

非手术的近视管理方法与脉络膜的研究进展

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摘要:近视形成机制极为复杂,近年来提出的“巩膜缺氧学说”认为巩膜缺氧、重塑可能是近视形成的关键因素,而脉络膜厚度及脉络膜血流变化可能在视网膜巩膜通路中发挥重要作用参与调节眼球生长。研究发现脉络膜变薄伴随着近视的发生和发展,而角膜塑形镜、阿托品滴眼液和环境光暴露等干预措施可增加脉络膜厚度,提示脉络膜增厚是近视进展的保护因素。因此,本文对近视与脉络膜的关系及近视的光学、药物和环境干预措施对脉络膜产生的变化进行综述,旨在更好地了解此类非手术的干预措施对脉络膜的影响。

关键词:近视;脉络膜厚度;脉络膜血流;干预措施

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Advancements in non-surgical management of myopia and choroidal research

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Abstract:The mechanisms of development of myopia are extremely complex. The “scleral hypoxia theory” proposed in recent years suggests that scleral hypoxia and remodeling may be a key factor in the development of myopia. Choroidal thickness and choroidal blood flow changes may play an important role in the retinal scleral pathway signaling and participate in the regulation of eyeball growth. Studies have shown choroidal thinning to be associated with the onset and development of myopia. Interventions such as orthokeratology, atropine eye drops and exposure to ambient light can increase choroidal thickness, suggesting that choroidal thickening is a protective factor for myopia progression. Therefore, this paper reviews the relationship between myopia and choroid, and the changes induced in the choroid by optical, drug and environmental interventions used for improvement of myopia, aiming to better understand the effects of such non-surgical interventions on choroid.

Key words: Myopia; Choroidal thickness; Choroidal blood flow; Intervention measure

预计 2050 年全球近视人口数量将达到 47.5 亿^[1]。随着近视发病年龄逐步低龄化,高度近视发生率大幅度增加,同时与近视相关的并发症(如青光眼、白内障、脉络膜新生血管等)发病率随之也上升^[2]。

脉络膜位于视网膜和巩膜之间,含有丰富的血管组织,除了能够为外层视网膜提供血液供应、调节眼部温度、分泌生长因子外,还可以参与调控视觉信号对眼屈光发育的影响^[3]。动物研究^[3]显示促进眼球生长及近视发生发展的环境因素可使脉络膜变薄,而近视的干预措施如使用角膜塑形镜和低浓度阿托品等可增加脉络膜的厚度,提示脉络膜增厚是近视的保护因素。目前,临床常用的近视干预措施

对脉络膜的影响尚未见系统综述。因此,本文对近视与脉络膜的关系及近视的光学、药物、环境干预措施对脉络膜的影响进行综述,以期更好地了解非手术近视管理方法对脉络膜产生的影响。

1 近视与脉络膜的关系

早期的动物研究表明^[4],脉络膜随着视网膜图像焦点的变化而变化,可通过调整自身厚度使视网膜移动形成清晰的图像。当暴露在近视离焦的环境时,眼球生长减慢,脉络膜迅速增厚。相反,当暴露在远视离焦的环境时,眼球生长增加,脉络膜迅速变薄^[5],在人眼中亦发现同样的规律^[6]。以上研究表

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明脉络膜可以调节眼球生长及正视化的进程。然而,正视化进程的加速将导致近视发生的可能。近视发生的机制极为复杂,目前尚未完全阐明。“巩膜缺氧重塑”学说认为一些视觉信号经视网膜色素上皮到达脉络膜血管丛而影响巩膜重塑,脉络膜厚度及脉络膜血流变化在此通路中可能发挥重要作用^[7]。多巴胺(dopamine, DA)^[8]、全反式维甲酸(all-trans retinoic acid, atRA)^[9]及腺苷(adenosine, Ado)^[10]等视网膜信号分子可影响脉络膜厚度,其中 DA 受体激动剂及 Ado 受体拮抗剂均可抑制眼轴生长,引起脉络膜增厚^[11-13]。atRA 在脉络膜产生并转运至巩膜,可上调转化生长因子 $\beta 2$ 表达,影响巩膜重塑,进而控制近视的发展^[14]。在人眼中,近视儿童及即将近视的正视儿童脉络膜呈现变薄趋势,且以中心凹最为明显^[15]。高度近视人群脉络膜变薄更为明显,这种现象与高度近视相关的视网膜病变及视力的损害相关^[16-17]。以上表明脉络膜变薄伴随着近视的发生和进展,脉络膜变薄的程度与屈光不正程度相关。脉络膜厚度变化的原因还未阐明,可能与脉络膜血流变化有关。豚鼠近视模型研究发现脉络膜变薄伴随着脉络膜血流灌注的减少,可导致邻近的巩膜和视网膜相对缺氧,引发一系列变化,最终诱导眼轴的增长和近视的发生发展^[18]。综上,脉络膜厚度及血流变化似乎是眼球生长的一个重要生物标志,影响近视的发生及进展。

