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糖尿病相关眼表疾病研究进展

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[摘要] 糖尿病是由多种病因引起以糖代谢紊乱为主的常见全身病,已逐渐成为全球严重的公共卫生问题。以往对糖尿病性视网膜病变的相关研究较多,但糖尿病相关的眼表疾病尚未得到充分认识。糖尿病可增加眼表疾病的风险,包括眼干燥症、角膜炎症、持续的角膜上皮缺陷,甚至形成致盲性的角膜溃疡。本文重点概述糖尿病与眼表疾病的相关性,介绍角膜神经的变化可作为评估糖尿病性神经病变的指标,探讨糖尿病相关眼表疾病的治疗方式,为糖尿病患者早期筛查、诊断和治疗眼表病变提供帮助。

[关键词] 眼表疾病;糖尿病;角膜神经病变;眼干燥症;睑板腺功能障碍

[中图分类号] R 587.1 **[文献标志码]** A

Research progress of diabetes-related ocular surface diseases

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[Abstract] Diabetes mellitus is a common systemic disease mainly caused by glucose metabolism disorder, which has gradually become a serious public health problem in the world. There have been many studies on diabetic retinopathy, but the ocular surface diseases related to diabetes have not been fully understood. Diabetes can increase the risk of ocular surface diseases, including dry eye disease, keratitis, persistent defects in the corneal epithelium, and even the formation of blinding corneal ulcers. This paper focuses on the correlation between diabetes mellitus and ocular surface diseases, introduces the changes of corneal nerve as an index to evaluate diabetic neuropathy, and discusses the treatment of diabetic related ocular surface diseases, so as to provide help for early screening, diagnosis and treatment of diabetic patients with ocular surface diseases.

[Key Words] ocular surface diseases; diabetes mellitus; corneal neuropathy; dry eye disease; meibomian gland dysfunction

糖尿病(diabetes mellitus, DM)是一种体内胰岛素分泌缺陷或胰岛素作用障碍所导致的以高血糖为特征的代谢性疾病,是全球患病率最高的系统性疾病之一^[1-2]。据国际糖尿病联盟统计,2017 年全球 DM 患病人数已达 4.25 亿,预计到 2030 年和 2040 年将分别超过 5.92 亿人和 6.4 亿人^[3],而中国以 1.144 亿的患病人数位居全球第一位^[4]。糖尿病正成为严重的公共卫生问题。

DM 会导致各类并发症的发生,如神经病变、视网膜病变、肾病和心血管疾病等^[3]。目前糖尿病的眼部并发症已成为发达国家致盲的主要原因。以往关于糖尿病性视网膜病变(diabetic retinopathy, DR)的研究较多,人们对其已有相对深入的认

识^[3,5],而 DM 相关的眼表并发症,包括角膜、泪腺和睑板腺等,尚未得到充分认识。有研究^[5]表明,高达三分之二的 DM 患者在其患病期间会出现糖尿病性角膜病变,发生角膜神经密度下降和敏感性降低等病理表现^[6],直接影响角膜上皮创伤愈合,并间接增加持续性角膜上皮缺损和角膜感染的发生几率^[7],这些改变均可能导致失明,因此探讨 DM 对眼表的影响至关重要。本文简要概述 DM 与眼表之间的关系,并讨论 DM 相关眼表疾病的治疗方法。

1 糖尿病角膜神经病变

糖尿病角膜神经病变(diabetic corneal

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neuropathy, DCN)是常见的糖尿病眼部神经并发症,可使角膜感觉、营养及代谢功能发生障碍,易引起患者发生糖尿病性角膜病变(diabetic keratopathy, DK)。Schultz等^[8]认为,DM患者一生中发生DK的风险为47%~64%。目前认为,角膜神经病变是导致角膜病反复发生、难治愈的根本原因。

