technique used in the reduction of myopia by flattening the cornea by the rigid orthokeratology contact lenses. The pattern of lens wear in this correction technique allows for the correction of myopia for short periods of time. The lenses are worn overnight to temporarily alter the corneal shape by corneal thinning, are removed during the day when the visual acuity would be improved temporarily [31]. The Berkeley Orthokeratology study demonstrated a significantly greater reduction of myopia in orthokeratology contact lens wearers, in comparison to a control group. However, the study was not clinically significant [9, 32].

The Longitudinal Orthokeratology Research in Children study was explored the effects of Orthokeratology contact lenses worn for 2 years on children in Hong Kong. At the study end, the there was a significant difference in the axial length between the lens wearers and the control group, 0.29 and 0.54 mm, respectively. The study was not clinically significant, represents the need for large scale studies to achieve clinical and statistical significance [31, 33].

With additional studies that can reduce peripheral hyperopic defocus more effectively, there is more potential for reduction of myopia progression and axial elongation.

## 2.2 Pharmacological management

### *2.2.1 Atropine*

Atropine is a non-selective muscarinic antagonist that has been the most effective in slowing the progression of myopia. One theory for the mechanism of atropine is the role of scleral remodeling in myopia and axial elongation. The expression of the muscarinic receptors (mAChRs) results in the proliferation of fibroblasts in the scleral collagenous matrix, which promotes scleral remodeling and ultimately axial elongation [34]. Some axial elongation induced morphological scleral changes include lamellar arrangement of collagen fibers in myopic eyes rather than the tight interwoven collagen fibers in emmetropic eyes, the reduction in fibril diameter, a dispersed range of fibril diameters, and an increased number of abnormal fibrils represent are representations [35, 36]. It is theorized that atropine receptor blockage interrupts scleral fibroblast proliferation and consequential axial elongation of the eye. Although the mechanism of atropine remains obscure, there are several working theories on the action and effect of this drug on myopia progression and axial elongation.

The Atropine in the Treatment of Myopia (ATOM) study was conducted from 1999 to 2004, which explored the effect of atropine 1% instilled nightly in children in Singapore for 2 years. The study contained two phases: a 2-year treatment phase and a 1-year washout phase. At the end of the 2-year study period, there was a

77% reduction in myopia progression with an unaltered axial length, compared to the control [37, 38]. The study was originally conducted in Asia but was adopted by other countries due to its encouraging results [39–43]. Following a successful 2-year treatment phase, the patients displayed rebound phenomenon in the 1-year washout phase. During this phase, there was an increase in both refractive error and axial length [37, 38]. The instillation of topical atropine was generally tolerated with some short- and long-term side effects. Short-term side effects are red eyes, photophobia, dilatation, increased intraocular pressure and glaucoma, and long-term side effects include retinal vascular diseases and cataract formation [37, 38]. The ATOM study was proved highly effective in reducing the rate of axial elongation and myopia progression, but was associated with such expected side effects.

Following the ATOM1 study was a 5-year clinical trial, which investigates low-dose atropine on reducing the progression of myopia, and subsequently decreasing the side effects. ATOM2 participants were randomly assigned to receive 0.5, 0.1 or 0.01% concentration of atropine for 24 months, followed by a 1-year washout phase. The results of ATOM2 study reveals that 0.01% is a viable concentration for reducing myopia progression and increasing the safety profile [44, 45].

While both ATOM and ATOM2 studies display efficacy in reducing myopia progression, both studies reveal a dose-dependent rebound phenomenon during the washout period. More recently, The Low-Concentration Atropine for Myopia Progression (LAMP) study was conducted to evaluate the efficacy and safety of low concentrations of atropine eye drops including 0.05, 0.025 and 0.01% compared to a placebo. The LAMP study revealed that all three low concentrations of atropine reduce myopia without a discernable adverse effect on the visual quality of life, and 0.05% was the most effective in controlling the spherical equivalent progression and the axial elongation over the 1-year study period [46]. Numerous studies have compared the effect of atropine to other optical strategies, such as single vision lenses, multifocal lenses, rigid gas permeable contact lenses, and orthokeratology [47–49].

