Myopia and Mioret®

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Background

- Myopia, once simply considered a harmless refractive error, is nowadays approached as a complex multifactorial ocular disorder across all ethnicities with both genetic and environmental implications;
- Myopia traditionally progresses slowly and unpredictably with no visible signs;
- The World Health Organization estimates that 42% of vision impairment in the world is due to an uncorrected refractive error, with myopia as the leading cause[1]:
  - Thus, 1.44 billion people have myopia, equal to 22.6% of the world's population;

1. Bourne RR, Stevens GA, White RA, et al; Vision Loss Expert Group. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Health. 2013;1:e339-e349.

Myopia classification*

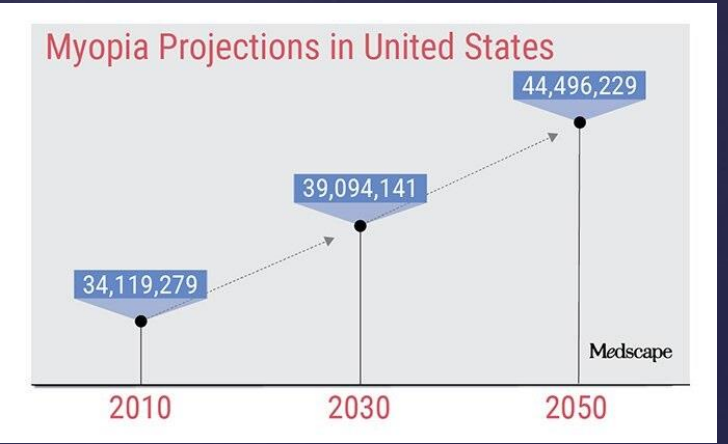
- Normal myopia:
  - usually associated with values below 5 negative diopters (D) or with eyeball axial length under 26 mm;
  - Classification:
    - Myopia: ≤ –0.50 diopter;
    - High Myopia: ≤ –5.00 diopter.

- Degenerative myopia:
  - *Sin.* Pathological myopia;
  - Continuous axial length prolongation and reduced scleral thickness;
  - Accompanied by retinal pigment epithelium (RPE) and choroidal atrophy;
  - Major cause of blindness worldwide due to complications (retinal detachment, macular choroidal degeneration, glaucoma and cataract);

* *2015 report of the joint World Health Organization and Brien Holden Vision Institute Global Scientific Meeting on Myopia. https://www.who.int/blindness/causes/MyopiaReportforWeb.pdf*

Myopia incidence is increasing worldwide

- In urban east Asia almost 90% of the students are nowadays nearsighted due to a 20% incidence increase in the last 50 years[1];
- Worldwide, the incidence has doubled in the last 25 years, thus more than 40% of the children are nearsighted[2];
- Moreover, half of the world's population is projected to be nearsighted by 2050[3];



1. Lin LL, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. Ann Acad Med Singapore. 2004;33:27-33.
2. Theophanous C, Modjtahedi BS, Batech M, Marlin DS, Luong TQ, Fong DS. Myopia prevalence and risk factors in children. Clin Ophthalmol. 2018;12:1581-1587.
3. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology. 2016;123:1036-1042

Is any rationale for this increase?

- This silent epidemic, that has no fully explanation to date, can be at least in part explained by the widespread sedentary behavior and the long-term use of computer, tablet and mobile phone since early childhood;

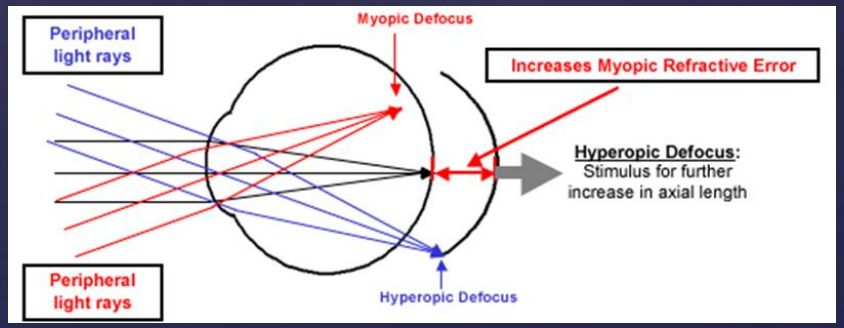
Environmental, Socioeconomic & Lifestyle Risk Factors of Myopia

