引文格式:陈若瑜,曹丹,张良. 糖尿病视网膜病变药物治疗研究进展[J]. 眼科新进展,2022,42(3):244-248. doi:10.13389/j.cnki.rao.2022.0050

【文献综述】

糖尿病视网膜病变药物治疗研究进展△

陈若瑜 曹 丹 张 良

作者简介:陈若瑜(ORCID:0000-0002-0691-9056),女,1997年5月出生,贵州贵阳人,在读硕士研究生。研究方向:眼底病。E-mail:ruoyu6616@163.com
通信作者:张良(ORCID:0000-0002-0454-8001),男,1966年5月出生,河南邓州人,博士,主任医师,博士研究生导师。研究方向:眼底病。E-mail:zhangliang5413@163.com

收稿日期:2020-11-30
修回日期:2022-02-13
本文编辑:董建军
△**基金项目**:广东省基础与应用基础研究基金项目(编号:2021A1515010113);白求恩·默克糖尿病研究基金(编号:2018-133);广州市科技计划项目(编号:202102080008)

作者单位:510515 广东省广州市,南方医科大学第二临床医学院(陈若瑜);510080 广东省广州市,广东省人民医院眼科,广东省医学科学院(陈若瑜,曹丹,张良)

【摘要】 糖尿病视网膜病变(DR)是慢性高血糖引起的视网膜微血管并发症。全身危险因素、炎症、氧化应激参与了DR的发生与发展。全视网膜光凝术是预防DR患者视力下降的一线治疗方法,但激光的破坏性会带来一系列眼部并发症。与激光治疗相比,药物治疗能够对DR病情发展的多个环节进行干预,同时也能更好地保留视网膜的解剖结构、减少激光相关并发症。本文从控制全身危险因素的药物、血管保护剂、抗炎药、抗氧化剂、中医中药、纳米药物等多个方面对DR的药物治疗研究进展进行综述,旨在为DR患者制定全面、多元化的治疗方案提供新思路。

【关键词】 糖尿病视网膜病变;黄斑水肿;药物治疗;抗氧化剂
【中图分类号】 R774.1

糖尿病视网膜病变(DR)是糖尿病患者常见的微血管并发症,也是导致工作年龄人群失明的重要原因[1]。流行病学调查显示,我国约有25%的糖尿病患者同时患有DR[2]。随着人们生活水平的提高,DR患者人数逐年增长。面对如此庞大的DR患者群,采取积极的防控措施是预防患者视力进一步下降的关键。最新的糖尿病防治指南认为,全视网膜光凝术(PRP)是预防DR患者视力下降的一线治疗方法[3]。PRP主要针对晚期DR患者,而且激光的破坏性可能会导致患者在治疗后出现周边视野缺损、黄斑水肿等并发症。因此,早期控制DR病情、减少治疗过程中出现的并发症成为近年来眼科医师关注的重点。目前,越来越多的研究旨在寻找DR药物治疗的新靶点,并对新药的治疗效果及作用机制进行深入探讨。本文拟对DR药物治疗的研究进展作一综述。

1 控制全身危险因素的药物

积极降血糖、降血压、纠正血脂异常有助于抑制DR的发生发展。近年来的研究表明,控制全身危险因素的药物对糖尿病患者的视网膜具有独立保护作用,这为DR患者选择更合适的系统治疗药物提供了有用的参考。

1.1 降糖药

1.1.1 二甲双胍 二甲双胍是一种应用广泛的降糖药。在一项临床回顾性研究中,长期使用二甲双胍控制血糖的糖尿病患者发生重度非增生型DR及增生型DR的风险明显降低[4]。近年来研究表明,二甲双胍对DR患者的益处不仅仅局限于控制血糖。在DR动物模型中,二甲双胍可有效减少炎症因子释放,抑制内皮细胞增殖、迁移以及新生血管形成[5]。此外,二甲双胍还能纠正异常生物节律、调节Müller细胞功能[6],从而抑制DR的发生发展。

1.1.2 钠-葡萄糖共转运蛋白2抑制剂 钠-葡萄糖共转运蛋白2(SGLT-2)抑制剂(恩格列净、达格列净等)是一类新型降糖药,可抑制近端肾小管管壁内的SGLT-2重吸收葡萄糖。近年来研究发现,SGLT-2不仅分布在肾小管,还分布在视网膜[7]。SGLT-2抑制剂可减少视网膜对葡萄糖的摄取,阻止视网膜周细胞在高糖环境下发生肿胀、凋亡,从而保护血-视网膜屏障[8]。一项长达6年的队列研究结果表明,与传统降糖药相比,SGLT-2抑制剂更能显著降低DR进展的风险[9]。因此,SGLT-2抑制剂对视网膜可能具有独立保护作用,在降低血糖的同时可有效抑制DR的进展。

