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糖尿病角膜病变的研究进展

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[摘 要] 糖尿病及其眼部并发症严重影响了患者的生存质量，其中糖尿病角膜病变的发病率逐渐增高，受到人们的广泛关注。糖尿病可损害角膜神经以及角膜上皮、基质和内皮等各层结构，引起干眼和损伤愈合延迟等临床表现。目前，糖尿病角膜病变的治疗措施主要包括全身应用胰岛素降糖治疗和针对干眼症状的缓解治疗，角膜营养治疗以及干细胞疗法将成为新的解决方案。本文将就糖尿病角膜病变的主要损伤特点及最新治疗进展进行综述，以期为后续探索糖尿病角膜病变的有效治疗手段提供帮助。

[关键词] 糖尿病并发症；角膜病变；治疗

Research progress on diabetic keratopathy

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Abstract Diabetes mellitus and its complications seriously affect the quality of life of patients. Diabetic keratopathy, one of diabetic complications, has been widely concerned for its increasing incidence. Diabetes mellitus damages the corneal nerve, epithelium, stroma and endothelium, causing clinical manifestations such as dry eye and delayed corneal wound healing. Currently, the main treatments of diabetic keratopathy include systemic hypoglycemic treatment and relief treatment for dry eye symptoms. Corneal nutrition treatment and stem cell therapy are expected to be new solutions. In this article, we will review the main characteristics of diabetic keratopathy and the latest progress on its treatment, aiming to explore more effective treatments for diabetic keratopathy.

Keywords diabetes complication; corneal disease; treatment

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糖尿病是一种以持续性血糖升高为主要特征的慢性代谢性疾病，截至2019年，全球的成年糖尿病患者人数已达4.63亿[1]。常见的糖尿病并发症包括糖尿病肾病、糖尿病视网膜病变和糖尿病周围神经病变。在眼部，高血糖不仅会损伤视网膜，同样也会损害眼表组织，尤其是角膜。

糖尿病角膜神经病变被认为是糖尿病周围神经病变的一种表现形式，除影响角膜神经外，高血糖还对角膜上皮、基质和内皮层造成了不同程度的损害，导致患者出现干眼、损伤后愈合延迟等症状，严重影响了糖尿病患者的视觉和生活质量。本文围绕糖尿病角膜病变的损伤特点，同时结合其临床特征及最新的治疗进展进行探讨。

1 糖尿病角膜病变的损伤机制

1.1 糖尿病角膜神经病变

角膜是人体内神经最密集也最敏感的组织之一，角膜神经由感觉神经、交感和副交感神经纤维组成，能够感受温度、触摸和疼痛等[2]。Davidson等[3]观察到糖尿病大鼠角膜对高渗溶液刺激的敏感性明显下降，提示糖尿病损害了角膜感觉敏感性。

在糖尿病引起的角膜神经形态改变中，最显著的变化为神经纤维密度降低，其他还包括总神经纤维长度改变以及神经分支减少等[4-5]。多项临床研究[6-8]观察到两种类型糖尿病患者角膜神经密度明显下降。Yorek等[9]通过对糖尿病小鼠的观察，认为伴有胰岛素抵抗的2型糖尿病对角膜神经形态的影响更显著。这些角膜神经参数的改变可能为角膜敏感性的下降提供了合理的解释。

目前认为氧化应激、神经营养障碍和炎症机制在糖尿病角膜神经病变发病过程中起主要作用。在2型糖尿病患者体内，高血糖和高脂血症导致葡萄糖自氧化、蛋白质糖基化以及脂质过氧化，这些因素共同引起线粒体呼吸链中活性氧(reactive oxygen species，ROS)的产生过多[10]。积累的ROS引起神经元和施万细胞DNA损伤诱发细胞凋亡，线粒体功能障碍则导致轴突不能再生[11]。而持续的慢性高血糖又导致角膜细胞代谢障碍，角膜细胞不能分泌足够且有效的神经营养因子和生长因子，神经营养障碍从而影响了神经的再生和存活[7]。此外，持续性血糖升高引起的氧化应激导致血管内皮功能障碍，造成周围神经微血管缺血进而发生糖尿病周围神经病变[12]，结膜和角膜缘的血管为角膜供氧，高血糖导致的微循环障碍也促进了糖尿病角膜神经病变的发生发展。在炎症机制方面，ROS的过量产生引起核因子κB(nuclear factor kappa B，NF-κB)的激活，NF-κB可作为一种转录因子调控多种炎症介质的生成，糖尿病周围神经病变患者体内的白细胞介素-6(interleukin-6，IL-6)和肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)水平明显升高，提示炎症机制的重要作用[13]。

