Myopia: A Review and Summary

Part 2: Pathogenesis and Pathophysiology – Complications of Myopia

Introduction

In the first part of this series, we looked at the epidemiology of myopia and some of the key statistics behind the condition. We also briefly touched on some of the potential causative factors behind the condition.

This article seeks to examine more deeply the pathophysiology of complications arising from progressive long-term myopia.

In part 1, we looked at the risk factors for myopia and briefly at the mechanisms suspected to be at play in globe elongation.
These mechanisms include:

1. Hyperopic Peripheral defocus blur.
2. Reduced lighting levels.
3. Accommodative lag or High AC/A ratio.
4. Binocular vision anomalies.
5. Prolonged accommodation.
6. Lack of outdoor time – various potential mechanisms.

Mechanisms of Myopisation

Hyperopic Peripheral defocus Blur

When a myopic refraction (or low hyperopic refraction) is corrected by a lens, the image shell centrally aligns with the Fovea / central retina. However, more peripherally, the image shell produces hyperopic defocus blur [1].

A mechanism not fully understood, which appears to be retinally driven, leads to globe elongation to bring these peripheral rays into focus. Of course, once the axial length increases, myopia increases (or hyperopia reduces) and at some point, new spectacles will be provided for the new refractive error. The same issue with image shell peripherally will occur and globe elongation will continue.

How exactly this mechanism is driven by the visual system is not fully known, but as explained in the previous article, experiments on mice showed that globe elongation continued even after the optic nerve was severed [2,3]. This suggests that some form of mechanism is driven by the retina, choroid, sclera or some combination of these and other systems. How this works is still not known.

Reduced lighting levels

Again, primarily from animal models, deprivation of daylight and higher levels of illumination produced globe elongation in several animal experiments. Ultimately, it appears that light can affect myopia development in one of three main ways:

- Luminance / illuminance levels
- Wavelengths incident on the eye
- Colour contrast

Animal studies have shown, for example, that even bright levels of artificial light can protect against experimental myopia development. [4,5]

Studies have shown that patterns of colour and illuminance levels play a role in altering the accommodative effort in children and the effect on emmetropisation [6].

Other studies showed retina to sclera signalling controlling ocular growth, as well as a range of genes which affect the predisposition to how much light affects growth of the eye [7].

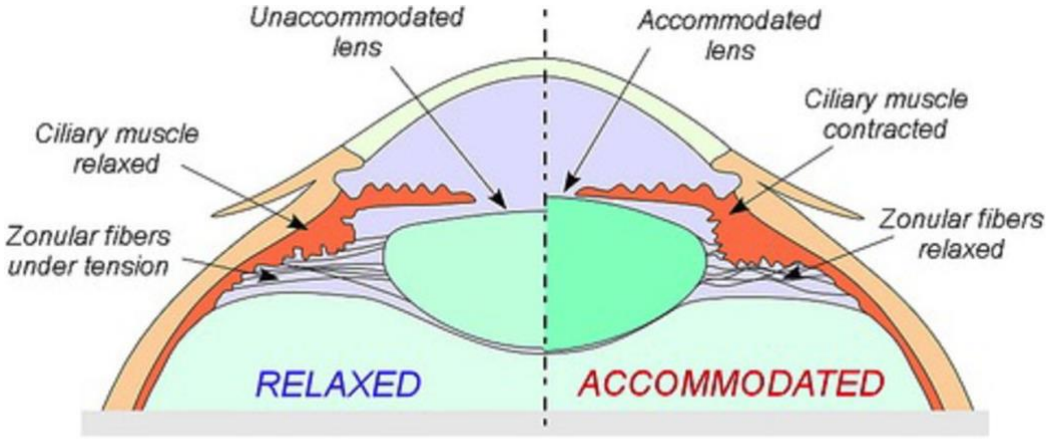
Many animal models, however, showed that deprivation of light, either totally, or almost totally, seemed to play a significant role in globe elongation. Why and how this caused globe elongation is not understood.

Accommodative lag or High AC/A ratio

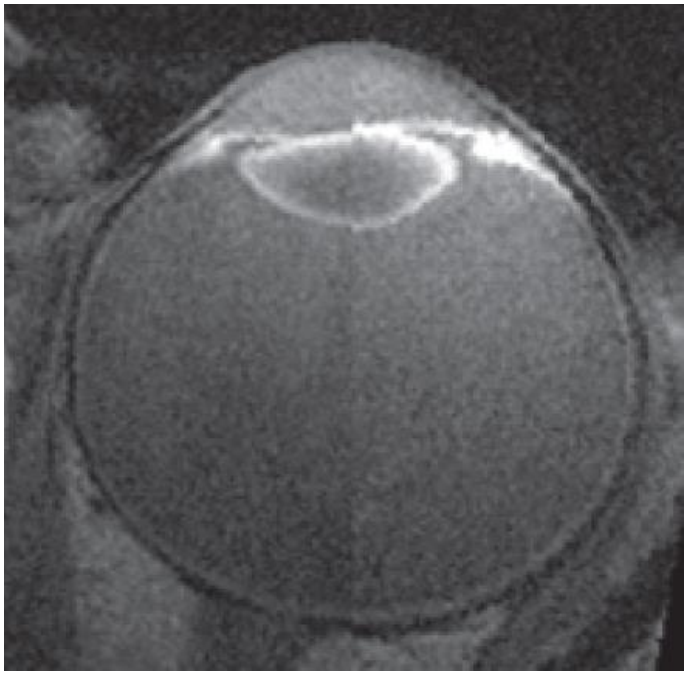
The overall mechanism of accommodation and associated vergence (as well as changes in pupil size) play a role in myopisation. However, it is not fully understood to what extent these mechanisms affect the rate and overall degree of myopia progression.

