

【述评】

糖尿病视网膜病变的危险因素与预防控制[△]

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糖尿病病程、青春期为 DR 不可改变的危险因素。糖尿病病程与 DR 的发生和发展密切相关,患糖尿病 5 年、10 年和 15 年后,约 25%、60% 和 80% 的 1 型糖尿病患者并发 DR。患糖尿病 20 年后,几乎所有 1 型糖尿病患者和 60% 的 2 型糖尿病患者眼底将出现不同程度的 DR 表现^[10-11]。在 2 型糖尿病进展为 PDR 的患者中,有 2% 的患者病程短于 5 年,

25%的患者病程为25年或更长时间^[12]。青春期是1型糖尿病患者发生DR的危险因素,青春前期患糖尿病会增加DR的发病风险^[13]。此外,妊娠也可影响DR的发生,是DR不易改变的危险因素。糖尿病患者(尤其是1型糖尿病患者)在妊娠期DR和DME可以快速进展,1型糖尿病患者在妊娠期发生DR的可能性是2型糖尿病患者的3倍,但这种进展通常是短暂的,产后可快速消退^[14],而妊娠期间才发生的糖尿病一般无DR发生。

除不可改变的危险因素外,还有一些可控的因素影响DR的发生和进展,血糖是其中一个关键因素。血糖控制不良的糖尿病患者发生DR的风险将增加4倍,早期强化和持续的控制血糖可以减少包括DR在内的糖尿病并发症^[15-16]。糖尿病控制和并发症试验(DCCT)和英国前瞻性糖尿病研究(UKPDS)结果显示,严格控制血糖并保持糖化血红蛋白(HbA1c)低于7%可以有效预防或延缓DR的进程^[17-18]。但选择降糖药物时需注意药物的不良反应,已有研究表明,噻唑烷二酮类药物吡格列酮可增加DME的发生风险,当与胰岛素联合使用时DME风险增加更显著,提示DME患者应谨慎使用吡格列酮^[19]。基于不同人群的研究发现,高血糖是1型糖尿病患者并发DR的重要危险因素,相比之下,血压是2型糖尿病患者发生DR的危险因素^[16]。血压相关的血管变化与糖尿病血管异常相互影响,糖尿病患者出现DR的风险可随收缩期臂间血压差的增加而增大,强化血压控制可以显著降低DR发生和进展的风险^[20]。血脂异常与DR之间的关系仍未完全清楚,不同研究和试验的结果不一致。有研究发现甘油三酯是导致中国糖尿病患者DR发生的独立危险因素,控制血脂水平可延缓DR的进展,而其他研究则表明甘油三酯、总胆固醇水平与DR之间没有显著相关性^[21-23]。对于新诊断的糖尿病患者,若脂质代谢异常,仍建议降低胆固醇、甘油三酯水平以预防微血管并发症发生。最近的研究报道,尿微量白蛋白 $\geq 300 \text{ mg} \cdot \text{g}^{-1}$ 、肾小球滤过率 $< 60 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ 将增加DR的患病风险^[24]。在丹麦一项研究中,通过使用降糖药、血管紧张素转化酶抑制剂和他汀类药物对高血糖、高血压、血脂异常和尿微量白蛋白的多因素干预,使包括DR在内的糖尿病微血管并发症的风险降低了50%^[25]。

在眼部生物学特征方面的研究发现,短眼轴是DR发生、发展的危险因素,长眼轴是DR的保护性因子,高度近视发生DR的概率明显低于正常眼,其保护机制可能与眼轴延长影响眼部血流量、血流动力学以及氧需求量等有关^[26];此外,在屈光参差患者的双眼中,度数较低眼更易发生DR^[27];圆锥角膜患者可能因糖尿病而停止DR进展^[28],角膜、巩膜生物力学特征等眼球生物学参数与DR发生、发展及预后直接相关。

除上述因素外,肥胖、代谢综合征、缺乏运动锻炼、炎症标志物、脉络膜厚度、遗传因素等可能与DR发生、发展之间存在不同程度的关联,但目前尚无统一论。

3 DR的预防与治疗

3.1 预防DR发生 对DR进行病因预防旨在减少糖尿病患者并发DR,加强有效的糖尿病管理是防止DR发生、延缓DR进展的基础,如改善生活方式、坚持糖尿病饮食、适当运动锻炼、戒烟、遵医嘱药物治疗控制血糖与血压、定期监测血糖水平等。预防性DR筛查在防止DR发生中起关键作用,由于许多DR患者早期无明显自觉症状,通常会导致治疗延迟。据报道,印度近一半的糖尿病患者在视力受到严重损害后才去眼科就诊^[29],在中国,首次去眼科就诊的糖尿病患者中有67%被发现患有严重威胁视力的DR^[30]。糖尿病患者中5%~10%的患者在1年内眼底可由无视网膜病变发展为DR,若能早筛查、早监测则有助于早期防控DR。因此,如果在初始检查中未发现眼底有DR表现,建议每1~2年重新进行眼底DR筛查,对于轻度、中度、重度NPDR和PDR患者,应分别每6~12个月、3~6个月、少于3个月和少于1个月进行眼底检查以明确DR的进展情况。