Combination studies have explored the effects of atropine and an optical correction for greater myopia control. Shih et al. demonstrated that multifocal lens wearers treated with 0.5% atropine have a greater reduction of axial elongation and myopia progression, compared to placebo group [50]. Atropine eye drops for the treatment of myopia control has gained wide popularity in Asian countries, and more recently it has been adopted by the Western countries as well. With further investigation and modification to the treatment regimen that evades rebound phenomenon, atropine has the potential to be the conventional treatment of myopia.

### *2.2.2 Pirenzepine*

Pirenzepine is a selective M1 muscarinic receptor antagonist with a similar mechanism as atropine in halting myopia progression and axial elongation. A study conducted by Siatkowski et al. developed a 2% pirenzepine gel that displayed great efficacy in reduction of refractive error compared to the placebo group. Additionally, the average axial length increase at 1 year was 0.19 mm for patients in pirenzepine treatment group compared to 0.23 mm for those in the placebo group. While the results are statistically significant, they are clinically insignificant [51]. The adverse events in patients treated with pirenzepine were mild to moderately severe and included mydriasis, erythema of eyelids and ocular itching [9, 51, 52]. Overall, the study displayed good safety and efficacy for use in myopia control. Future studies are warranted to compare the efficacy and safety of pirenzepine and atropine in slowing the progression of myopia and axial elongation. Atropine eye drops for the treatment of myopia control has gained wide popularity in Asian

countries, and more recently it has been adopted by the Western countries as well. With further investigation and modification to the treatment regimen that evades rebound phenomenon, atropine has the potential to be the conventional treatment of myopia.

*2.2.3 Anti-hypoxic drugs*

Anti-hypoxic drugs such as salidroside and formononetin have shown anti-hypoxic effects to treat scleral hypoxia in myopia [53, 54]. Scleral hypoxia, which is induced by Hypoxia-Inducible Factor-1α (HIF-1), triggers a signaling cascade for myofibroblast trans-differentiation leading to scleral extracellular collagenous matrix remodeling in progressing myopia [55]. Formononetin is known decrease HIF-1α, vascular endothelial growth factor (VEGF) and prolyl hydroxylase domain-2 (PHD-2), which are protective in hypoxia-induced retinal neovascularization [54]. Salidroside is protective against for hypoxia-induced cardiac apoptosis and pulmonary hypertension [56, 57].

In animal models with experimentally induced myopia, anti-hypoxic drugs down-regulated HIF-1α expression and the phosphorylation levels of eIF2α and mTOR to inhibit the development of form deprivation myopia, without affecting the normal ocular growth in guinea pigs [55]. Due to encouraging results in animal models, the use of anti-hypoxic drugs shows great potential for treatment of myopia in human eyes.

### 2.3 Surgical management

Surgeons have recently advocated for surgical intervention to halt the progression of myopia, axial elongation and weakening of the posterior sclera. Macular buckle surgery or posterior reinforcement (PSR) surgery is proven to be effective in reinforcing the weakened posterior sclera. A scleral buckle is used to apply direct mechanical force onto the posterior pole, which slows the axial elongation. Shen et al. documented significantly higher Best-Corrected Visual Acuity (BCVA) and lower refractive error in the group who underwent macular buckle surgery compared to the control group [58]. Additionally, patients who underwent PSR surgery have a shorter mean axial length and lower mean refractive error than the control group [59, 60].

Macular buckling surgery has also been used myopic macular hole with retinal detachment and posterior staphyloma, which displayed high reattachment rates and improved visual acuity [61, 62]. Recent studies have experimented with different buckle materials, shapes, techniques and other modifications for the best correction of myopia and its complications [63–65]. With more advanced techniques and modifications, the surgical technique can be utilized as conventional treatment of myopia to reduce myopia progression and axial elongation.

