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- (收稿日期:2021-12-30,修回日期:2022-01-18)

引用本文:薛朔,毛一凡,王春芳.糖尿病视网膜病变危险因素的研究进展[J].安徽医药,2023,27(5):863-867.
DOI:10.3969/j.issn.1009-6469.2023.05.004.



◇ 综述 ◇

糖尿病视网膜病变危险因素的研究进展

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摘要: 糖尿病视网膜病变(DR)是高血糖导致的视网膜微血管或神经的病变,是糖尿病常见的慢性并发症之一,目前已经成为工作人群中首要的致盲眼病。现对DR相关危险因素进行综述,使糖尿病病人远离视力损害的风险,降低DR的患病率与致盲率,维持糖尿病病人的视力健康及生活质量。

关键词: 糖尿病视网膜病变; 危险因素; 研究进展

Research progress on risk factors of diabetic retinopathy

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Abstract: Diabetic retinopathy (DR), as the abnormality of retinal microvascular or retinal neuropathy, is caused by hyperglycemia and is one of the common chronic complications of diabetes. It has been the primary factor resulting in blinding eye disease in the working population. This article reviews the risk factors related to DR to avoid certain risks for diabetic patients, reduce the prevalence and blindness rate of DR, and maintain the visual health and quality of life of diabetic patients.

Key words: Diabetic retinopathy; Risk factor; Progress in research

糖尿病视网膜病变(diabetic retinopathy, DR)是糖尿病(diabetes mellitus, DM)最常见的并发症^[1],已经成为全球成年人失明的最主要原因之一^[2]。随着

DM患病率逐年升高且呈年轻化趋势,DR导致视力障碍的病人人数只增不减,在所有中重度视力障碍甚至致盲原因中所占比例越来越大^[3]。DR不仅影

响病人视觉质量,与病人健康相关的生活质量及幸福感也有关。随着DR的病情进展,病人的工作和生活能力会持续下降^[4],一些DR病人还会出现不同程度的焦虑或抑郁^[5]。DR在我国糖尿病人群中患病率约为18.5%~27.9%,且北部地区的患病率(28.7%)高于南部地区(26.9%),已经成为我国一个严重的公共卫生问题,需要对DR的流行病学进一步研究,对DR实施最佳筛查和对DR相关危险因素进行干预^[6-7]。

DR相关危险因素可以分为不可控制因素和可控制因素。不可控制因素包括:性别、年龄、糖尿病类型及病程和妊娠等;可控制因素是指可以通过治疗得到控制的相关危险因素如高血糖、高血压、高血脂、糖尿病肾病、体质量指数(body mass index, BMI)和白内障手术等。

1 DR的不可控制相关危险因素

1.1 糖尿病类型 一项纳入22 896例DM病人的荟萃分析显示1型糖尿病(type 1 diabetes, T1DM)病人中DR患病率为77.3%,而2型糖尿病(type 2 diabetes, T2DM)病人中DR患病率为25.2%,提示T1DM相比于T2DM罹患DR风险更大。在增殖性DR(proliferative diabetic retinopathy, PDR)、糖尿病黄斑水肿(diabetic macular edema, DME)及存在视力危害的DR(vision-threatening diabetic retinopathy, VTDR)中,T1DM病人患病率(32.39%、14.25%、38.48%)均显著高于T2DM(2.97%、5.57%、6.92%)病人^[1]。Kindt等^[8]研究T1DM脐血样本发现DR3-DQ2和DR4-DQ8风险单倍型携带者的MHC基因内CpG位点甲基化状态存在差异。因此,T1DM病人较T2DM病人更需要定期关注视网膜病变的情况。

1.2 性别 性别在糖尿病视网膜病变中是必须考虑的因素^[8]。我国一些学者研究并未发现性别与DR患病风险存在明显相关性,OR值为0.94,1.03^[6-7,9]。然而,最新一项对T2DM病人横断面研究显示女性与DR患病率独立相关(OR值为1.14),其中60岁以上、糖尿病病程超过10年或生活在相对中等经济地区的T2DM女性病人患病风险较高(OR值分别为1.09、1.12、1.14),研究显示受教育程度、家庭收入、自我保健意识等社会经济因素的性别差异可能在一定程度上导致DR患病风险的性别差异^[10]。

1.3 年龄 年龄是DR的独立危险因素^[6,9]。Luis等^[11]对T1DM病人按发病年龄依次分组后结果发现DR发病风险随着年龄增长而升高。后来,Liu、Zhang等^[7,9]研究分析显示,DM发病年龄较小是DR的独立危险因素(OR值分别为0.97、0.99, $P<0.05$)。