2 近视干预措施对脉络膜的影响

2.1 光学干预措施

佩戴角膜塑形镜是近视的一种光学干预措施,对近视的控制效果已得到临床的认可。目前普遍认为其机制与重塑角膜形态、减少周边视网膜远视离焦有关^[19],但还有待进一步阐明。佩戴角膜塑形镜后能增加脉络膜厚度,也可改善脉络膜血流灌注^[20]。Li 等^[21]发现佩戴角膜塑形镜 1 个月后脉络膜明显增厚,在 6 个月后保持相对稳定,塑形术后早期的脉络膜厚度变化可能作为近视控制效果的预测指标。角膜塑形术后颞侧的脉络膜厚度变化大于鼻侧,可能由于脉络膜鼻侧靠近视盘,脉络膜萎缩更为明显^[22]。此外,研究还发现角膜塑形术后日均近距离工作时间对脉络膜厚度影响最大,使用日均近距离工作时间可以对角膜塑形术后中央凹下脉络膜厚度的变化进行个性化预测^[23]。角膜塑形后不仅可以改变视网膜周边离焦状态,还可以改变角膜高阶像差及眼球生物力学^[24],但角膜塑形镜引起的脉络膜改变是否与以上因素有关仍需进行多维度的

研究。

佩戴多焦点软性角膜接触镜也可以控制近视进展^[25]。多焦点软性角膜接触镜主要有同心环和非球面渐变两类设计^[26],其周边附加的正焦度可以减少视网膜周边远视离焦量,从而达到控制近视进展的作用^[27]。多焦点软性角膜接触镜对脉络膜厚度也有一定的影响。Prieto-Garrido 等^[28]发现 Misight 双焦点软镜对脉络膜的影响与眼轴控制效果有关,眼轴控制较好的患者脉络膜明显增厚,但这种增厚效应只持续了 1 年,之后便出现下降。这表明脉络膜参与了 Misight 对近视的控制作用,但视网膜对离焦的信号的反应可能有时间限制。在 Breher 等^[29]的研究中,成人佩戴了两种不同设计但离焦量均为 $+2.5 \text{ m}^{-1}$ 的多焦点软性角膜接触镜,30 min 后脉络膜厚度均发生了微小但不具有统计学意义的变化。考虑到相关研究较少且随访时间较短,其结果可能存在偏倚,不同设计的多焦点软性角膜接触镜对脉络膜厚度的影响还需要进一步的研究。

此外,多种不同设计的周边离焦型框架眼镜也应用于控制近视进展,如:“成长乐”镜片(Myovision, Carl Zeiss)、多点正向光学离焦设计的“新乐学”(defocus incorporated multiple segments, DIMS)及高度非球面微透镜设计的“兴趣控”(Stellest, ESSILOR)等。周边离焦镜片在矫正中央区域屈光不正的同时能使视网膜周边区域的物象呈现近视离焦的状态^[30]。近视儿童佩戴 DIMS、Stellest 及 Multi-foucs(贝视得全视护,中国)的周边离焦型框架眼镜可使脉络膜厚度明显增加^[31-33]。不同的是, DIMS 使脉络膜厚度持续增加了 2 年,而 Stellest 及 Multi-foucs 使脉络膜增厚 1 年,之后逐渐恢复至基线水平。这种差异可能是由于视网膜对不同设计的镜片的适应性不同,从而导致对脉络膜厚度的影响随时间的推移而有所不同。

2.2 药物干预措施

一项 Meta 分析显示阿托品、哌仑西平、环戊通滴眼液均能延缓近视进展^[34]。除此以外,消旋山莨菪碱及喜巴辛亦被报道对近视防控有一定的作用^[35-36]。阿托品滴眼液是目前应用于临床且循证医学证据等级最高的药物。阿托品是一种非选择性 M 受体拮抗剂,近年来被广泛用于控制儿童近视进展^[37]。阿托品确切机制和作用部位尚不清楚,可能与非调节机制学说、巩膜调控学说、M 受体学说及周边离焦学说等有关^[38]。Yam 等^[39]使用 0.05%、0.025%、0.01% 低浓度阿托品对 314 例近视儿童进行随访研究,结果显示 3 组脉络膜厚度 2 年的变化