- People growing up in an urban environment have a higher risk of myopia than people from rural regions[1];
- Prevalence of myopia increases with increasing years of education[2];
- Time spent outdoors is protective against incident myopia independently of physical activity level[3];
- Increased time spent on activities involving near vision might be associated with myopia in primary school children[4];

1. *Zhang M, Li L, Chen L et al. Population density and refractive error among Chinese children. Invest. Ophthalmol. Vis. Sci. 51(10), 4969–4976 (2010).*
2. *Dirani M, Shekar SN, Baird PN. The role of educational attainment in refraction: the Genes in Myopia (GEM) twin study. Invest. Ophthalmol. Vis. Sci. 49(2), 534–538 (2008).*
3. *Guggenheim JA, Northstone K, McMahon G et al. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. Invest. Ophthalmol. Vis. Sci. 53(6), 2856–2865 (2012).*
4. *Yingyong P. Risk factors for refractive errors in primary school children (6–12 years old) in Nakhon Pathom Province. J. Med. Assoc. Thai. 93(11), 1288–1293 (2010).*

What triggers myopia enhancement?

- Reading black text on white paper overstimulated retinal OFF pathways and the choroid becomes about 16 μm thinner in only one hour; The opposite is noted when reading white text on black paper[1].
- Retinal image defocus induced by intense near work, with fewer breaks, and sustained reading at distance less than 30 cm stimulates myopia enhancement[2];
- The lag of accommodation (deficit in the accommodative response) might trigger the growth of the posterior segment leading to axial elongation and myopia[3].



1. *Aleman, A., Wang, M. & Schaeffel, F. Reading and Myopia: Contrast Polarity Matters. Sci Rep 8, 10840 (2018).*
2. *Ibrahim F. Hepsen, Cem Evereklioglu, Huseyin Bayramlar- The effect of reading and near-work on the development of myopia in emmetropic boys: A prospective, controlled, three-year follow-up study. Vision Research 41. 2001, 2511-2520;*
3. *McBrien NA, Young TL, Pang CP, Hammond C, Baird P, Saw SM et al. Myopia: recent advances in molecular studies; prevalence, progression and risk factors; emmetropization; therapies; optical links; peripheral refraction; sclera and ocular growth; signalling cascades; and animal models. Optom Vis Sci 2009; 86: 45–66*

Myopia and genetics

- There are many evidences supporting a genetic implication especially in high myopia;
- Familial aggregation studies, heritability estimates, segregation analyses, linkage studies and genome-wide association studies (GWAS) have provided consistent data regarding the genetic basis of myopia:
  - Children with myopic parents may be predisposed to myopia because of inheriting factors[1];
  - There is a high heritability of refractive error endophenotypes, including AL, anterior chamber depth and corneal curvature[2];
  - A multifactorial mode of inheritance, including recessive, dominant and X-linked forms, has been revealed[3];
  - Stickler's syndrome, Wagner disease, Knobloch syndrome and Marfan syndrome have mutations involving syndromic myopia[4];
  - In linkage studies, many of the loci found for myopia apply to high myopia only[5];
  - Most loci identified from GWAS have only been for high myopia[6];
  - The possibility of multiple and varied gene–gene interactions contributing to refractive phenotypes is high;

1. *Zadnik K, Satariano WA, Mutti DO, Sholtz RI, Adams AJ. The effect of parental history of myopia on children's eye size. JAMA 271(17), 1323–1327 (1994).*
2. *Sanfilippo PG, Hewitt AW, Hammond CJ, Mackey DA. The heritability of ocular traits. Surv. Ophthalmol. 55(6), 561–583 (2010).*
3. *Klein AP, Duggal P, Lee KE, Klein R, Bailey-Wilson JE, Klein BE. Support for polygenic influences on ocular refractive error. Invest. Ophthalmol. Vis. Sci. 46(2), 442–446 (2005).*
4. *Hornbeak DM, Young TL. Myopia genetics: a review of current research and emerging trends. Curr. Opin. Ophthalmol. 20(5), 356–362 (2009).*
5. *Online Mendelian Inheritance in Man. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine*
6. *Verhoeven VJ, Hysi PG, Saw SM et al. Large scale international replication and meta-analysis study confirms association of the 15q14 locus with myopia. The CREAM consortium. Hum. Genet. 131(9), 1467–1480 (2012).*

