REVIEW ARTICLE

Preventing Myopia

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SUMMARY

Background: Nearsightedness (myopia) has become more common around the world recently, mainly because of changes in visual, educational, and recreational behavior. The question arises how the risk of myopia and its progression can be reduced. This would lessen the prevalence and severity of myopia and also lower the risk of secondary diseases that impair visual acuity.

Methods: The PubMed/Medline database was selectively searched for pertinent literature.

Results: The risk of myopia is lowered by exposure to daylight and increased by activities performed at short visual distances (close-up work). A person with little exposure to daylight has a fivefold risk of developing myopia, which can rise as high as a 16-fold risk if that person also performs close-up work. Two meta-analyses and a large randomized clinical trial from Asia have shown that the progression of myopia over two years of observation can be lessened by up to 0.71 diopters by the administration of atropine eye drops in a concentration that has practically no serious side effects. At higher doses, myopia progresses more severely than in the placebo group after the cessation of therapy. This is an off-label treatment. A weaker effect on progression has been shown for multifocal optical corrections that include both a distance correction and a correction for near vision.

Conclusion: Effective pharmacological and optical measures are now available to lessen the progression of myopia. The increasing prevalence of myopia should motivate pediatricians, parents, and schools to pay attention to risk factors such as close-up work and lack of daylight exposure, particularly in view of the increased use of digital media.

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Nearsightedness (myopia) is the most common visual disorder among young people. An excessively long eyeball *(Figure)* results in the focal point falling in front of the retina. Consequently, distant objects appear indistinct, while nearby objects appear sharp. Myopia is treated using concave glasses lenses or contact lenses and in selected cases can be corrected surgically. Surgery alters optical factors but not the length of the eyeball. Myopia usually begins at elementary school age, and progression usually ends after puberty. Continued progression after the age of 25 years is exceptional (1).

Methods

For the clinical part of this investigation, a search was performed in Medline/PubMed on February 13, 2017, with no limitations on date of publication. The MeSH terms used were "myopia" AND ["prevention and control" OR "atropine" OR "lenses" OR "sunlight"]. This resulted in 126 hits. Next, a text search was performed for "myopia control AND [atropine OR lenses OR sunlight]" in articles published on or after January 1, 2016. This yielded 40 additional hits.

Epidemiology

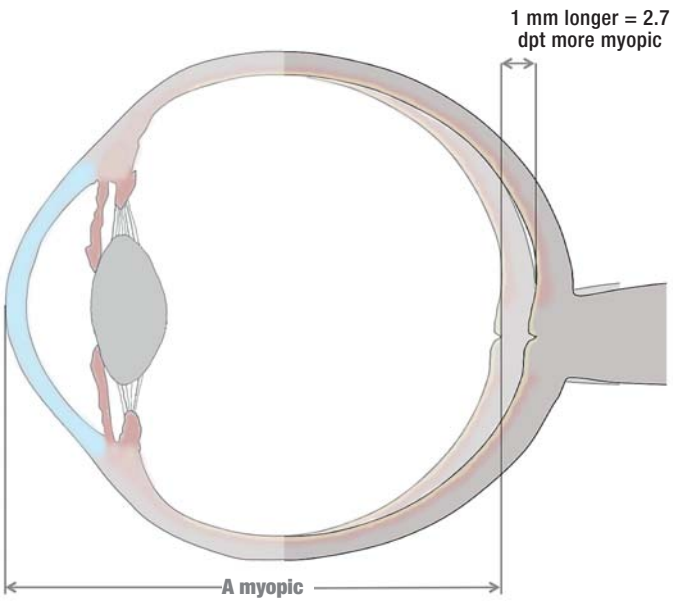
In 2015 it was reported in Nature that the prevalence of myopia in large Southeast Asian cities had risen from approximately 20% in the years after the Second World War to a current level of more than 80% (2). Such changes cannot be explained by genetic factors alone; rather, they must be interpreted simply as the remarkable ability of the visual system to adapt to altered environmental conditions, specifically a shift in visual habits from long to short distances and from open to enclosed spaces. In the same year, the European Eye Epidemiology (E3) consortium published prevalence figures indicating a clear increase in Europe too: 15% in those aged 75 years, 34% in those aged 50 years, and 46% in those aged 25 years (3). There are currently no European figures for children or adolescents that indicate a further increase.

In 2016, a meta-analysis was published predicting changes up to 2050 *(Table 1)*. Worldwide, the myopia rate is expected to be 50%; the proportion with high myopia (more severe than –6 diopters [dpt]) is estimated at 10%. The prevalence of myopia in western Europe in 2050 is expected to be 56% (4). The World Health Organization (WHO) lists myopia among the 5 eye disorders whose control is high-priority.