DR传统筛查通常包括最佳矫正视力(BCVA)、散瞳眼底检查以及广域眼底照相。荧光素眼底血管造影检查还可发现视网膜缺血或新生血管。光学相干断层扫描(OCT)检查可发现并随访DME患者的病情变化。随着数字化信息技术的发展,互联网、人工智能(AI)、移动设备在糖尿病和DR的疾病管理、筛查和预防中发挥了重要作用。通过智能手机如应用程序和可穿戴设备可以为糖尿病患者提供饮食和运动指导,血压、血糖监测和设置用药提醒等辅助糖尿病管理^[31]。目前,基于远程医疗的DR筛查已在多个国家和地区实施,视网膜照片通过远程眼科平台传输到集中阅片中心,由受过训练的分级员在远程阅读中心进行阅片,并将报告发送给初级保健诊所,然后将其提交给眼科医生转诊^[32]。这种筛查方式可在糖尿病人群中及时发现DR患者,早期进行干预和治疗,此外还能降低因患者依从性差而失访的可能性。远程医疗和移动设备的结合为DR筛查带来了便利,便携式手持视网膜相机将采集的眼底照片通过互联网传输到阅片中心,使DR的筛查不受地域的限制,可以覆盖到更多的患者^[33]。AI在DR筛查中的运用日趋成熟,基于AI的技术如深度学习系统(DLS)筛查DR具有较高的敏感性和特异性^[34]。最近的一项研究评估了基于AI的DLS,结果显示,DLS检测出威胁视力的DR灵敏度为99.42%,DME灵敏度为97.19%^[35]。眼底筛查是DR一级预防中的关键部分,普及DR筛查可有效降低DR发

生,对已出现的 DR 进行早期干预和治疗,延缓 DR 进展,但与此同时仍有很多问题需要解决,如增加足够训练有素的眼保健专业人员、广泛投放筛查设备等。

3.2 控制 DR 发展 激光光凝、药物治疗和手术治疗是控制 DR 进展、挽救 DR 视力的主要治疗策略。在糖尿病患者中有超过三分之一的患者患 DR,其中又有三分之一的患者患威胁视力的 DR,即重度 NP-DR、PDR 和 DME。激光光凝目前仍是治疗 DR 的金标准,也是其他治疗方法的基础,因光凝可长久改善视网膜缺血的效果仍无可替代。全视网膜光凝 (PRP) 通过对黄斑区之外的整个外周视网膜进行激光光凝,减少视网膜供氧需求,从而防止新生血管形成,早期行 PRP 可将高风险 PDR 的发生率降低一半,此外还可降低玻璃体积血行玻璃体切割手术的发生率,及时行 PRP 有助于延缓 DR 病情进展,保护视功能^[36]。

近年来治疗 DR 的药物不论是在研究阶段还是临床应用阶段都取得了显著的进展。玻璃体内注射糖皮质激素如曲安奈德、地塞米松缓释剂等,能抑制眼内病理性炎症因子的表达,减轻黄斑水肿。此外,眼内注射抗血管内皮生长因子 (VEGF) 药物,如雷珠单抗、阿柏西普和康柏西普,可有效减轻 DME,并且在短期内可降低 DR 发展为 PDR 的风险,提高患者有用的视力。美国糖尿病视网膜病变临床研究网络 (Diabetic Retinopathy Clinical Research Network, DRCR. Net) 显示,DME 患者接受抗 VEGF 药物治疗或抗 VEGF 药物联合激光光凝治疗效果均优于仅激光光凝治疗^[37]。一项评估从贝伐单抗或兰尼单抗转为阿柏西普治疗顽固性 DME 的 Meta 分析显示,进行转换疗法后患者的 BCVA 和中央黄斑厚度均得到显著改善且无不良事件发生^[38]。所以,对于多次进行同一种抗 VEGF 药物眼内注射后视力无明显改善的顽固性 DME 患者,可考虑转换药物治疗法。抗 VEGF 药物或糖皮质激素治疗可明显提高 DME 患者视力,但并不能完全抑制参与 DME 发病过程中炎症因子、趋化因子等相关细胞因子的作用,并且两者的作用均不持久,需要长期、反复注射给药,还可能出现注射后眼内炎、高眼压及白内障等并发症。除眼内注射药物外,口服依那普利和氯沙坦特异性阻断肾素-血管紧张素系统可延缓 DR 的发生和进展^[39]。在轻度视网膜病变的 1 型糖尿病合并高血压患者中使用坎地沙坦治疗可以有效延缓 DR 发展,但对重度视网膜病变的患者疗效则不太明显^[40]。一项针对 DR 患者进行强力霉素治疗的临床试验研究结果表明,口服低剂量强力霉素可能诱导 DR 消退或减慢其进展至 NPDR 或 PDR^[41],强力霉素可能是针对 DR 炎症成分的潜在治疗策略。Omega-3 具有抗炎和抑制新生血管生成的作用,PREDIMED 地中海饮食与糖尿病微血管并发症研究结果显示,在膳食中