1.1 DCN与DM周围和自主神经病变 无论在1型还是2型DM中都会出现一些角膜神经参数的变化,如角膜基底神经纤维密度、长度和分支密度的减少等,这均与DM周围和自主神经病变相关^[9-10]。有研究^[11]表明,糖尿病周围神经病变患者角膜基底神经纤维长度和分支密度明显低于无DM患者和无糖尿病周围神经病变患者。Chen等^[9]证实,利用角膜共聚焦显微镜(corneal confocal microscopy, CCM)测量的角膜神经纤维长度的减少可预测糖尿病周围神经病变的发展。2016年的一项荟萃分析^[10]得出,使用CCM评估的角膜神经纤维密度、长度和分支密度在糖尿病周围神经病变患者中均显著降低,而CCM可用于早期发现DM周围神经病变的神经损伤。并且Misra等^[12]发现,使用CCM评估角膜基底神经密度的变化优先于神经病变的临床和电生理检查所检测到的其他功能的变化,角膜敏感性与自主神经分析负相关,提示CCM和角膜敏感性检测可作为评估糖尿病周围神经病变和自主神经病变的替代指标。并且CCM评估的参数对糖尿病自主神经病变的诊断具有高度敏感性和特异性。因此,CCM是一种快速、无创、可靠的亚临床糖尿病自主神经病变的诊断工具^[10]。

DCN也属于DM并发症的一部分,氧化应激是糖尿病并发症的发病机制之一。在高糖环境时,线粒体产生的过多的超氧化物可损伤蛋白质、破坏DNA、影响能量代谢及细胞信号转导,同时通过多元醇通路、己糖胺途径、糖基化终末产物途径及蛋白激酶C途径等代谢通路的活化,最终引起神经元损害^[13]。神经生长因子(nerve growth factor, NGF)及神经递质,包括P物质、降钙素基因相关肽等,表达和功能的异常可导致神经传导减慢,神经滋养血管破坏,神经受累^[14-15]。其中神经递质表达减少还可影响角膜上皮细胞的有丝分裂并降低其代谢,从而减弱上皮功能和活力^[16]。因角膜神经系统病变较为复杂,其具体发展机制,还需进一步研究。

1.2 DCN与DR 在1型DM患者中,CCM呈现出来的角膜细胞改变,包括上皮细胞和内皮细胞密度降低、角膜细胞密度增加、以及小神经纤维的改变,如角膜神经纤维密度、神经分支密度降低,神经纤维长度和宽度降低^[17]。该研究^[17]还表明,发生视网膜病变后,糖尿病患者的角膜细胞和小神经纤维病变严重程度增加。但Bitirgen等^[18]发现,在无DR的2型糖尿病患者中也可以观察到角膜神经纤维密度、长度和分支密度的降低,并且随着视网膜病变的进展而加剧。另有研究^[19]表明,DCN与DR的病情严重程度具有显著的相关性,随着DR严重程度增加,DCN也逐渐加重,当因屈光介质混浊无法观察到眼底病变时,DCN可作为DR病情程度预测指标。DM患者在未发现视网膜微血管病变时,已经存在角膜神经纤维的改变,该改变可作为早期干预DR的筛查指标。因此,角膜神经纤维的变化可预测糖尿病视网膜病变的发展,但仍需要进一步验证。

2 角膜异常

DM可引起角膜上皮细胞、角膜基质和基底膜的改变,导致角膜上皮病变和粘连障碍^[20]。此外,DM中角膜神经的丢失可使神经营养支持减少,加速上皮细胞的损失并减少增殖,导致异常基底层产生和上皮细胞与异常基底膜的粘附不足^[2]。研究^[21]发现,糖尿病大鼠模型中角膜伤口愈合延迟,伴有内皮生长因子受体激活减少,此外还观察到包括 β -连环蛋白和闭锁小带-1的紧密连接蛋白的表达减少,表明糖尿病角膜中细胞与细胞的连接遭到了破坏。并且,高血糖可导致角膜厚度增加,紧密连接的破坏和基底上皮细胞的丢失,严重影响角膜上皮基底膜复合物的功能^[22]。有研究^[23]发现,2型糖尿病患者中,其角膜基质存在厚度可变的异常胶原纤维束。部分DM患者角膜上皮的基底膜和前弹力层连接能力较正常人差,特别是在角膜上皮修复时的滑动及有丝分裂过程中较慢,这可能是部分DM患者出现持续性角膜上皮缺损的病理基础之一^[24]。在诱导患有1型糖尿病的猴子中,也发现了相似的胶原纤维束^[25]。重要的是,糖尿病性角膜基质会积聚糖基化终末产物(advanced glycation end products, AGEs),这可能导致胶原蛋白交联,并引起中央角膜厚度增加,同时AGEs也可引起2型糖尿病小鼠和1型糖尿病大鼠角膜基质中IV型胶原