All theories regarding accommodation's effect on myopia rely on the Helmholtz model of accommodation (1855).

It is evident from many studies that a high AC/A ratio and high accommodative lag can lead to myopisation [8].



ACCOMMODATION IN THE NORMAL EYE



The Helmholtz theory of accommodation shown above and a split MRI scan showing the accommodated vs unaccommodated state in the same eye.

We've seen from peripheral hyperopic defocus blur how the retinal image quality can affect the tendency for the globe to grow as well. Retinal image quality will be worse in the distance as the pupil will be larger and therefore peripheral wavefront aberrations will be increased. In near work, the syncope of accommodation, convergence and pupil constriction take place. The smaller pupil will reduce the size and number of peripheral aberrations, yet it seems that these peripheral aberrations play a major role in myopisation.

However, very few studies have shown any significant differences between average pupil sizes in emmetropes and myopes in multiple visual states. These studies have some flaws, including primarily investigating adult populations, for example.

The nature of accommodation is also important it appears. Unstable and less accurate accommodation could be a cue for myopisation, or, to put it another way, a hinderance to emmetropisation [9]. Studies have shown myopes appear to have less stable and accurate accommodative mechanisms.

Also, recent studies in Chinese children have shown that when they play games on smartphones, they tend to hold the devices even closer than they would hold reading material. They do this for long periods and the accommodative (and convergence) effort is very high. This leads to higher levels of accommodative lag and could exacerbate myopisation [10].

One element of spending more time outdoors is that there will be less near work tasks performed and, even where they are, they tend to be at longer working distance, less concentrated (more lifting of the head to look in the distance), lower accommodative effort due to smaller pupils and higher contrast and generally shorter 'bursts' of accommodative effort.

Binocular vision anomalies

Blur sensitivity appears to be reduced in myopes, but only monocularly. In binocular conditions, this does not occur. Therefore, if there is a breakdown in binocularity, this blur sensitivity could reduce the emmetropisation cues.

Myopic children appear to have higher AC/A ratios too. This seems to be linked also to a higher accommodative lag. Therefore, accommodative instability and hyperopic defocus are more likely to occur in such circumstances.

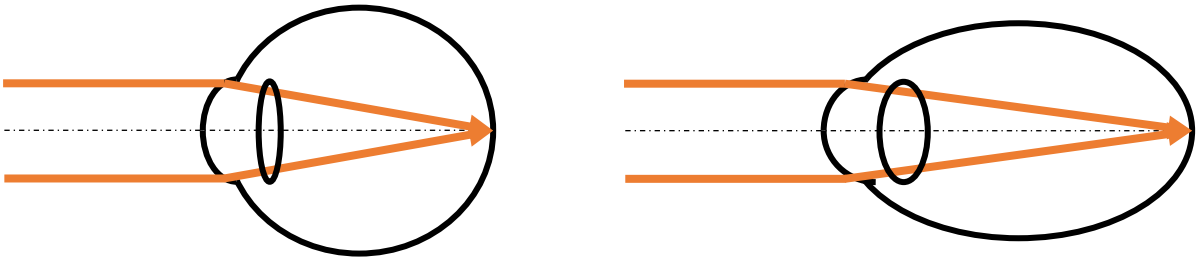
This also seems to lead to higher near esophoria in myopes. Apparently, where Ortho-K is used as a therapy in myopia management, the zone of clear binocular vision becomes more divergent, and accommodation improves with lower accommodative lag [11].

Prolonged Accommodation

During accommodation, there is transient increase in axial length (AL). The longer and higher the accommodative demand, the greater this transient increase in AL and the longer it takes for it to recoil once the accommodative effort ceases [12]. The choroid appears to play an important role in this recoil and it appears to be thinner in myopes. However, whether this is a cause of myopia, or due to higher myopia is unknown. Myopes have also been shown

to have thicker ciliary muscles. This may alter the forces imposed on the globe during accommodation.

Accommodation has been shown to reduce the equatorial globe 'height', resulting in a reflexive increase in AL to maintain globe volume.



RELAXED EYE ACCOMMODATING EYE

Lack of Outdoor Time

As already mentioned above, one logical effect of increased outdoor time is reduced near work, longer working distances, smaller pupil size and increased depth of focus, reduced accommodation and higher light levels reaching the retina. Higher light levels will also lead to improved contrast and reduced blur.

There are other theories as to why increased outdoor time is at least a protective mechanism against the onset of myopia. Some recent papers show that once myopia commences, outdoor time may have little or no effect on myopia progression

The other mechanisms which have been theorised include:

- Increased Vitamin D exposure
- Increased Dopamine levels
- Improved 'body clock' function through stimulation of Ganglion cell receptors (melanopsin)
- Increased violet light levels
- Favourable composition of light and higher average light intensities
- Temporal frequency of light exposure
- Other neurotransmitters involved in light mediated refractive error regulation: - Nitric Oxide, EGR-1 / ZENK, 5-HT (serotonin), GABA, Retinoic acid, etc.