The biological mechanisms of myopia

Animal experiments have shown that fine control of increase in eyeball length is determined visually: If the

FIGURE



A myopic eye is longer than an emmetropic eye with normal vision: Myopia increases by 2.7 diopters (dpt) for each 1 mm increase in length

focal plane lies behind the retina (e.g. due to a diffusing lens), growth is accelerated, and myopia develops. These alterations in growth can also be triggered selectively in local areas of the visual field without intact accommodation and with no intact optic nerve. It appears that the retina can control the increase in eyeball length itself, by evaluating image sharpness alone (5). Various elements of biochemical signal cascades have been identified as playing a role in this control (6). Dopamine, which is released in the retina in line with image brightness, inhibits eyeball length increase (7). A dopamine antagonist blocked this inhibiting effect of bright light on myopia in chickens (8).

The probability of becoming nearsighted is also determined by one's genetic background. Nearsighted parents have a higher probability of having nearsighted children. The refractive error of monozygotic twins is highly correlated (9). Selective breeding for chickens that become either only slightly or very myopic results in a division into 2 populations after as little as 2 generations, one slightly and one very myopic (10). Genome-wide association studies (GWASs) have so far found more than 40 gene loci at which mutation contributes to increased risk of myopia, although each individual locus often only contributes a fraction of a percentage point (11). However, it has also been shown that the effect of visual behavior is several times greater than that of genotype (in one study, by a factor of 51.3 versus 7.2) (12).

Consequences of myopia

Initially patients are given optical aids so that they can see sharp images of objects at long distances. In the German health care system, the costs of these are only borne by insurers in exceptional cases. In Asia the costs of myopia are estimated at US$709 per person per year; optical aids account for 65% of this sum (13). In 2009 the worldwide cost of refractive errors was estimated at US$269 billion (14). An advantage of moderate myopia, at least, is that as accommodative ability declines with increasing age one can read at close range without glasses.

In adulthood, at least, myopia is the greatest risk factor other than age for a number of degenerative eye diseases. The cause of this is the tissue lengthening associated with myopia, particularly at the rear of the eye. This is one of the reasons reducing progression at an early age is an important goal of therapy. The population-based Rotterdam Eye Study showed that 2.3% of the adult population was severely visually impaired (sight in better eye less than 0.3). The risk of such visual impairment in those with myopia between –6 dpt and –10 dpt (1.8% of adults) was increased approximately threefold. In those with myopia more severe than –10 dpt (0.4% of adults), the risk of developing a degenerative eye disease was increased by a factor of as much as 22 (15). The most common cause of bilateral visual impairment, accounting for 39% of cases, was myopic macular degeneration; this was followed by cataract at 17% and glaucoma at 5%.

When optical coherence tomography is used to diagnose degenerative changes in the rear portion of the eye, it should be borne in mind that the sensitivity and specificity of this procedure is reduced in high myopia; this makes early detection of degenerative changes in the optic nerve more difficult (16).

The effects of environmental factors

As long ago as 1935, W. Duke-Elder wrote that, "The régime of modern schools imposes far too much application to books upon young children at an age when they require all their available vitality for physical growth and development." Almost 100 years later, digital media also require more close-up work.

A meta-analysis (17) of 19 cohort studies clearly showed the effect of a lack of light on the development of myopia. The standard illumination in indoor spaces is 500 lx, whereas outdoors illumination levels of 5000 lx on a cloudy day and 100 000 lx in sunlight can be measured. The US Orinda Study, one of those included in the meta-analysis, showed that in third-grade children the risk of developing myopia fell by around 10% within 5 years for every hour's exposure to daylight per week.

An Australian cohort study with 1344 participants aged 19 to 22 years found that the probability of myopia doubled if participants were exposed to less than 30 minutes' daylight per day. The objectivity of this research was enhanced by photographic analysis of sunlight-induced UV autofluorescence of the conjunctiva (18). Similarly, 2 clinical studies confirmed that seasonal variations in illumination had an effect: In Denmark, 235 children aged 8 to 14 years with myopia

were evaluated before and after a period of 6 months each. During this period, progression was 0.26 dpt in children with 2782 cumulative hours of daylight exposure and 0.32 dpt in children with 1681 hours (19).

In the USA, in 358 children with a mean age of 10 years progression was 0.35 dpt during the six months including winter and 0.14 dpt during the six months including summer (20).