蛋白表达发生变化,导致细胞粘附受损,促进凋亡和抗增殖途径,导致角膜上皮受损^[22]。Di等^[26]证实,患糖尿病的小鼠角膜中多形核细胞的积累会形成过量的炎症反应,导致促炎细胞因子增多和伤口愈合延迟。因此,DM会严重影响角膜上皮屏障功能和角膜上皮愈合功能,这大大增加了眼表疾病的风险,如眼干燥症(dry eye disease,DED)、浅表点状角膜炎、复发性角膜糜烂、持续性上皮缺损和神经营养性角膜溃疡等^[5]。

3 眼干燥症

DED是由于泪液的质或量或流体动力学异常引起的泪膜不稳定及眼表损害,从而导致眼部不适的一类疾病,患病率为5.5%~33.7%^[27],而DM患者中DED患病率可高达50%^[28]。造成糖尿病性干眼病变的原因有很多,其中最常见的就是泪膜异常和睑板腺功能障碍。

3.1 泪膜异常 糖尿病周围神经病变理论上可以增加DED的风险,有约一半的DM患者会出现干眼症状^[29]。Misra等^[30]发现,DM患者泪膜稳定性有一定程度受损。高血糖导致的泪腺微血管的损伤和糖尿病性自主神经病变导致的泪腺神经支配受损,均可以减少泪液的产生^[31]。糖尿病周围神经病变导致的角膜神经纤维密度下降,从而使得角膜的敏感性受损和反射性流泪减少,从而导致泪膜稳定性降低^[32]。DM患者泪液产生减少或泪液蒸发增加可导致泪液渗透压升高。

3.2 睑板腺功能障碍 睑板腺功能障碍(meibomian gland dysfunction,MGD)是一种慢性、弥漫性睑板腺异常,其在DM患者中的患病率约为75%^[33]。有研究^[34]显示,胰岛素以剂量依赖方式刺激人睑板腺上皮细胞的增殖,血糖过高可导致上皮细胞进行性丢失,从而增加睑板腺疾病的风险。此外,DM患者脂质层分布不均匀与DED具有显著相关性^[35]。MGD的发生与睑板腺腺体分泌物中胆固醇的浓度升高相关,睑板腺脂质成分的改变打破了泪膜中脂质层的稳定性,同时也为细菌生长提供了环境,进而形成恶性循环,加重干眼的发生。眼干燥症的严重程度与周围神经病变的程度和DR的严重程度密切相关^[36]。然而,随着疾病时间延长,角膜敏感性降低,即使存在严重眼表损伤,患者通常也是无症状的,DM患者由于DED的存在进一步

增加了角膜上皮损伤的风险。因此,对于DM患者,除了视网膜检查外,还需要定期检查眼表损伤和干眼症状。

4 结膜异常

结膜异常在DM患者中也很常见,包括结膜微血管改变、结膜毛细血管丢失、大血管扩张、血管分布不均和杯状细胞数量少^[37]。患有眼干燥症的DM患者的结膜还显示出促炎细胞因子的增加^[38]。在DM患者中结膜菌群存在异常,其主要细菌菌株是葡萄球菌^[39]。

有研究^[40]表明,在结膜小动脉中,非增殖性糖尿病视网膜病变(non-proliferative diabetic retinopathy,NPDR)和增殖性糖尿病视网膜病变(proliferative diabetic retinopathy,PDR)患者的血流速度明显高于非糖尿病视网膜病变(no clinically visible diabetic retinopathy,NDR)的患者;在结膜小静脉中,NPDR患者的静脉血管直径、血流量、血流速度均高于PDR患者。因此,对结膜血流动力学的评估或许有助于糖尿病微血管病并发症的诊断评估和纵向监测。

5 DM眼科手术

糖尿病性角膜的结构和功能异常会增加手术并发症的风险,即使采用改良的手术技术,DM患者在各类眼科手术,如白内障、屈光手术、玻璃体切除术和全视网膜光凝术(panretinal photocoagulation,PRP),术后发生角膜并发症的风险仍高达80%^[41]。

有研究^[23]表明,DM不仅会造成白内障患者术后发生黄斑囊样水肿和糖尿病视网膜病变恶化等并发症,还会增加角膜并发症的风险,如持续性角膜水肿和上皮伤口愈合延迟,并且DM患者在后弹力层角膜移植术中移植失败的风险较高。由于DM患者可能发生复发性糜烂、持续的角膜上皮缺损、上皮下生长、角膜炎、不良伤口愈合等,其角膜屈光手术的风险更高。