Some sources are suggesting light therapy as a possible adjunct to myopia management treatments, but there is limited evidence to show its effectiveness at this stage [13].

Clinical Implications of Myopia - Complications

Whatever the causation of myopia, the potential for future ocular complications, particularly with high myopia are considerable.

These potential complications include:

- **Myopic Macular Degeneration (MMD)**
- **Glaucoma**
- **Retinal detachment**
- **Cataract**
- **Myopic Neo-vascularisation (MNV)**
- Lacquer cracks
- Posterior staphyloma
- Myopic choroidal atrophy
- Myopic traction maculopathy
- Myopic foveoschisis
- Myopic retinoschisis
- Dome shaped macula
- Myopic polypoidal choroidal vasculopathy (PCV)

In terms of the most common conditions, those highlighted in bold are most likely to occur.

MMD (Myopia Macular Degeneration) – the stretching effects of globe elongation clearly have a significant role to play in the pathogenesis of MMD. Also known as myopic choroidal atrophy, there are several definitions and classifications of this key comorbidity of high myopia. Avila et al[14] described five grades of myopic maculopathy. These were later updated by Tokoro[15] and, most recently, the Meta-PM classification of myopic maculopathy has been produced.

Myopic Maculopathy Meta-PM Classification

Meta-PM Classification	Visual Impairment	Pathologic Myopia Y/N?
Category		
Tessellated Fundus - Category 1	None	N
Diffuse Chorioretinal Atrophy - Category 2	Mild	Y
Patchy Chorioretinal Atrophy - Category 3	Parafoveal Scotoma	Y
Macular Atrophy - Category 4	Central Scotoma	Y
Plus Lesions		
Myopic MNV (including Fuch's Spots)	Central Scotoma, distorted vision	Y
Lacquer Cracks	Temporal scotoma owing to simple haemorrhage, distorted vision (in some cases)	Y

Modified from Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. Am J Ophthalmol. 2015; 159:877e883.

Many myopic fundi take on the classic ‘Tigroid’ appearance, also termed Tessellated fundus. This is primarily due to retinal thinning allowing choroidal features to show through.

Image 1 - ‘Tigroid’ Tessellated Fundus

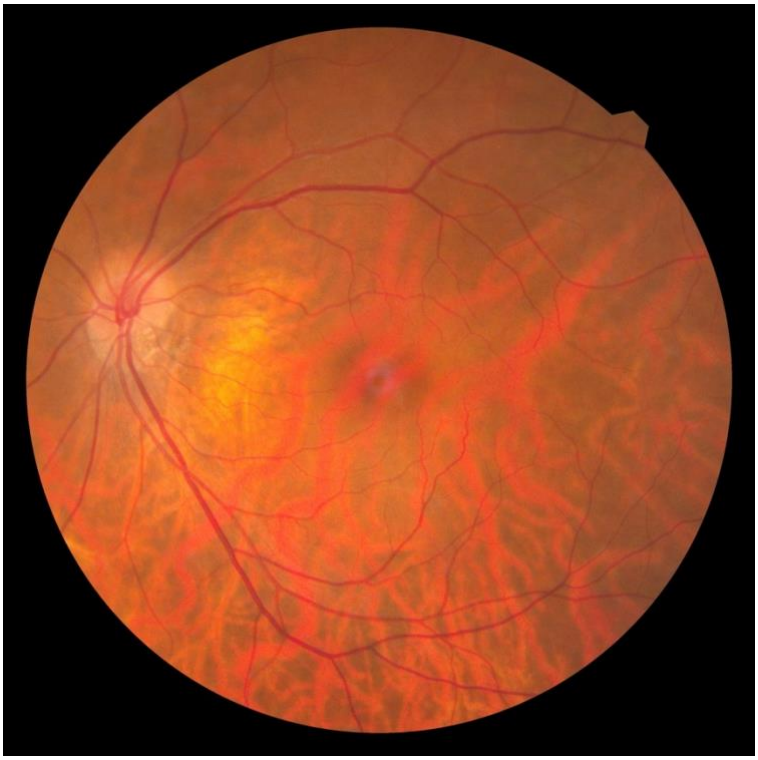


Image 2 - OCT B-Scan of Tessellated Fundus – notice choroidal thinning

In the B-Scan above, you can see there is significant choroidal thinning, which is extremely thinned near the disc. This can be seen on the colour fundus image as well, shown in *Image-1.*