Myopia and genetics

- Estimates of myopia prevalence in 7-year-old children :
  - 7.3% when neither parent is myopic;
  - 26.2% when one parent is myopic;
  - 45% when both parents are myopic;

Yap, M., Wu, M., Liu, Z.M., Lee, F.L. and Wang, S.H. (1993), Role of heredity in the genesis of myopia. Ophthalmic and Physiological Optics, 13: 316-319. doi:10.1111/j.1475-1313.1993.tb00479.x

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Myopia and oxidative stress

- oxidative stress plays a relevant role together with genetic and environmental factors[1];

- The antioxidant-oxidant status was recently evaluated in the aqueous humor samples collected from patients with myopia and healthy controls[2]:
  - total antioxidant capacity (TAC), oxidative stress parameters and total nitrite/nitrates were altered in myopic group, significantly in the aqueous humor of HM patients;
  - a significant correlation between oxidative stress with both VEGF and HGF in the same group of myopia patients was revealed;
  - Thus, oxidative stress might explain altered regulatory pathways in myopia;

1. *Bosch-Morell, F., Mérida, S., and Navea, A. (2015). Oxidative stress in myopia. Oxid. Med. Cell Longev. 2015:750637. doi: 10.1155/2015/750637*
2. *Mérida Salvador et al (2020). Imbalance Between Oxidative Stress and Growth Factors in Human High Myopia . Frontiers in Physiology vol 11, pg463*

Myopia and growth factors

- Transforming Growth Factor (TGF-β), basic Fibroblast Growth Factor (bFGF), and Insulin-like Growth Factor (IGF) focus on eye growth control deregulation[1];
- Genetic variants of cytokine Fibroblast Growth Factor 10 (FGF10) are associated with susceptibility to myopia and HM in young children[2];
- The connective tissue growth factor (CTGF) level is elevated in highly myopic eyes[3];
- Vascular Endothelial Growth Factor (VEGF) is responsible for choroidal neovascularization[4];

1. *Guo, L., Du, X., Lu, C., and Zhang, W. H. (2015). Association between insulin-like growth factor 1 gene rs12423791 or rs6214 polymorphisms and high myopia: a meta-analysis. PLoS One 10:e0129707. doi: 10.1371/journal.pone.0129707*
2. *Sun, W., Li, Y., Li, J., Zhang, X., Feng, Q., Zhang, Z., et al. (2019). Cytokine fibroblast growth factor 10 (FGF10) polymorphisms are associated with risk of myopia in young children. J. Cell. Biochem. 120, 15241–15247. doi: 10.1002/jcb.28790*
3. *Ding, X., Zhang, R., Zhang, S., Zhuang, H., and Xu, G. (2019). Differential expression of connective tissue growth factor and hepatocyte growth factor in the vitreous of patients with high myopia versus vitreomacular interface disease. BMC Ophthalmol. 19:25. doi: 10.1186/s12886-019-1041-1*
4. *Bosch-Morell, F., Mérida, S., and Navea, A. (2015). Oxidative stress in myopia. Oxid. Med. Cell Longev. 2015:750637. doi: 10.1155/2015/750637*

Myopia and OCT

- OCT technology has revealed many subtle changes, especially in highly myopic eyes:
  - A general reduction in retinal thickness within the horizontal central 80° as compared with non-myopic eyes;
  - The dome-shaped macula is the result of a localized variation in thickness of the sclera in the macular area;
  - The outer segment of the receptor layer (outer plexiform layer, myoid, and ellipsoid zones) was thickened with increased axial length;
  - The total thickness of the peripheral region is significantly less compared with emmetropic controls;
  - The choroid becomes very thin and even completely absent in time;
  - The density of choroidal vasculature and circulation is reduced;
  - Intrachoroidal cavitation (ICC) is typically located immediately inferior to the optic nerve in highly myopic eyes;

Cheng SC, Lam CS, Yap MK. Retinal thickness in myopic and non-myopic eyes. Ophthalmic Physiol Opt. 2010;30(6):776-784. doi:10.1111/j.1475-1313.2010.00788.x
Ng DS, Cheung CY, Luk FO, et al. Advances of optical coherence tomography in myopia and pathologic myopia. Eye (Lond). 2016;30(7):901-916. doi:10.1038/eye.2016.47