使用耦合液和视网膜激光透镜进行氩激光光凝后,DM患者的角膜染色评分增加,角膜敏感性降低,泪膜破裂时间缩短,因此DM也是内眼手术后发生DED的危险因素^[42]。在某些情况下,LASIK可加重DR。仅对控制良好的DM患者且未诊断出DR才建议进行LASIK手术^[43]。这些研究结果均

表明,任何一种眼科手术后,DM患者的角膜并发症都应得到特别关注,即使是微创手术。

6 糖尿病眼表并发症的治疗

与其他糖尿病并发症一样,严格控制血糖是预防和治疗DM相关眼表疾病公认的前提,也是必不可少的条件^[2]。目前DM眼表并发症的预防与治疗方法主要是局部滴用人工泪液及局部使用抗炎药物,如非甾体类抗炎药、类固醇和环孢菌素A等,其有助于维持健康的眼表和清晰的视觉质量,也可缓解眼表炎症,促进再上皮化^[44]。随着科技的进步,新型有效的分子生物学治疗方法开始涌现。

6.1 自体血清 自体血清含有大量的生长因子,有利于促进角膜伤口愈合和神经再生^[2]。局部自体血清可加速DM患者玻璃体切除术后角膜上皮愈合^[45],局部应用脐带血清和血小板来源的血浆也被认为是促进角膜神经再生和上皮愈合的有效方法^[46]。

6.2 P物质 P物质是一种11氨基酸的肽,存在于角膜感觉神经中,属于感觉神经递质的速激肽家族^[47],可提供神经营养支持并促进角膜上皮细胞的增殖和迁移,以维护眼表健康^[48]。P物质可减轻高血糖引起的角膜上皮细胞凋亡,并通过神经激肽-1受体信号通路加速角膜上皮愈合^[2]。而胰岛素样生长因子1(insulin-like growth factor 1, IGF-1)也可促进角膜神经的再生并可帮助维持眼表稳态^[49]。局部应用P物质和IGF-1衍生物可促进糖尿病家兔的神经营养不良性角膜病变中角膜上皮细胞的增殖和迁移^[48]。

6.3 醛糖还原酶抑制剂 醛糖还原酶抑制剂可通过减弱山梨糖醇-醛糖还原酶途径的激活来减少神经损伤并促进角膜上皮再生^[3],可有效改善DM患者白内障手术后角膜上皮的损伤,提高角膜敏感性^[50],并促进角膜上皮伤口愈合^[51]。

6.4 神经生长因子 NGF可通过杯状细胞刺激受损神经元的再生和黏蛋白的产生,改善角膜神经病变的眼表完整性,提高角膜敏感性^[52-53]。Park等^[54]证实,局部NGF可缓解炎症和高血糖诱导的人角膜上皮细胞凋亡。Kim等^[55]表明,口服尼麦角林可促进糖尿病大鼠角膜的创伤愈合,这可能与角膜和泪液中NGF的增加有关。

6.5 其他物质 抗氧化剂,如肌肽和 β -胡萝卜素,目前也被证实有利于预防DM相关的角膜病

变^[56-57]。Di等^[26]研究表明,骨髓间充质干细胞可以减轻过度的炎症反应,激活角膜祖细胞,并增强糖尿病角膜上皮的愈合。

虽然基因、分子和干细胞治疗^[58]等实验性的项目已被开发,但许多问题亟待解决,如不同生物分子作用于糖尿病角膜病变的具体机制,究竟哪种影响因子在角膜病变过程中起主导作用,能否找到生物治疗糖尿病眼表疾病的最优组合,生物制剂应用时可能产生的不良反应等。相信随着医学研究的深入,这些问题都能被克服从而转化为临床应用。

综上所述,DM对眼表完整性、角膜敏感性、角膜上皮再生、泪液产生和睑板腺功能都有不利影响。糖尿病性角膜病变是很常见的眼部病变,其严重程度可以从轻度DED到致盲性的角膜溃疡。糖尿病性角膜神经病变常常发生在视网膜病变和糖尿病造成的身体其他部位的神经病变之前,因此,使用CCM检测出的角膜神经丛参数改变是评估糖尿病性神经病变的可行性较高的指标之一。虽然目前存在一部分药物可有效地预防和治疗DM相关的眼表疾病,但仍需要进一步地研究开发更好的治疗方法。本文重点概述糖尿病与眼表疾病的相关性,旨在增强患者和医疗从业者对DM患者眼表疾病的认识,对DM患者的优化管理具有重要意义。

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