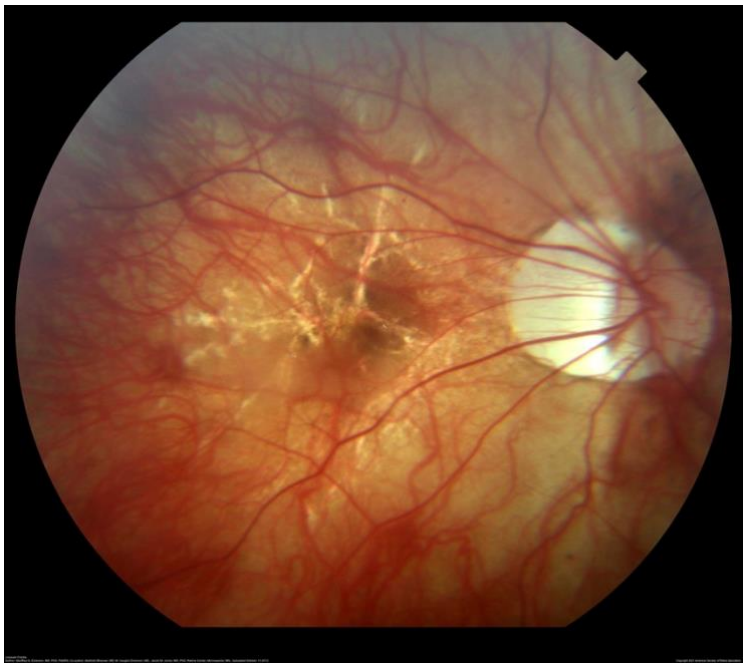


Image – 3. Fundus Image showing Lacquer Cracks in a right eye with marked scleral crescent and evident retinal thinning. (Courtesy of American Society of Retina Specialists).

Image – 4. Fundus Image showing myopic chorioretinal atrophy with Foster Fuch's spot and severe retinal / choroidal thinning and disc atrophy.

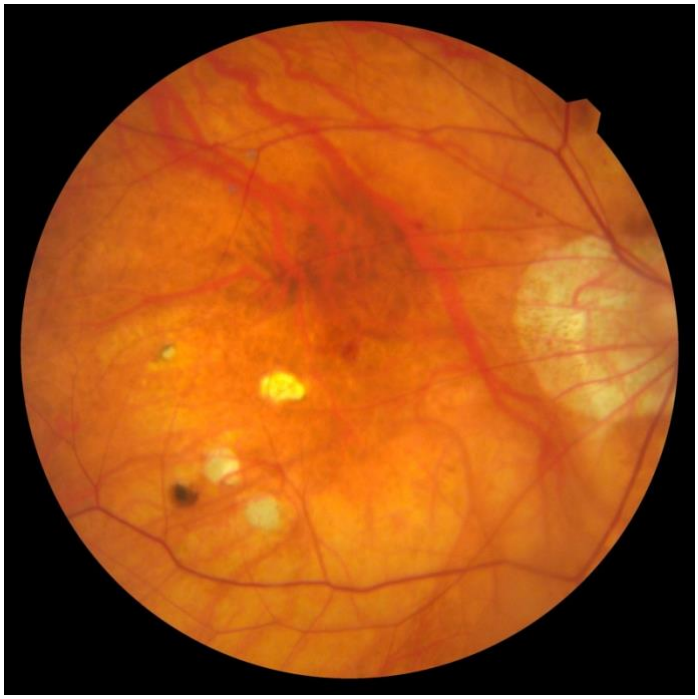
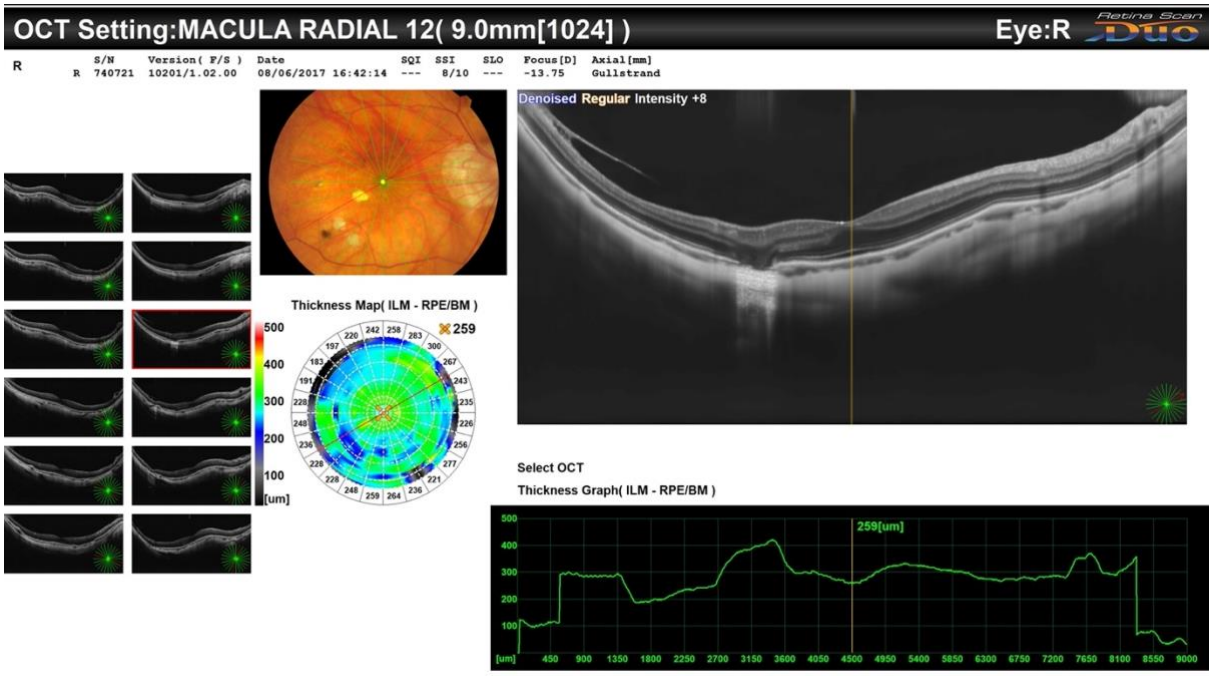


Image 5 – B-Scan of same eye as Image 4.