## 3. Conclusion

The global prevalence of myopia is in an increasing trend, with estimates of myopia and high myopia affecting nearly 5 billion and 1 billion people, respectively, in 2050 [1]. As a major public health concern, it is essential to develop interventions that sufficiently delay or stop the progression of myopia. Of the above discussed treatments, all have shown to reduce the progression of myopia, but atropine has been the most popular and effective in reducing progression and axial elongation. Despite the expected side effects, its rebound phenomenon and its obscure

mechanism, atropine has achieved global popularity. With changes in lifestyle, health education, government and other health systems, the importance and acceptance of myopia control will significantly diminish number of people affected. Additionally, the implementation of a conventional, safe and effective intervention for myopia control will significantly reduce the personal, societal and economic burden, and decrease the disease progression and the risk of future myopia-induced ocular complications.

## Conflict of interest

There are no financial conflicts of interest.

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## References


[1] Holden BA et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology. 2016;**123**(5):1036-1042

[2] Morgan IG et al. The epidemics of myopia: Aetiology and prevention. Progress in Retinal and Eye Research. 2018;**62**:134-149

[3] Cook RC, Glasscock RE. Refractive and ocular findings in the newborn. American Journal of Ophthalmology. 1951;**34**(10):1407-1413

[4] Goldschmidt E. Refraction in the newborn. Acta Ophthalmologica. 1969;**47**(3):570-578

[5] Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. Neuron. 2004;**43**(4):447-468

[6] Gordon RA, Donzis PB. Refractive development of the human eye. Archives of Ophthalmology. 1985;**103**(6):785-789

[7] Ehrlich DL et al. Infant emmetropization: Longitudinal changes in refraction components from nine to twenty months of age. Optometry and Vision Science. 1997;**74**(10):822-843

[8] Smith MJ, Walline JJ. Controlling myopia progression in children and adolescents. Adolescent Health, Medicine and Therapeutics. 2015;**6**:133-140

[9] Saw SM et al. Myopia: Attempts to arrest progression. The British Journal of Ophthalmology. 2002;**86**(11):1306-1311

[10] Myrowitz EH. Juvenile myopia progression, risk factors and interventions. Saudi journal of ophthalmology. 2012;**26**(3):293-297

[11] Walline JJ. Myopia control: A review. Eye Contact Lens. 2016;**42**(1):3-8

[12] Smith EL 3rd. Spectacle lenses and emmetropization: The role of optical defocus in regulating ocular development. Optometry and Vision Science. 1998;**75**(6):388-398

[13] Gwiazda J. Treatment options for myopia. Optometry and Vision Science: Official Publication of the American Academy of Optometry. 2009;**86**(6):624-628

[14] Hung LF, Crawford ML, Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. Nature Medicine. 1995;**1**(8):761-765

[15] Hung GK, Ciuffreda KJ. Quantitative analysis of the effect of near lens addition on accommodation and myopigenesis. Current Eye Research. 2000;**20**(4):293-312

[16] Curtin BJ, Jampol LM. The myopias: Basic science and clinical management. Harper & Row, 1985;**6**(2):132

[17] Chung K, Mohidin N, O'Leary DJ. Undercorrection of myopia enhances rather than inhibits myopia progression. Vision Research. 2002;**42**(22):2555-2559

[18] Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. Clinical & Experimental Optometry. 2006;**89**(5):315-321

[19] Gwiazda J et al. Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. Investigative Ophthalmology & Visual Science. 2011;**52**(5):2749-2757

[20] Hasebe S et al. Effect of progressive addition lenses on myopia progression in Japanese children: A prospective, randomized, double-masked, crossover trial. Investigative Ophthalmology & Visual Science. 2008;**49**(7):2781-2789

[21] Cheng D et al. Randomized trial of effect of bifocal and prismatic bifocal spectacles on myopic progression: Two-year results. Archives of Ophthalmology. 2010;**128**(1):12-19