Myopia and OCT

- Choroidal thickness can be used as a biomarker for myopia progression, and also, the calculation of choroidal vascular index (CVI, the vessel-area-to-stromal-area ratio using a validated automated algorithm);
- OCT A monitors the choroidal vasculature and the foveal avascular zone;
- Newer UWF-OCT systems allow wider scans (100°) that accurately depict the staphyloma shape;

Hoang Q.V., Chua J., Ang M., Schmetterer L. (2020) Imaging in Myopia. In: Ang M., Wong T. (eds) Updates on Myopia. Springer, Singapore

Management of Myopia

- There are many options, with pros and cons:
  - Spectacles;
  - Contact lenses;
  - Overnight orthokeratology;
  - Surgery:
    - Laser refractive surgery
    - Radial keratotomy
    - Phakic intraocular lens (IOL) correction
    - Refractive lens exchange
    - Intraocular lens implantation

Myopia Complications

- Although high myopia carries the highest risk of complications and visual impairment, low and moderate myopia also have considerable risks*:
  - Retinal detachment;
  - Myopic macular degeneration (MMD):
    - Lacquer cracks;
    - Fuchs spot;
    - Choroidal neovascularization (CNV);
    - Chorioretinal atrophy;
    - Posterior staphyloma;
  - Glaucoma;
  - Cataract;

*Annechien E. G. Haarman, Clair A. Enthoven, J. Willem L. Tideman, Milly S. Tedja, Virginie J. M. Verhoeven, Caroline C. W. Klaver; The Complications of Myopia: A Review and Meta-Analysis. Invest. Ophthalmol. Vis. Sci. 2020;61(4):49. doi: https://doi.org/10.1167/iovs.61.4.49.

Can Myopia progression be prevented?

- Randomized controlled trials, including bifocal lenses, progressive additional lenses and contact lenses have failed to show major promise[1];
- 0.05% atropine was most effective in controlling spherical equivalent progression and axial length elongation over a period of 1 year[2];
- Increasing time outdoors[3]:
  - high natural light levels (containing violet light) is protective against myopia by the shorter wavelength itself and through the increased vitamin D production and the release of dopamine;

1. *Leo SW, Young TL. An evidence-based update on myopia and interventions to retard its progression. J. AAPOS 15(2), 181–189 (2011).*
2. *Yam JC, Jiang Y, Tang SM, 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. doi:10.1016/j.ophtha.2018.05.029*
3. *Sherwin JC, Reacher MH, Keogh RH, Khawaja AP, Mackey DA, Foster PJ. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. Ophthalmology 119(10), 2141–2151 (2012).*

Myopia and the diet

- Vegetarian diets have an increased prevalence of refractive errors compared with omnivorous children[1];
- Energy intake, protein, fat, vitamins B1, B2 and C, phosphorus, iron and cholesterol can interfere with myopia[2];

1. *Niroula DR, Saha CG. Study on the refractive errors of school going children of Pokhara city in Nepal. Kathmandu Univ. Med. J. (KUMJ) 7(25), 67–72 (2009).*
2. *Edwards MH. Do variations in normal nutrition play a role in the development of myopia? Optom. Vis. Sci. 73(10), 638–643 (1996).*

Dietary supplementation in Myopia

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What is Mioret® ?

- Mioret® and Mioret Retard® are dietary supplements, produced by OFFITALIA;

- They promote normal microcirculation and protect cells from oxidative stress.
- Also, they have a toning effect on the eye and contribute to the maintenance of normal visual ability.

- The formulations are including:

  - HESPERIDIN
  - BLUEBERRY, titrated into ANTHOCYANOSIDES
  - MARIGOLD, titrated LUTEIN
  - RHODIOLA
  - VITAMIN E
  - ZINC.