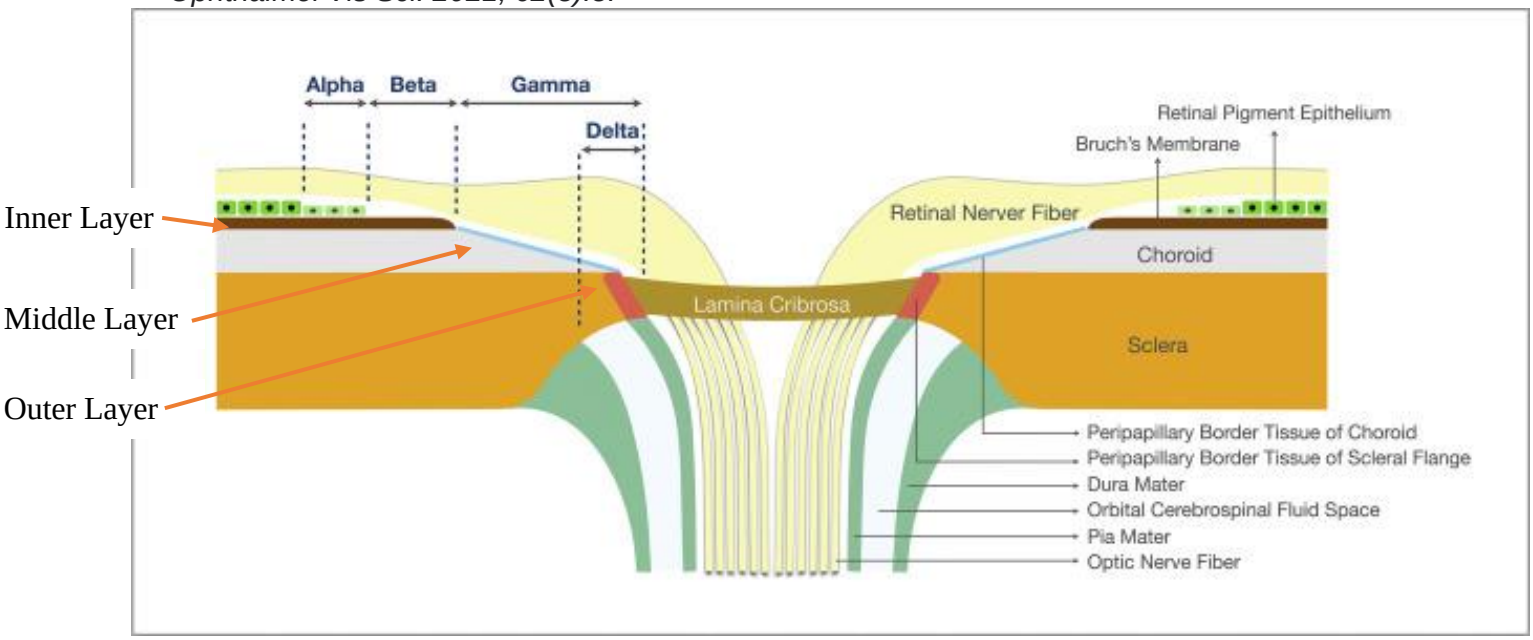


Images 4 and 5 show an eye with more advanced chorio-retinal atrophy from myopia. You can see atrophy patches and a Foster Fuch's spot. On the B-Scan, there is clear evidence of a window defect where the RPE is not present; ultimately this is classed as GA (geographic atrophy). You can also see remnants of an ERM (Epi-retinal membrane) on the left of the B-Scan image. It's evident just how traction can occur in such patients, leading to detachments or schisis.

Myopic Optic Neuropathy / Glaucoma – Many highly myopic patients show considerable amounts of optic disc atrophy and in many cases optic neuropathy – either resembling glaucoma or defined as glaucoma. Often this is not mentioned when people discuss myopic macula atrophy, but typically, optic nerve head damage coexists with myopic maculopathy. Studies have shown that the prevalence for glaucoma in myopes is the same as emmetropes until patients have myopia ≤-8.00D SER[16,17]. The causative factors for myopic glaucoma are many and the subject matter is huge, but we'll take a brief look at the morphological changes which seem to bring about a higher prevalence of glaucoma in very high myopes.

Looking at the normal morphology of the optic nerve head shown below in *Image 5,* you can see that there are multiple zones and tissue areas. We can consider the optic nerve head opening as three distinct layers as labelled, Bruch's membrane is the innermost layer, the Choroid is the middle layer and the Scleral flange opening with the lamina cribrosa is the outermost layer.

Morphology of the Optic Nerve Head *– Ohno-Matsui et al, IMI Pathologic Myopia Invest Ophthalmol Vis Sci. 2021; 62(5):5.*



Without going into too much detail, in myopic (non-highly myopic eyes) there tends to be a shift of the inner layer temporally, meaning that there is an overhang of Bruch's membrane nasally. This tends to lead to the development of an increased Gamma zone with absence of Bruch's membrane[18].
In high myopia, the increase in the Gamma zone is significant and as axial elongation occurs, it increases considerably.
Globe elongation leads to stretching and thinning of the lamina cribrosa, making it more susceptible to damage. Concurrently, these morphological changes alter the ratio between IOP anterior to the lamina cribrosa and the CSF (cerebro spinal fluid) pressure posterior to the lamina cribrosa. This leads to a steepening of the translaminar cribrosa pressure gradiant and this may be one of the leading causes of increased glaucoma risk in high myopes (≤-8.00D SER)[19,20,21].