添加 Omega-3 可降低 DR 发展至威胁视力阶段的风险,而富含 Omega-3 的亚麻籽油能调节视网膜中 Omega-3 受体 GPR120 和 GPR40 的基因表达和蛋白含量,有望在防治 DR 中发挥作用^[42]。羟苯磺酸钙可调节和改善毛细血管通透性、增强血管壁抵抗力,对包括 DR 和糖尿病肾病在内的糖尿病微血管病变具有一定的保护作用。多项研究表明,口服羟苯磺酸钙联合其他治疗如视网膜光凝、抗 VEGF 药物等可获得更好的疗效^[43]。

DR 进展至 PDR 期导致的玻璃体积血、新生血管膜和牵拉性视网膜脱离是 DR 引起视力下降和失明的主要原因,当患者病情进展至严重 PDR 期则需要进行玻璃体切割手术治疗。玻璃体切割手术的典型适应证包括:未清除的玻璃体积血,波及黄斑的牵拉性视网膜脱离,合并孔源性和牵拉性视网膜脱离,致密的黄斑前玻璃体积血等。在出现玻璃体积血后 1~6 个月内进行玻璃体切割手术治疗的患者其预后优于 1 年后接受手术者^[44]。在玻璃体切割手术前预先进行玻璃体内抗 VEGF 药物注射可缩短手术时间、减少术中出血和早期复发性玻璃体积血,并且能促进术后复发性玻璃体积血吸收,获得更好的预后,但不能减少晚期复发性玻璃体积血、复发性视网膜脱离或相关的二次手术的发生率^[45]。在玻璃体切割术中行 PRP 可有效减少术后活动性新生血管形成,提高手术成功率及改善预后。一直以来很多书籍及文章中提及 DR 进展至晚期所引起的失明时,常将其描述为“不可逆转”,这种表述是不恰当的,容易使患者及非专业人士对 DR 的预后产生误解,甚至可能使患者丧失继续治疗的信心,建议修改为“不易逆转”或“难以逆转”。DR 进展至 PDR 期并非一定导致不可逆性失明,若能及时治疗,将有可能最大程度恢复及保留有用的视力。

4 小结与展望

近年来,有关 DR 治疗的研究取得了显著进展,尽管玻璃体内注射药物的治疗策略改变了 DR 传统的治疗方法,但仍需进一步了解 DR 相关分子生物学机制,研究新的药物靶标。值得注意的是,中药在 DR 防治方面的作用逐渐受到关注,基于中药的研究将可能有助于发现 DR 治疗靶点的新分子。在 DR 的治疗中,激光光凝、药物以及玻璃体切割手术的运用应充分结合患者的个体情况,有针对性地采取最佳的治疗方式。DR 的发生和进展并非不可控,改善糖尿病患者自我管理行为,良好地控制血糖、血压,改变饮食和生活方式是防控 DR 的核心,提高患者和医护人员对 DR 的风险意识,了解 DR 发生涉及的危险因素并及时采取干预措施有助于防控 DR。此外,应呼吁并加强普及预防性 DR 筛查,目前,AI 在 DR 筛查中表现出巨大潜力,且已有多个基于 AI 的 DR 筛查模型,然而仍存在一些问題,如测试准确率

与实际临床之间存在一定差距,或上传图片质量不一,有些甚至无法达到筛查要求等,今后需要更多的研究关注并解决这些问题,建立系统的DR筛查程序和网络,对糖尿病患者并发DR切实做到早发现、早治疗。

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Risk factors for diabetic retinopathy and its prevention and treatment

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[Abstract] Diabetic retinopathy (DR) is one of the most common complications of diabetes. With the development of diabetes, DR will threaten the vision of diabetic patients to different degrees and even lead to low vision or blindness. The risk factors related to DR include but not limited to the course of diabetes, hyperglycemia, hypertension, puberty, pregnancy, axial length and so on. Improving awareness about DR and taking measures to control risk factors is helpful to prevent the occurrence of DR. As to the prevention and controlling strategies of DR, the importance of effective diabetes management, continuing systemic risk factors control, strengthening regular screening, and building a well-established screening system still need to be emphasized. Laser photocoagulation, drug therapy, and vitrectomy are currently the main treatments to delay the progress and alleviate visual impairment of DR. However, the pathogenesis of DR is not completely clear, and more research is needed to pay attention to new targets and methods for the treatment of DR.

[Key words] diabetic retinopathy; risk factors; prevention; control; treatment strategy