[22] Fulk GW, Cyert LA, Parker DE. A randomized clinical trial of bifocal glasses for myopic children with esophoria: Results after 54 months. Optometry. 2002;**73**(8):470-476

[23] Yang Z et al. The effectiveness of progressive addition lenses on the progression of myopia in Chinese children. Ophthalmic & Physiological Optics. 2009;**29**(1):41-48

[24] Sankaridurg P et al. Spectacle lenses designed to reduce progression of myopia: 12-month results. Optometry and Vision Science: Official Publication of the American Academy of Optometry. 2010;**87**(9):631-641

[25] Kanda H et al. Effect of spectacle lenses designed to reduce relative peripheral hyperopia on myopia progression in Japanese children: A 2-year multicenter randomized controlled trial. Japanese Journal of Ophthalmology. 2018;**62**(5):537-543

[26] Walline JJ et al. The contact lens and myopia progression (CLAMP) study: Design and baseline data. Optometry and Vision Science. 2001;**78**(4):223-233

[27] Grosvenor T et al. Rigid gas-permeable contact lenses for myopia control: Effects of discontinuation of lens wear. Optometry and Vision Science. 1991;**68**(5):385-389

[28] Khoo CY, Chong J, Rajan U. A 3-year study on the effect of RGP contact lenses on myopic children. Singapore Medical Journal. 1999;**40**(4):230-237

[29] Walline JJ et al. Multifocal contact lens myopia control. Optometry and Vision Science. 2013;**90**(11):1207-1214

[30] Anstice NS, Phillips JR. Effect of dual-focus soft contact lens wear on axial myopia progression in children. Ophthalmology. 2011;**118**(6):1152-1161

[31] Leo SW, Young TL. An evidence-based update on myopia and interventions to retard its progression. Journal of AAPOS. 2011;**15**(2):181-189

[32] Polse KA et al. The berkeley orthokeratology study, Part II: Efficacy and duration. American Journal of Optometry and Physiological Optics. 1983;**60**(3):187-198

[33] Cho P, Cheung SW, Edwards M. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: A pilot study on refractive changes and myopic control. Current Eye Research. 2005;**30**(1):71-80

[34] Barathi VA, Weon SR, Beuerman RW. Expression of muscarinic receptors in human and mouse sclera and their role in the regulation of scleral fibroblasts proliferation. Molecular Vision. 2009;**15**:1277-1293

[35] Curtin BJ, Iwamoto T, Renaldo DP. Normal and staphylomatous sclera of high myopia. An electron microscopic study. Archives of Ophthalmology. 1979;**97**(5):912-915

[36] McBrien NA, Gentle A. Role of the sclera in the development and pathological complications of myopia. Progress in Retinal and Eye Research. 2003;**22**(3):307-338

[37] Lee CY et al. Effects of topical atropine on intraocular pressure and myopia progression: A prospective comparative study. BMC Ophthalmology. 2016;**16**:114

[38] Chua WH et al. Atropine for the treatment of childhood myopia. Ophthalmology. 2006;**113**(12):2285-2291

[39] Brodstein RS et al. The treatment of myopia with atropine and bifocals. A long-term prospective study. Ophthalmology. 1984;**91**(11):1373-1379

[40] Li SM et al. Atropine slows myopia progression more in Asian than white children by meta-analysis. Optometry and Vision Science. 2014;**91**(3):342-350

[41] Clark TY, Clark RA. Atropine 0.01% eyedrops significantly reduce the progression of childhood myopia. Journal of Ocular Pharmacology and Therapeutics. 2015;**31**(9):541-545

[42] Kothari M, Rathod V. Efficacy of 1% atropine eye drops in retarding progressive axial myopia in Indian eyes. Indian Journal of Ophthalmology. 2017;**65**(11):1178-1181

[43] Polling JR et al. Effectiveness study of atropine for progressive myopia in Europeans. Eye (London, England). 2016;**30**(7):998-1004

[44] Chia A et al. Atropine for the treatment of childhood myopia: Safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the treatment of myopia 2). Ophthalmology. 2012;**119**(2):347-354