Prevalence of Glaucomatous Optic Neuropathy (%)	Axial Length (mm)
12%	<26.5mm
28.5%	26.5-28.0mm
32.6%	28.0-29.0mm
36%	29.0-30.0mm
42.1%	>30.0mm

Globe elongation increases risk of myopic glaucoma considerably[22].

Retinal Detachment – It is well known that myopia increases the risk of rhegmatogneous retinal detachment, particularly post cataract surgery. However, high myopia also means that those suffering this comorbidity tend to be younger than non-high myopes, even post phaco-emulsification surgery[23].

Image 6 – Rhegmatogenous Retinal Detachment (Courtesy of American Society of Retina Specialists).

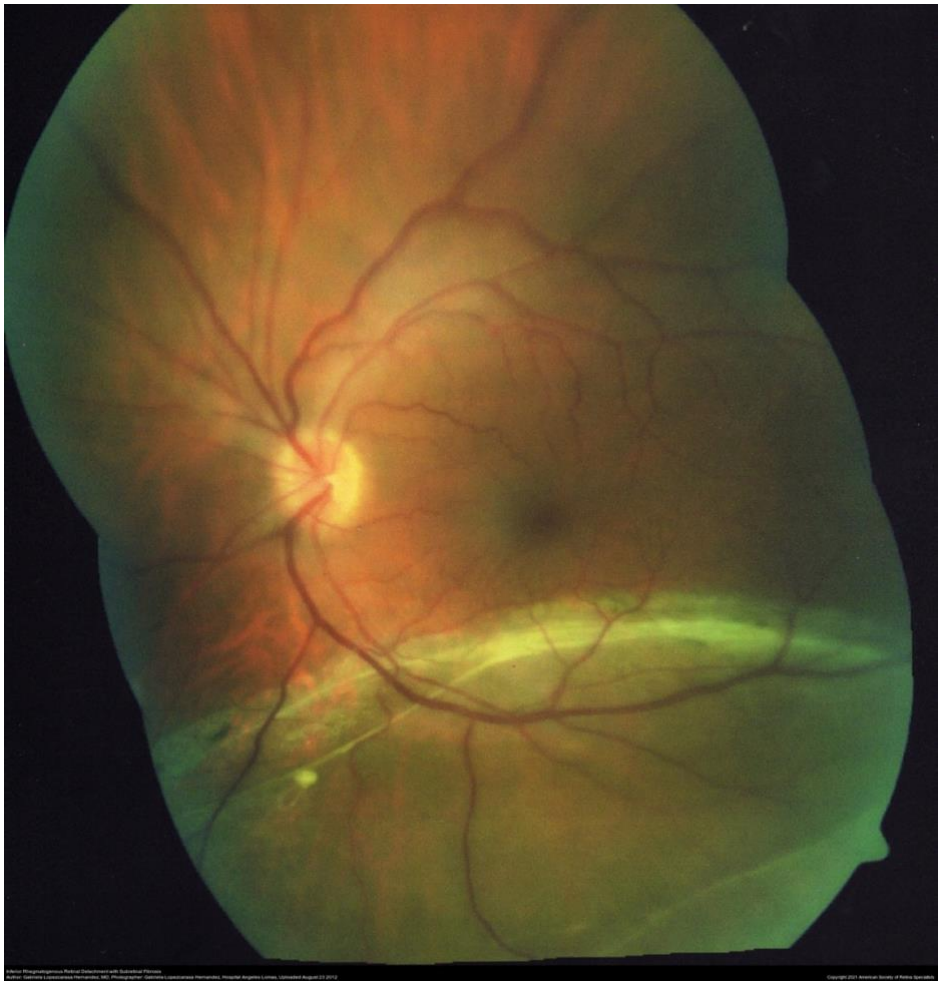
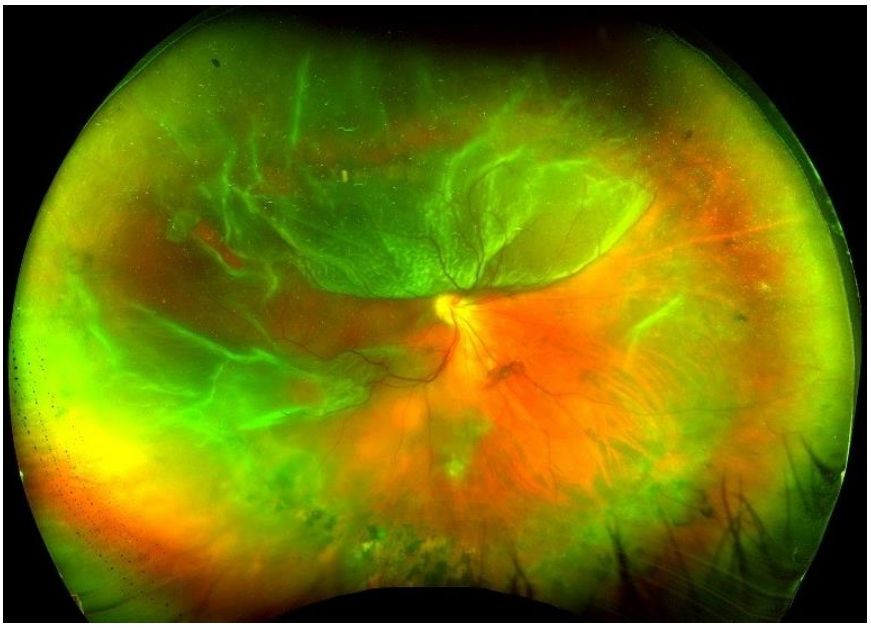


Image 7 – Rhegmatogenous Retinal Detachment (Courtesy of American Society of Retina Specialists).