1.1.3 胰高血糖素样肽-1受体激动剂 胰高血糖素样肽-1(GLP-1)受体激动剂(利拉鲁肽、艾塞鲁肽等)可刺激胰岛素的分泌和合成,同时还在糖尿病微血管并发症的防治中发挥多效作用。在动物模型中,GLP-1受体激动剂的局部应用可提高视网膜内谷胱甘肽还原酶的水平,激活DNA修复蛋白,减轻氧化应激反应对视网膜的损伤[10]。GLP-1受体激动剂还可减少视网膜神经细胞凋亡及胶质细胞活化,阻止紧密连接蛋白在高糖环境下变性,保护视网膜神经-血管单元[11-12]。也有研究表明,GLP-1受体激动剂的快速降血糖作用会促进DR的早期恶化[13],这可能与视网膜血管内渗透压迅速降低导致血管渗漏增加有关[14]。GLP-1受体激动剂对DR患者的利

弊还有待进一步探讨。

1.2 降血压药 肾素-血管紧张素系统的激活与DR的发展密切相关。血管紧张素可上调血管内皮生长因子(VEGF)的表达,加重视网膜血管渗漏,刺激新生血管的形成[15]。2015年的一项Meta分析表明,肾素血管紧张素酶抑制剂及血管紧张素受体拮抗剂类药物能降低糖尿病患者发生DR的风险,且前者的疗效优于后者[16]。抑制肾素-血管紧张素系统通路的激活不仅有助于改善糖尿病合并高血压患者的全身状态,还能抑制DR病情进一步发展。

1.3 降脂药

1.3.1 他汀类 血脂异常参与了DR的发展,他汀类药物是最常用的降脂药之一。研究表明,糖尿病患者早期应用他汀类药物可降低患者发生DR及糖尿病性黄斑水肿(DME)的风险[17-18]。近年来,越来越多的研究证实,除了降血脂外他汀类药物对视网膜还可发挥多效保护作用,在抑制视网膜炎症反应、改善血管内皮功能失调、减少血管重塑及增生等方面均有显著效果[19-20]。

1.3.2 非诺贝特 非诺贝特是过氧化物酶体增殖激活物受体α激动剂,能够有效纠正血脂异常。Chew等[21]研究提示非诺贝特可显著降低DR进展的风险,而这种疗效并不仅仅依赖于非诺贝特的降血脂作用。在DR动物模型中,非诺贝特可改善视网膜血管渗漏,保护血-视网膜屏障[22]。而且,非诺贝特还能调节脂肪酸及葡萄糖氧化代谢过程,维持视网膜内神经细胞的能量供需平衡,抑制神经凋亡[23];同时它还可下调白细胞介素(IL)-1β、IL-6、VEGF等炎症因子表达,在抗凋亡及抗炎方面发挥一定作用[24-25]。

1.4 纠正贫血的药物 对于合并糖尿病肾病的DR患者,贫血的发病率显著升高,系统缺血缺氧也是加速DR进展的危险因素。补充红细胞生成素(EPO)是改善贫血的重要手段。值得注意的是,除了肾脏外,EPO还可由多种组织产生,并能与不同的受体结合对视网膜发挥多效生物作用[26]。在动物实验中,EPO可抑制小胶质细胞的吞噬作用,维持血-视网膜屏障的完整性[27]。此外,Samson等[28]研究发现,EPO在氧化应激反应早期具有神经保护及抗凋亡的作用。也有研究提示,随着视网膜缺血加重,EPO可能会放大VEGF的作用,这提示EPO也可能与晚期DR的病情恶化有关[29]。

2 血管保护剂

2.1 羟苯磺酸钙 羟苯磺酸钙是一种血管保护剂,常用于治疗糖尿病并发的微血管病变,可通过多种途径预防血管损伤。研究表明,羟苯磺酸钙可有效抑制NF-κB、IL-6、IL-8、肿瘤坏死因子-α等细胞因子的表达,减少炎症引起的微血管异常[30]。另有研究表明,羟苯磺酸钙可下调VEGF及其受体的表达、抑制细胞自噬相关PI3K/AKT/mTOR通路的激活;它也能减少血管内皮细胞丢失及抑制新生血管生成,具有抗凋亡及抗氧化作用[31-32]。