值分别为 $(21.15 \pm 32.99) \mu\text{m}$ 、 $(3.34 \pm 25.30) \mu\text{m}$ 、 $(-0.30 \pm 27.15) \mu\text{m}$, 表明脉络膜厚度与阿托品的浓度呈依赖性反应, 阿托品浓度越高, 脉络膜增厚幅度越大。0.01% 阿托品还被发现可以抑制远视离焦所致的脉络膜变薄^[40]。早期有研究提出眼睛对光学模糊反应是由无长突细胞的活动驱动的^[41], 多巴胺能无长突细胞可能在检测离焦信号中发挥重要作用^[42], 而 Mathis 等^[12]发现阿托品能刺激多巴胺的分泌, 视网膜多巴胺水平与脉络膜厚度呈正比。因此, 阿托品有可能通过影响毒蕈碱胆碱能无长突细胞反应来干扰视网膜中的多巴胺能信号传导, 从而抑制远视离焦信号。

对于近视进展快速者, 临床常采用光学联合药物的干预措施, 以期得到更好的控制效果。研究发现^[43]相比使用角膜塑形镜或者低浓度阿托品, 低浓度阿托品联合角膜塑形镜的干预措施能使脉络膜增加的幅度更大, 同时对近视控制效果也更佳。这种效应同样也存在 0.3% 阿托品联合近视离焦的干预措施中^[44]。以上表明近视的光学与药物干预措施相结合的双重治疗对脉络膜的影响存在叠加效应, 也可以提高近视控制的效果, 这为近视的管理措施提供了新的参考依据和思路。

2.3 环境干预措施

近视发生与遗传及环境因素有关, 环境因素主要为长时间近距离工作及极少的户外暴露^[45]。增加户外暴露时间可以减少近视的发生及进展, 机制可能与光照、多巴胺的释放及近距离工作时间等因素有关^[46]。环境光暴露会影响脉络膜厚度变化^[47]。研究发现^[48]与黑暗的环境相比, 人短期暴露在 500 lx 及 1 000 lx 的照明下可使眼轴缩短, 并能增加脉络膜厚度, 当光照强度越大, 此种效应越明显, 此前也有相似研究报道^[49]。这些发现均提示环境光暴露对眼球生长的影响可能是通过脉络膜机制介导的。

近年来, 研究发现重复低强度红光 (repeated low-level red-light, RLRL) 控制近视的同时可诱导脉络膜增厚, 且增厚的效果优于角膜塑形镜^[50]。Xiong 等^[51]研究结果显示 RLRL 在治疗期间可持续诱导脉络膜增厚, 治疗 1、3、6、12 个月后脉络膜厚度的变化均值分别为 $17.957 \mu\text{m}$ 、 $6.594 \mu\text{m}$ 、 $-1.391 \mu\text{m}$ 、 $7.342 \mu\text{m}$, 治疗 3 个月后的黄斑脉络膜厚度变化可预测治疗 12 个月后的近视控制效果。然而, RLRL 对于不同年龄段及不同程度的近视人群是否具有同样效应还有待进一步的研究。此外, 研究还发现短波长的紫外光对近视有一定的控制作

用, 并能诱导脉络膜增厚, 但紫外光对近视的控制作用属于初步研究阶段, 目前尚未应用于临床^[52]。

3 总结

综上所述, 在近视管理方法中, 佩戴角膜塑形镜、Mishigt 双焦点软镜以及周边离焦框架眼镜的光学措施均能增加脉络膜厚度。以阿托品为代表的药物措施可以增加脉络膜厚度, 并具有浓度依赖性, 而药物联合光学措施可叠加脉络膜的增厚效应。在环境干预措施中, 直接的户外光照对脉络膜的影响报道罕见, 但使用低强度红光及增加环境中的光暴露也可以增加脉络膜厚度。

目前关于脉络膜和近视的研究多在于阐明彼此的关联性, 也有研究认为可将脉络膜厚度及脉络膜血流灌注作为近视发生及发展的预测指标, 在此基础上研发可作用于脉络膜的新型药物或治疗仪器, 以指导临床应用。然而, 脉络膜厚度及血流灌注在控制近视进展中如何发挥作用以及脉络膜在近视发生和发展的过程中变薄的原因还有待我们进一步研究和探索。

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