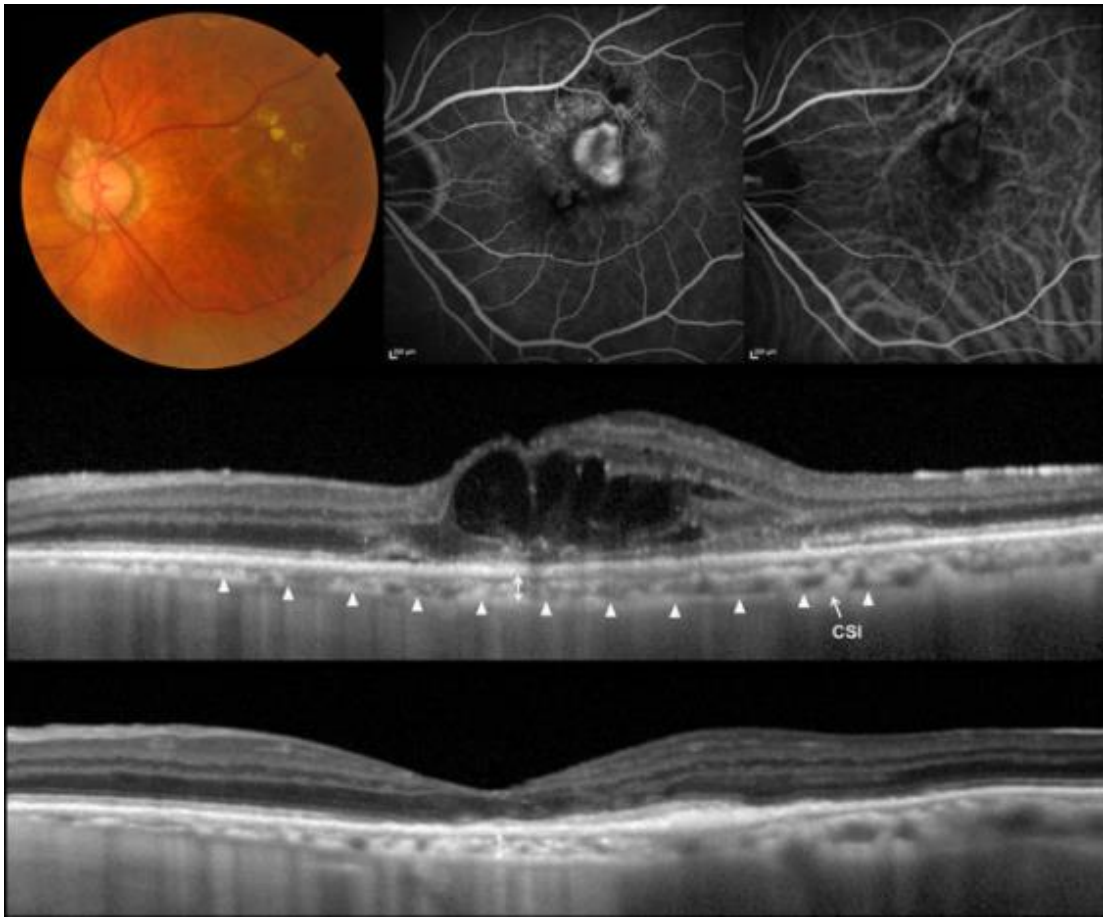
Cataract – this is another common pathology which has a higher prevalence in myopes and particularly high myopes. High myopia is the leading cause of pre-senile cataracts, followed by Diabetes[24].

Although cataract is normally considered an easily treatable cause of sight impairment, Phaco-emulsification surgery in myopes, and particularly in high myopes, is fraught with increased risks of complications[25].

Myopic Neovascularisation (MNV)

Myopic neovascularisation (MNV) is a form of choroidal neovascularisation (CNV) associated with high levels of myopia / pathologic myopia.
With the stretching of the globe, the choroid and retina are increasingly thinned and the transport mechanisms normally well managed by the RPE and Bruch's membrane are also affected. Essentially, some of the common long-term effects of ageing occur at an accelerated rate and are found in younger patients where they are highly myopic [26].

Ultimately, the exact cause is unknown, though some studies even suggest that those at a genetically higher risk of myopia have a natural tendency towards MNV and other studies suggest there are changes in the haemodynamic status of the choroid due to its morphological changes from globe stretching [27].