2.2 舒洛地特 舒洛地特是一种高度纯化的糖胺聚糖,长期以来被用于治疗有血栓形成风险的血管疾病。近年来的研究表明,舒洛地特可部分修复高糖破坏的血管内皮糖萼层结构,减少炎症因子聚集,减轻血管渗漏[33-34]。Song等[35]研究发现,口服舒洛地特12个月,可显著减小轻、中度非增生型DR患者的渗出症状,改善黄斑水肿。由此可见,舒洛地特也具有血管保护作用,但目前临床上仍较少将该药用于DR的早期治疗,其疗效及作用机制还有待进一步探讨。

3 抗炎药

3.1 抗VEGF药物 玻璃体内注射抗VEGF药物是目前治疗DME的一线用药,抗VEGF药物与PRP的疗效对比一直是研究热点。队列研究结果表明,抗VEGF药物与PRP相比,前者可显著减少DR患者周边视野丢失,降低黄斑水肿发生率[36],但抗VEGF药物并不能改善患者视网膜无灌注区。这提示对于一些高风险患者,抗VEGF联合PRP治疗可能更有助于延缓DR病情进展[37]。关于抗VEGF与PRP联合治疗的先后顺序,Cao等[38]研究发现,对高危增生型DR患者先进行抗VEGF治疗,再进行PRP治疗可更好地减轻患者视网膜炎症,促进新生血管回退。而且对于玻璃体视网膜粘连范围更广、增殖更活跃的年轻增生型DR患者,术前3~5 d应用雷珠单抗可显著减少术中出血、提高手术效率[39]。然而,在抗VEGF药物治疗过程中,患者普遍存在依从性差、失访率高的现象[40],针对这一难题,新型眼内植入物抗VEGF药物传递系统可持续抑制眼内VEGF水平长达半年,其长效、缓释的优势可明显延长患者的治疗间隔,减少治疗次数[41]。但是目前该技术还处于临床试验阶段,其主要研究对象是湿性老年性黄斑变性患者,未来有望推广到DME的治疗。

3.2 糖皮质激素 多种炎症因子参与DR的发病过程,虽然抗VEGF药物是DME的一线用药,但仍有30%左右的患者对抗VEGF药物无反应[42]。糖皮质激素的抗炎效果更广谱,地塞米松玻璃体内缓释植入剂可大幅延长药物在眼内的作用时间,减少治疗次数。非劣效性临床研究结果表明,地塞米松玻璃体内缓释剂治疗组与抗VEGF组相比,患者1年后的视力预后无显著差异[43],但前者能有效改善DR患者视网膜周边的无灌注区炎症反应[44]。而且,对于3~6针抗VEGF药物治疗后无应答的DR患者,换为地塞米松缓释剂治疗仍有可能减轻黄斑水肿、改善视力[45]。值得关注的是,长期连续进行抗VEGF药物治疗会增加患者发生血栓相关疾病的风

险[46]。因此,最新的指南推荐针对有心血管事件高风险的DR患者,玻璃体内激素治疗可作为一线方案[47]。虽然大量循证研究结果证实了局部应用糖皮质激素类药物对DR及DME患者有益处,但长期眼内应用激素会显著增加高眼压及白内障的发病率。因此对于不同患者,应充分考虑个体差异,合理选择不同的眼内抗炎药物。

3.3 其他抗炎药物 除了抗VEGF类药物及糖皮质激素外,还有一些关键的炎症因子可作为DR治疗的新靶点。在DR炎症级联反应中,蛋白激酶-C位于VEGF等炎症因子的上游,是介导血-视网膜屏障破坏及新生血管形成的关键。蛋白激酶-C阻断剂可有效抑制该共同途径,更大限度地减轻视网膜血管渗漏[48]。此外,DR患者玻璃体液中的IL-6[49]、IL-10[50]、细胞间黏附分子-1[51]等炎症因子水平与DR的严重程度成正比。这些炎症因子在DR病情进展中的作用需要进一步研究探索,它们有望成为新的药物治疗靶点。

4 抗氧化剂

慢性高血糖引起的氧化应激反应在DR的病情进展中发挥关键作用。近年来的研究表明,多种天然抗氧化剂对DR患者有益。白藜芦醇是葡萄、蓝莓等水果中存在的植物多酚,是一种强效抗氧化剂。在DR动物模型中,白藜芦醇可有效抑制NADPH氧化酶基因表达,清除氧自由基,减少氧化应激反应造成的视网膜损伤[52]。藏红花素也是一种植物提取物,可作为强效抗氧化剂和神经保护剂,辅助治疗难治性DME[53]。其作用机制可能与抑制小胶质细胞的氧化应激和炎症反应有关[54]。此外,维生素C、维生素E补充剂在抑制多元醇途径,减轻自由基引起的连锁损伤方面也发挥显著作用[55]。