进一步单因素分析显示,60~70岁(50~60岁)与大于70岁组(60~70岁)的OR值分别为0.75、0.73($P<0.001$)。Song等^[6]发现在70岁以前,DM病人DR的患病率从30~39岁组人群的12.55%持续上升到60~69岁组的20.44%;而70岁以后DM病人的DR患病率开始下降,80岁以上DM病人的总DR患病率为11.22%。这些研究进一步分析,一方面认为DR与严重的全身疾病相关,这一结果可能与生存偏差有关。另一方面认为老年DM病人随着年龄增长,糖尿病病程延长,而糖化血红蛋白(HbA1c)降低,胰岛素使用量减少,表明老年人的血糖可能更好管理。因此,在70岁以前,年龄是DR的危险因素,随着年龄的增长,DR患病率增高;而在70岁以上的老人中,年龄被确定为一个保护因素^[6-7,9]。

1.4 糖尿病病程 糖尿病病程已经是公认的DR最强的相关危险因素,任何DR的患病率随着糖尿病病程的延长而增加^[6-7,9]。Liu等^[9]对中国六省8个临床中心的病人进行横断面研究,提示随着糖尿病病程延长,DR的患病风险越高。Luis等^[11]对T1DM病人从发病开始随访,DR累积发病率从0.7%(5年病程)上升至21.8%(15年病程)。Zhang等^[7]研究发现我国北方地区糖尿病平均病程(8.91年)明显长于南方地区(7.15年),认为南北方地区DR患病率的差异可能来源于DM病程的不同。欧洲一项关于线粒体与增殖性糖尿病视网膜病变的研究表明^[12],在单倍群H型线粒体DR病人中,较长的糖尿病病程是PDR的显著危险因素($P=0.0001$)。在UK型线粒体DR病人中,糖尿病病程不是PDR的显著危险因素($P=0.55$)。这可以部分解释具有类似的糖尿病病程DR病人,其DR的严重程度可不一致。

1.5 妊娠 妊娠与DR的进展显著相关,会加速DR进展^[13]。Junko等^[13]对93例DM病人在妊娠期的随访研究发现,有17%的病人出现DR,其中2例病人在孕早期出现改变,5例在孕中期,5例在孕后期,4例在分娩后出现改变。此外,糖尿病病程较长或妊娠前有糖尿病视网膜病变的病人在妊娠时视网膜病变进展率会显著增加。Masahiko等^[14]研究结果表明糖尿病病人在妊娠期体内血管内皮生长因子相关分子和炎症相关分子发生改变,提示其可能参与了妊娠期DR的发生。建议DM病人在孕前应被告知进行DR评估,孕妇应在孕早期接受筛查,无DR的孕妇应在28周内再次进行筛查^[15]。英国专家共识对妊娠期DR的建议:如果DR在晚期妊娠发生进展,建议在产后12个月内进行筛查。并认为妊娠期进行性糖尿病黄斑水肿(diabetic macular edema, DME)的最佳治疗方案是玻璃体内注射类固醇^[16]。

2 DR的可控制相关危险因素

2.1 血糖控制 糖尿病长病程和高HbA1c与DR有直接的关系^[17]。HbA1c每增加一个单位,从无并发症转变为DR合并冠心病的风险和死亡率分别增加30%和67%,从单纯DR转变为DR合并冠心病的风险和死亡率分别增加16%和43%^[18]。长期暴露于高糖可能诱导视网膜Muller细胞活化,血糖水平的高低漂移可能触发Muller的早期激活,加速视网膜Muller的损伤而促进DR的早期发展^[19]。短期血糖波动可能促进T2DM病人DR的发生或发展,而以HbA1c为代表的长期血糖波动似乎在T1DM或T2DM病人的DR中起着更重要的作用。良好的血糖和血压控制仍然是降低DR进展和视力丧失风险的最重要的可控危险因素^[20]。因此需要定期筛查这些并发症并优化血糖控制^[17]。

2.2 高血压 高血压是DR的危险因素^[17]。Vfoo等^[21]对亚洲T2DM病人血压变异与DR的研究分析显示:平均收缩压(systolic blood pressure, SBP)与中度DR显著相关,SBP变异程度与中度DR无显著相关性。只有当HbA1c<7%时,SBP变异程度与中度DR显著相关。Liu等^[22]基于人群的横断面研究显示控制不良的高血压($OR=1.97$)和未治疗的高血压($OR=2.01$)与DR发生有关,血压控制较好的高血压病人DR患病率(29%)较控制不良的高血压病人患病率(42.5%)和未治疗的高血压病人(31%)的患病率低,并且随着SBP的升高DR患病风险越高,SBP每增加一个标准差,其DR患病风险增加38%,舒张压并没有明显的类似相关关系,建议DM病人更应该严格地控制血压。Zhou等^[23]荟萃分析表明在有针对性地严格控制血压的情况下,DR的发生率相对风险降低了17%以上。最近研究表明血管紧张素转换酶抑制剂的降压药物可降低DR的患病风险,提高DR消退的可能性^[24]。