In Taiwan, 571 children aged 7 to 11 years were randomized for behavior in school recess. Those in one study arm had to spend their recesses outdoors, and those in the other arm remained inside the school building. The first group spent 80 minutes more per day outdoors. Their risk of myopia fell by half after one year (21). Two comparable studies were conducted in schools in China: Of 1903 children aged 7 years, half were required to spend 40 minutes per day more than usual outdoors. Their risk of myopia fell from 40% to 30% in 3 years. In children with existing myopia, progression was 1.4 dpt in the intervention group and 1.6 dpt in the control group (22). A similar study of 3051 children with a mean age of 8 years found that 20 minutes' additional daylight exposure per day reduced the risk of myopia from 9% to 4% in one year and progression from 0.3 dpt per year to 0.1 dpt per year (23).

Lack of daylight is a greater risk factor for myopia than duration of close-up work: The Sydney Adolescent Vascular and Eye Study, a longitudinal cohort study with 5 years' follow-up, found that the likelihood ratio for myopia in children aged 6 years who had little outdoor time and large amounts of near-vision time was 15.9. With little outdoor time and little near-vision time, the ratio was 5.3. The control group consisted of children who spent large amounts of time outside and had little near-vision time (24). Multiple cohort studies, most recently the Gutenberg Health Study (25), have confirmed that the rate and severity of myopia are positively correlated with school and training qualifications.

TABLE 1

Prevalence of myopia by region

Region	Prevalence (%) at 3 points in time		
	2010	2030	2050
Asia-Pacific, high-income	29	58	66
Australasia	27	44	55
Caribbean	21	37	52
Central Africa	7	14	28
Central Asia	17	33	47
Central Europe	27	42	54
Central Latin America	27	42	55
East Africa	5	12	23
East Asia	47	57	65
Eastern Europe	25	39	50
North Africa and Middle East	23	39	52
North America, high-income	35	49	58
Oceania	7	13	24
South Asia	20	38	53
Southeast Asia	39	52	62
Southern Africa	8	18	30
Southern Latin America	23	41	53
Tropical Latin America	20	36	51
West Africa	7	14	27
Western Europe	29	45	56
Worldwide	**28**	**40**	**50**

Modified according to (4)

Pharmacological therapy

As early as 1874 it was reported that atropine eye drops inhibited the progression of myopia (26). However, until now there has been only one randomized, controlled clinical trial with sufficient statistical power: the Atropine in the Treatment of Myopia (ATOM) Study. This study, consisting of 2 sequential substudies and conducted in Singapore, tested 4 different doses over a 2-year observation period: In ATOM-1, placebo was compared to atropine 1% (one drop in the conjunctival sac every evening) in 346 children with a mean age of 9 years. In those receiving atropine, progression fell from 1.20 dpt to 0.28 dpt (27). ATOM-2 subsequently evaluated other concentrations of atropine (0.5%, 0.1%, and 0.01%) in 400 children with the same mean age. At these doses, progression was 0.30 dpt, 0.38 dpt, and 0.49 dpt respectively (28). Notably, one year after the end of treatment 0.01% remained the most effective dose, whereas the 3 higher doses showed a rebound effect: Progression was faster after the end of treatment than before treatment (29). One point to criticize is that the ATOM project consisted of 2 sequential studies, so the effect of atropine 0.01% was only compared with a historical and parallel placebo group; also, in ATOM-1 only one eye was treated, while in ATOM-2 both eyes were treated. No reduction in the effect of atropine over time was reported.

A 2014 meta-analysis includes 7 case series and 4 smaller clinical trials, excluding the ATOM study. It concludes that atropine drops reduce the progression of myopia by a mean of 0.55 dpt per year in Asian children and 0.35 dpt per year in Caucasian children (30).

In contrast to these positive effects, there are potential side effects such as glare caused by mydriasis and reduced visual acuity at short distances due to accommodative iridoplegia. Drops are therefore administered only once a day, at bedtime, so that any side effects occur during sleep. One small study concludes that side effects become significant at concentrations above 0.02% (31).

The ATOM-2 study reports a mean mydriasis of 1.1 mm and a reduction in accommodation of 4.9 dpt (normal accommodative power at this age is

TABLE 2

Effects of various interventions on myopia progression

Intervention	Mean difference in progression between intervention and placebo or multifocal glasses (dpt/year)	95% confidence interval of difference in progression (dpt/year)	p-value
Atropine 1%	0.68	[0.52; 0.84]	<0.0001
Atropine 0.1%	0.53	[0.26; 0.77]	<0.0001
Atropine 0.01%	0.53	[0.21; 0.85]	<0.0001
Cyclopentolate	0.33	[−0.02; 0.67]	0.06
Multifocal contact lenses	0.21	[−0.03; 0.48]	0.13
2 hours/day sunlight	0.14	[−0.17; 0.46]	0.39
Varifocal glasses	0.14	[0.02; 0.26]	0.02

Modified according to (40); dpt, diopters

approximately 15 dpt) after 2 years' treatment with atropine 0.01%. This is not clinically significant (28). The side effects of atropine 0.01% are thus mild, although some individual children continue to report visual disturbances during treatment. There is an urgent need for further randomized clinical trials in a Caucasian population to establish this treatment approach better so that evidence-based guidelines can be developed.