5 中医中药

随着祖国医学的发展,越来越多的中药被用于早期DR的辅助治疗。复方血栓通是一种由三七、丹参、黄芪为主要成分的中药复方制剂。研究表明,复方血栓通可改善细胞代谢过程,抑制Hippo信号通路,阻止异常血管生成[56-57]。盐酸川芎嗪可抑制氧化应激反应,保护视网膜血管内皮细胞,减轻毛细血管渗漏[58]。芪明颗粒是一种由黄芪、葛根、枸杞为主要成分的复方制剂,Meta分析提示其对DME也有一定的治疗作用[59]。虽然已有大量的研究证实中药制剂对DR有一定疗效,但是其作用机制以及复方制剂中的具体起效成分仍有待进一步探讨。

6 纳米药物

基于纳米材料的药物传递系统如纳米胶囊、纳米悬浮液、纳米药物载体等,可显著提高药物的溶解性和生物利用度。而且纳米材料还具有良好的靶向性,可通过无创的方式进行药物的特异性传递,有效减少药物对周围细胞的副作用[60]。在DR动物模型中,抗VEGF适配体纳米粒子可快速穿过角膜屏障进入眼内,靶向抑制VEGF,其疗效可等同于阿柏西普、贝伐单抗等传统抗VEGF药物[61]。曲安奈德纳米载体滴眼液也可安全、长效地作用于眼内,降低多种炎症因子水平[62]。除此之外,多种抗氧化剂、基因表达调控因子也可经过纳米技术修饰后作用于特定靶点,抑制DR病情进展,减少DR并发症[63-65]。纳米修饰可辅助多种具有治疗潜力的药物穿过角膜及视网膜屏障,作用于DR疾病进展中的特定环节,促进DR治疗药物向多元化、靶向性发展。

7 总结与展望

综上所述,近年来的研究越来越关注DR的药物治疗,目的在于为DR患者制定更全面、更有效的治疗策略。首先,就控制全身危险因素的药物方面,一些降糖、降压、降脂药物对视网膜具有独立的保护作用,探明这些药物的作用机制与临床疗效有助于对DR患者进行针对性的系统用药,在改善患者全身状况的同时保护视网膜。其次,虽然DR的发病机制尚不甚明确,但保护视网膜神经-血管单元、抗炎及抗氧化仍然是治疗DR的重要环节,针对不同靶点的抗炎药在疗效上相互补充,有望使更多DR患者获益。此外,天然植物提取物的抗氧化作用及中药的早期预防作用不容忽视,植物药材易获得、低成本、副作用小,在一定程度上有助于提高患者的依从性。最后,纳米技术可显著提高药物的溶解性及生物相容性,辅助多种药物成分无创、靶向作用于DR病情进展中的特定环节,基于纳米材料的药物传递系统在DR治疗中的应用极具潜力。

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Advances in drug therapy for diabetic retinopathy

CHEN Ruoyu[1,2], CAO Dan[2], ZHANG Liang[2]

1. *The Second School of Clinical Medicine, Southern Medical University, Guangzhou* 510515, *Guangdong Province, China*
2. *Department of Ophthalmology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou* 510080, *Guangdong Province, China*

Corresponding author: ZHANG Liang, E-mail: zhangliang5413@163.com

【Abstract】 Diabetic retinopathy (DR) is a retinal microvascular complication caused by chronic hyperglycemia. Systemic risk factors, inflammation, and oxidative stress are involved in the occurrence and development of DR. Panretinal photocoagulation is the first-line treatment for preventing vision loss in DR patients. However, the destructive nature of lasers can bring a series of ocular complications. Compared with laser therapy, drug therapy can intervene in multiple links of DR development. Meanwhile, it can preserve the anatomical structure of the retina and reduce laser-related complications. In order to provide new ideas for the comprehensive and diversified DR treatment plans, this article reviews the advances in drug therapy for DR from such aspects as drugs controlling systemic risk factors, vascular protectants, anti-inflammatory agents, antioxidants, traditional Chinese medicine, and nanomedicine.

【Key words】 diabetic retinopathy; macular edema; drug therapy; antioxidant