2.3 血脂 Lucia等^[25]汇集了18个对DR和血脂的调查显示,没有得到血脂异常是DR的危险因素。但不能排除脂质水平与DR之间可能存在更温和的因果关系的可能性。Itoh等^[26]在对DM病人强化控制血脂治疗的一项随机对照研究提示,两组低密度脂蛋白胆固醇差异与DR事件减少率的关系与糖尿病病人一级预防研究一致。Aliyari等^[18]研究显示低密度脂蛋白每增加一个单位,病人(DR合并和冠心病)死亡风险增加2.4%。高密度脂蛋白每降低一个单位,病人(DR合并和冠心病)增加3%。Zhou等^[27]荟萃分析显示血脂与DR的进展尚不清楚,但非诺贝特已证实对DR有利。降脂药物的使用会降低DR发生率,使用降脂药物可以减少DME的发生率,

同时可一定程度上避免病人进行激光光凝和玻璃体切割术的风险^[28-29]。

2.4 糖尿病肾病 糖尿病控制及并发症研究(DCCT)显示在T1DM病人中,白蛋白排泄率(albumin excretion rate, AER)是PDR的第3位危险因素, AER每增加1 mg/24 h, PDR的患病风险增加3.1%^[30]。龚莹莹等^[31]研究显示在T2DM病人中,糖尿病肾病是DR发生的独立危险因素,糖尿病肾病的病人较无肾病病人DR的患病风险增长1.744倍。Hsieh等^[32]一项随访8年的多中心队列研究表明NPDR病人和PDR病人较无DR病人血清肌酐水平较高,肾小球滤过率较低,尿微量白蛋白/尿肌酐升高。并且,在一项横断面研究中发现:血浆低苯丙氨酸和低酪氨酸增加了T2DM中DR的风险,并与成癔相互作用显著。低苯丙氨酸和低酪氨酸联合应用对T2DM合并肾功能不全病人DR风险的影响进一步放大。这表明,在糖尿病肾病病人中,控制酪氨酸/苯丙氨酸代谢可能极大地降低DR的风险^[33]。同时,DR的严重程度是进展为糖尿病肾病的危险因素。因此,糖尿病视网膜病变可用于预测糖尿病肾病的临床病程^[34]。所以,积极治疗糖尿病肾病可能在防止DR恶化方面起到一定作用。

2.5 BMI BMI是DR的相关危险因素^[35,36]。Zhu等^[35]一项前瞻性队列研究的荟萃分析显示肥胖是NPDR的危险因素,肥胖与DR发病率的显著增加相关($RR=1.20$)。Chan等^[37]对亚洲成年人进行6年的BMI随访分析显示BMI是DM的显著危险因素,却是DR的保护因素,与BMI<25相比,超重和肥胖的DR相对风险分别为0.80,0.60。Melkamu等^[36]研究发现超重或者肥胖发生DR的概率是体重正常DM病人的4倍($OR=3.74$)。Mayinuer等^[38]研究显示饮食控制干预可显著降低发生DR的风险($OR=0.64$)。

2.6 白内障手术 白内障手术与DR的发病率相关^[39]。Jeng等^[40]研究显示在无DR的DM病人中,接受白内障手术的病人发生NPDR的风险增加48%,接受白内障手术的病人NPDR的累积发生率更高。白内障手术显著增加NPDR发展的风险,并且它的影响在手术后5年持续存在。英国一项针对白内障术后DME的多中心研究表明^[41],白内障手术一年后需要治疗的DME发病率(5.3%)较手术前1年(2.9%)升高。术后需要治疗的DME患病风险急剧增加,术后3~6个月期间发病率最高为6.8%,且风险与视网膜病变的术前分级有关:术前无DR,术后第一年DME的风险为1.0%,轻度NPDR者的风险5.4%,中度NPDR者的风险为10.0%,重度NPDR者风险为13.1%,PDR者的风险为4.9%。《中国糖尿病

病人白内障围手术期管理策略专家共识(2020年)》^[42]建议对于已有DR及DME治疗指征病人可预行视网膜光凝术,或者白内障摘除手术术前酌情行玻璃体腔注射抗VEGF药物治疗。术后密切观察DR情况并及时筛查处理。

3 总结与展望

一项系统回顾分析在美国、澳大利亚、欧洲等发达国家中有DR患病率下降趋势,这得益于人们意识到DR的危害,并积极控制血糖^[43]。筛查可有效降低DR对人群视力的损害,在英国和冰岛,已经进行了系统的国家DR筛查,DR已不再是工作人群失明的主要原因^[44-45]。但是在我国并未形成系统的筛查模式,人工智能识别DR系统的出现为我国系统筛查DR提供了可能性^[46]。国内外学者已有研究证实基于深度学习的人工智能识别DR系统在基层筛查过程中有较高的诊断效能^[47-48]。总之,通过早期筛查,并对DR相关危险因素进行预防及控制,DR是一个可防可控的致盲眼病。我国应尽早建立符合国情的医疗保健系统,定期筛查,对DM病人的可控制危险因素进行积极干预,使DM病人远离视力损害的风险,更好地保护DM病人的视力健康^[49]。

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(收稿日期:2021-12-17,修回日期:2022-01-20)