The mechanisms by which atropine inhibits the development of myopia are poorly understood. Atropine exhibits broadband binding to all muscarinic receptor subtypes (M1 to M5). In mammals, pupil constriction and near accommodation are controlled by the M3 receptor, so atropine triggers long-lasting cycloplegia very efficiently. In chickens, however, these functions are mediated by nicotinergic receptors, so accommodation and pupil reaction remain intact after atropine has been administered. Because atropine inhibits axial eye growth in chickens, the possibility of a role being played by accommodation can be ruled out (32).

However, inhibition of myopia generally requires much higher doses of atropine than would be expected from receptor binding curves. It is therefore suspected that atropine does not inhibit myopia by muscarinic mechanisms at all. Other factors that may be relevant include its binding to alpha-2 adrenergic receptors. Other agonists that bind primarily to alpha-2 adrenergic receptors inhibit myopia just as efficiently.

In addition, the chicken model showed that the myopia-inhibiting effect of atropine required availability of the gaseous transmitter nitric oxide (NO) in the retina: If the synthesis of nitric oxide is inhibited, atropine is no longer effective (33). Like dopamine, nitric oxide acts to signal light to the retina. Adrenergic receptors also control the activity of tyrosine hydroxylase, the key enzyme in dopamine synthesis, and thereby the dopamine level in the retina. As dopamine acts to signal light to the retina, atropine seems to signal light to the retina via both nitric oxide and dopamine (33).

Optical correction

Animal experiments have shown that increase in eyeball length is inhibited when the image falls in front of the retina and accelerated when it falls behind the retina. Because the retina controls the growth of the posterior pole of the eye throughout the visual field, peripheral visual acuity is also important (34). In contrast, accommodation is controlled almost exclusively by the fovea and moves the image as a whole over the entire visual field (35). Both these factors determine the sharpness of the image and explain why an absence of correction slows the development of myopia. In addition, where there are multiple simultaneous focal planes (as with multifocal contact lenses), the retina can determine the average position and adjust growth accordingly (36).

In 40 children aged 11 to 14 years with myopia, Anstice et al. found that multifocal contact lenses reduced progression from 0.7 dpt per year with normal contact lenses to 0.4 dpt per year (37). Lam et al. investigated 128 children aged 8 to 13 years with myopia. With monofocal contact lenses, progression was 0.4 dpt per year, while with multifocal contact lenses it was 0.3 dpt per year (38). Aller et al. reported progression of 0.8 dpt per year with standard contact lenses and 0.2 dpt per year with multifocal contact lenses in 86 children and adolescents aged 8 to 18 years with myopia (39). Controlled clinical trials with contact lenses provide solid evidence.

Summary

There is an observable increase in myopia worldwide. This is mainly due to changes in visual habits and light exposure. Asian countries are at the forefront of this change. In 2016, the publication of a meta-analysis on steps that might be taken to reduce the progression of myopia attracted a great deal of attention. It was based on research in Medline, EMBASE, the Cochrane Library, the WHO Registry, and the Clinical Trials database (40). Of a total of 2435 publications, 30 were identified as being suitable for analysis. The greatest effect found was for pharmacological intervention,

specifically atropine eye drops. *Table 2* summarizes the differences in progression for atropine eye drops versus standard glasses lenses and placebo treatments.

For clinical practice it should be remembered that atropine 0.01% eye drops are probably the most useful current way to reduce progression, but that this is a non-reimbursable, off-label treatment in Germany. The age up to which atropine eye drop treatment should be continued, the optimal length of treatment, and the nature of progression after the end of treatment are unknown. It also remains unproven whether atropine treatment may be useful as a prophylactic measure to prevent subsequent myopia, as has been shown for exposure to daylight.

KEY MESSAGES

- It is recommended that children be exposed to approximately 2 hours of daylight per day to prevent myopia.
- Progression of myopia can be reduced by administering atropine 0.01% eye drops as indicated and prescribed by the treating ophthalmologist. Effects must be monitored approximately every 6 months.
- If a child or adolescent wishes to wear contact lenses instead of glasses, multifocal, preferably PMMA ("hard") contact lenses can be considered. (PMMA lenses have a lower risk of infection than soft lenses.)
- There is an urgent need for further clinical trials conducted in Europe in order to add to current data, most of which comes from Asian populations.

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Conflict of interest statement
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