[45] Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2: Myopia control with atropine 0.01% eyedrops. Ophthalmology. 2016;**123**(2):391-399

[46] Yam JC et al. Low-Concentration Atropine for Myopia Progression (LAMP) Study: A randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. Ophthalmology. 2019;**126**(1):113-124

[47] Hsiao CK et al. Design and statistical analysis for the myopia intervention trial in Taiwan. In: Myopia Updates II. Tokyo: Springer Japan; 2000

[48] Lin H-J et al. Overnight orthokeratology is comparable with atropine in controlling myopia. BMC Ophthalmology. 2014;**14**(1):40

[49] Wan L, Wei CC, Chen CS, et al. The Synergistic effects of orthokeratology and atropine in slowing the progression of myopia. Journal of Clinical Medicine. 2018;**7**(9):259

[50] Shih YF et al. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. Acta Ophthalmologica Scandinavica. 2001;**79**(3):233-236

[51] Siatkowski RM et al. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: A 1-year, multicenter, double-masked, placebo-controlled parallel study. Archives of Ophthalmology. 2004;**122**(11):1667-1674

[52] Truong HT et al. Pirenzepine affects scleral metabolic changes in myopia through a non-toxic mechanism. Experimental Eye Research. 2002;**74**(1):103-111

[53] Xu ZW et al. SILAC-based proteomic analysis reveals that salidroside antagonizes cobalt chloride-induced hypoxic effects by restoring the tricarboxylic acid cycle in cardiomyocytes. Journal of Proteomics. 2016;**130**:211-220

[54] Wu J et al. Formononetin, an active compound of Astragalus membranaceus (Fisch) Bunge, inhibits hypoxia-induced retinal neovascularization via the HIF-1alpha/VEGF signaling pathway. Drug Design, Development and Therapy. 2016;**10**:3071-3081

[55] Wu H et al. Scleral hypoxia is a target for myopia control. Proceedings of the National Academy of Sciences of the United States of America. 2018;**115**(30):E7091-e7100

[56] Lai MC et al. Protective effect of salidroside on cardiac apoptosis in mice with chronic intermittent hypoxia. International Journal of Cardiologyl. 2014;**174**(3):565-573

[57] Huang X et al. Salidroside attenuates chronic hypoxia-induced pulmonary hypertension via adenosine A2a receptor related mitochondria-dependent apoptosis pathway. Journal of Molecular and Cellular Cardiology. 2015;**82**:153-166

[58] Shen ZM et al. Posterior scleral reinforcement combined with patching therapy for pre-school children with unilateral high myopia. Graefe's Archive for Clinical and Experimental Ophthalmology. 2015;**253**(8):1391-1395

[59] Li X-J et al. Posterior scleral reinforcement for the treatment of pathological myopia. International journal of ophthalmology. 2016;**9**(4):580-584

[60] Liu XD, Lu JH, Chu RY. Long-term studies on clinical therapeutic efficiency of posterior scleral reinforcement surgery. Zhonghua Yan Ke Za Zhi. 2011;**47**(6):527-530

[61] Theodossiadis GP, Theodossiadis PG. The macular buckling procedure in the treatment of retinal detachment in highly myopic eyes with macular hole and posterior staphyloma: Mean follow-up of 15 years. Retina. 2005;**25**(3):285-289

[62] Sasoh M et al. Macular buckling for retinal detachment due to macular hole in highly myopic eyes with posterior staphyloma. Retina. 2000;**20**(5):445-449

[63] Parolini B et al. Indications and results of a new l-shaped macular buckle to support a posterior staphyloma in high myopia. Retina. 2015;**35**(12):2469-2482

[64] Devin F et al. T-shaped scleral buckle for macular detachments in high myopes. Retina. 2011;**31**(1):177-180

[65] Stirpe M et al. A new adjustable macular buckle designed for highly myopic eyes. Retina, 2012;**32**(7):1424-1427