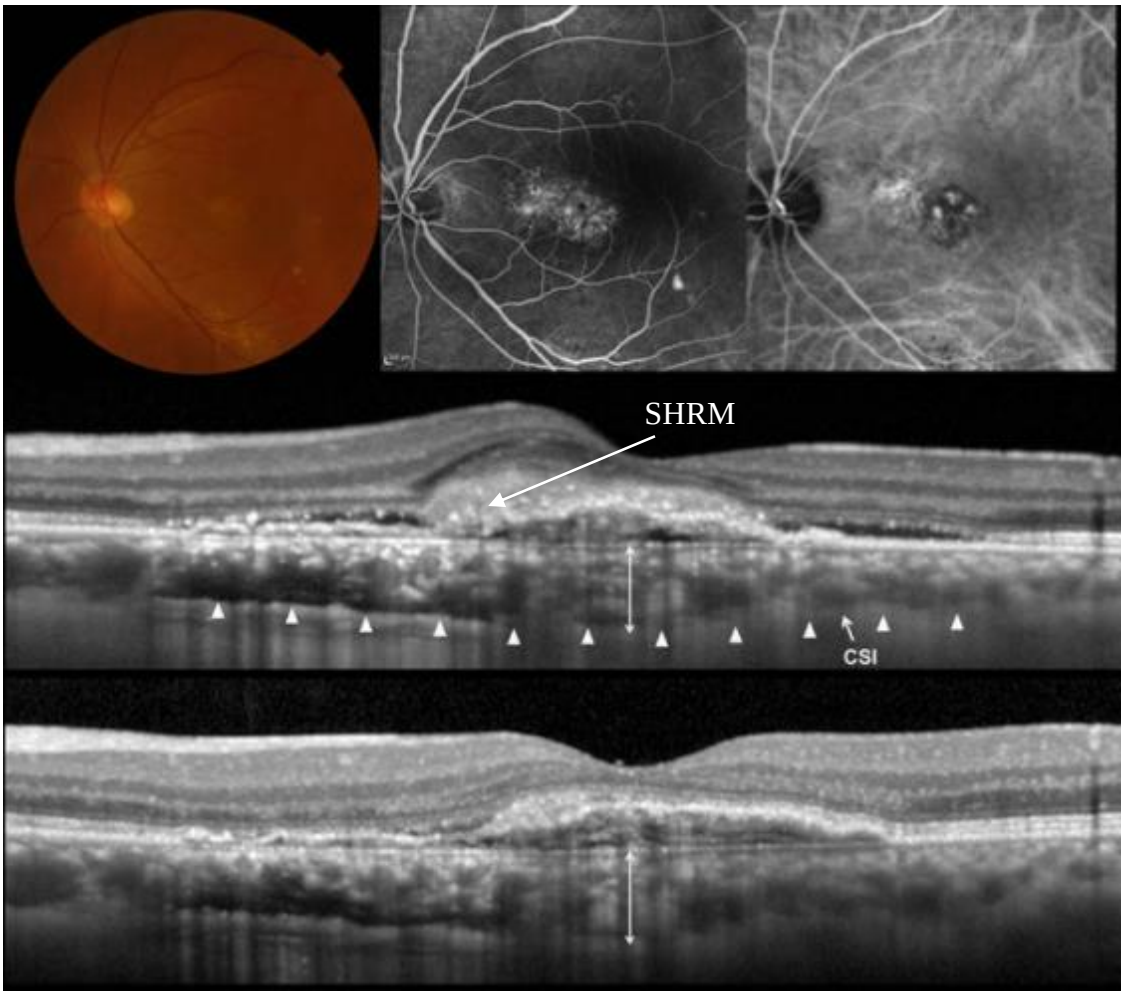
From Ellabban et al – Clinical Ophthalmology 2012:6 837-844

You can see from the image above that MNV can respond to anti-VEGF treatment and the lower B-Scan shows the result of such treatment. There is considerable thinning of the choroid as expected and loss of photoreceptors, but vision has been preserved centrally.

Polypoidal Choroidal Vasculopathy (PCV)

PCV is a fairly common term for a range of changes that exist in forms of maculopathy, including AMD, but also in conditions like MMD and even diabetic eye disease.

In some circumstances, it can present with very large empty PED (pigment epithelial detachments), but generally, there is a great deal of sub-retinal hyper reflective material (SHRM – often pronounced ‘shrem’).



This material builds up between the neuro-sensory retina and the RPE, hence the term ‘sub-retinal’. It is thought to be made up of a range of degenerative biproducts including fibrin, blood, fluid and fibrovascular tissue and it changes over time and post anti-VEGF treatment. Its presence may occur with GA (geographic atrophy) and can be a cause of significant visual loss. In the example image above (*courtesy of*

Ellabban et al – Clinical Ophthalmology 2012:6 837-844) we can see the 'before and after' images of PCV, with associated SHRM and the changes brought about by Lucentis injections. CSI represents the choroidal-scleral interface.

Summary

It is very evident that myopia, particularly high myopia, can lead to a range of sight threatening and severely sight threatening complications.
The pathogenesis of myopia is dependent on a complex and varied range of factors. Some of these factors can be altered simply by changing lifestyle and behaviour, whereas some elements can only be managed by specific optical appliances or only through altering genes.

Ultimately, myopia management therapies will be more effective if a combination of changes to lifestyle / behaviour and specific therapies (optical, pharmaceutical and morphological) takes place. Understanding the concepts and mechanisms at play will hopefully allow practitioners to better manage their patients.

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