INGREDIENTS

AVERAGE CONTENT	For 1 tablet	VNR % (*)
HESPERIDIN	150 mg	
BLUEBERRY e.s. Contribution in anthocyanosides	150 mg 1 mg	
RHODIOLA e.s. Contribution in salidroside	100 mg 1 mg	
MARIGOLD e.s. Contribution in luteina	100 mg 10 mg	
Vitamin E	30 mg	250
Zinc	10 mg	100

(* VNR Reference nutritional value)

" The product is glutine and lactose free".

http://www.offitalia.it/en/products/mioret-retard-tablets-supplement/

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Hesperidin

- Flavonoids have antioxidant properties, which can directly quench free radicals, inhibit enzymes of oxygen-reduction pathways and sequester transient metal cations;
- The bioflavonoid hesperidin is a specific flavonoid glycoside which is frequently found in oranges and lemons;
- Hesperidin:
  - has anti-inflammatory properties and significantly contributes to the intracellular antioxidant defense system;
  - Acts as a powerful agent against superoxide, singlet oxygen and hydroxyl radicals;
  - possesses highly potent properties in preventing striatal dopamine depletion;

Nones J, E Spohr TC, Gomes FC. Hesperidin, a flavone glycoside, as mediator of neuronal survival. Neurochemical Research. 2011 Oct;36(10):1776-1784. DOI: 10.1007/s11064-011-0493-3.

Anthocyanosides

- Have antioxidant, anti-inflammatory, neuroprotective and anti carcinogenic activity;

- Anthocyanosides:
  - promote rhodopsin synthesis and regeneration;
  - increase retinal blood flow and sensitivity;
  - improve visual acuity and dark adaptation;

Vorob'eva IV, Vorob'eva IV. Current data on the role of anthocyanosides and flavonoids in the treatment of eye diseases *Vestn Oftalmol*. 2015;131(5):104-110. doi:10.17116/oftalma20151315104-108

Peter H Canter,Edzard Ernst, Anthocyanosides of Vaccinium myrtillus (Bilberry) for Night Vision—A Systematic Review of Placebo-Controlled Trials THERAPEUTIC REVIEW| VOLUME 49, ISSUE 1, P38-50, JANUARY 01, 2004

Lutein

- Is a bioactive natural carotenoid extracted mainly from the petals of marigold, which have a lutein content 20 times higher than the leaves;

- Lutein:
  - is highly concentrated in the macula, cannot be synthesized and must be supplied in the diet;
  - protects the retina against oxidative stress and inflammation
  - Prevents / Improves age-related macular degeneration;

Buscemi S, Corleo D, Di Pace F, Petroni ML, Satriano A, Marchesini G. The Effect of Lutein on Eye and Extra-Eye Health. Nutrients. 2018;10(9):1321. Published 2018 Sep 18. doi:10.3390/nu10091321

Mei-Ling Peng, et al . Influence/impact of lutein complex (marigold flower and wolfberry) on visual function with early age-related macular degeneration subjects: A randomized clinical trial, Journal of Functional Foods, Volume 24,2016,Pages 122-130, ISSN 1756-4646,https://doi.org/10.1016/j.jff.2016.04.006.

Rhodiola

- Rhodiola rosea L. is a medicinal plant from the Crassulaceae family, with the main active substance salidroside, a phenylpropanoide;
- Rhodiola:
  - reduces general fatigue under certain stressful conditions;
  - has a potent antidepressant activity by inhibiting MAO A and B;

1. Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. Rhodiola rosea in stress induced fatigue--a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine. 2000;7(5):365-371. doi:10.1016/S0944-7113(00)80055-0

2. van Diermen D, Marston A, Bravo J, Reist M, Carrupt PA, Hostettmann K. Monoamine oxidase inhibition by Rhodiola rosea L. roots. J Ethnopharmacol. 2009;122(2):397-401. doi:10.1016/j.jep.2009.01.007

Vitamin E and Zinc

- Vitamin E, especially Alpha-tocopherol, is a powerful antioxidant;
- **Zinc** helps body absorb vitamin A and also plays an important role in the structure of proteins and cell membranes;

Rasmussen HM, Johnson EJ. Nutrients for the aging eye. Clin Interv Aging. 2013;8:741-748. doi:10.2147/CIA.S45399

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Conclusions…so far

- There are still many unresolved questions related to this complex multifactorial ocular disorder;
- To date, a low-dose formulation of atropine appears to be the most effective method in slowing the progression of myopia in children;
- Mioret ® and Mioret Retard ® might be considered as an adjunct in myopia controlling due to their complex formulation that provides consistent antioxidant and vasoprotective activity, and also dopamine modulation.

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