1.2 糖尿病角膜上皮病变

长期的血糖升高对角膜各层都造成了不同程度的损害，目前研究最多的是糖尿病对角膜上皮的损伤。角膜上皮细胞为非角化、分层的鳞状上皮细胞，细胞之间的紧密连接结构有助于角膜维持一定的含水量，保证角膜良好的透光性并抵御化学物质和病原微生物的入侵[14-15]。正常的角膜上皮组织形态结构对维持角膜正常生理功能有着必不可少的作用。

持续高血糖引起角膜上皮损伤的机制主要与晚期糖基化终产物(advanced glycation end products，AGEs)的积累有关。血浆中葡萄糖水平长期升高，AGEs在角膜各层中积累，通过NADPH或激活NF-κB并上调JNK和p38 MAPK表达，引起持续的氧化应激状态[16-18]，导致闭锁蛋白、层粘连蛋白等多种蛋白表达和分布异常[14]，抑制上皮细胞的增殖、黏附和迁移能力并诱导其凋亡[16,18-20]。高血糖还引起上皮基底膜增厚，并可在扫描电子显微镜下观察到角膜上皮细胞间紧密连接异常、存在裂隙，微绒毛数量减少且伴有水肿的异常形态[14]，严重影响了正常的角膜上皮功能。此外，P物质是角膜三叉神经末梢分泌的一种营养性神经肽，具有促进角膜上皮愈合及维持眼表稳态的作用[21]。研究[22]发现：在糖尿病患者的泪膜中，P物质含量明显减少且与角膜神经纤维密度呈负相关，提示在高血糖环境下受损的角膜神经营养功能下降，这进一步加重了糖尿病角膜上皮的损伤，使糖尿病患者容易发生神经营养性角膜病变[2]。

1.3 糖尿病角膜其他病变

角膜基质是角膜各层中最厚的部分，主要由角膜细胞及其分泌的胶原纤维组成。角膜基

质正常形态功能的维持决定了角膜的透明度和完整性[23]。糖尿病可引起角膜基质细胞数量的减少[5]，这可能与高血糖促进细胞凋亡相关。同时，在慢性高血糖的刺激下，角膜基质中的胶原纤维糖化并发生胶原交联，导致角膜基质的增厚[24]。此外，糖尿病患者角膜基质的胶原III水平升高，临床表现为角膜瘢痕的增加[25]。而有研究[23]发现：角膜神经的存在可使纤维化程度降低，这一结果为角膜基质与神经的相互作用提供了证据支持。

角膜内皮细胞之间紧密连接形成的物理屏障以及内皮细胞的离子泵功能，使角膜内皮在保持基质脱水状态中起至关重要的作用。持续性高血糖引起的细胞凋亡同样影响了正常角膜内皮细胞的数量和形态。研究[26-30]显示：两种类型糖尿病患者的角膜内皮细胞密度较健康人明显降低[26-28]，中央角膜厚度增加[29]，且与内皮细胞密度呈负相关，提示内皮细胞减少引起的离子泵功能障碍导致了角膜水肿[30]。由于角膜内皮不可再生，当内皮细胞由于各种损伤因素死亡时，残存的内皮细胞拉伸和迁移，导致内皮细胞变大且失去原有正常的六边形结构[15]。

2 糖尿病角膜病变临床特征

当发生糖尿病角膜病变时，患者可出现角膜知觉减退、干眼、损伤延迟愈合以及外伤后角膜感染等临床表现。

多项临床研究[4,6]表明角膜神经感觉障碍所致的角膜敏感性降低为糖尿病角膜病变典型的临床特征之一。DeMill等[4]通过测量泪液渗透压并进行Schirmer试验，发现糖尿病患者的干眼程度明显更加严重，且与糖尿病周围神经病变的严重程度呈正相关。同样，Sandra Johanna等[31]的研究也表明2型糖尿病患者有着更严重的睑板腺功能障碍。而由于角膜基质在很大程度上决定了角膜的厚度，基质水肿导致角膜增厚和透明度下降，在一定程度上影响了糖尿病患者的视力[28]。值得重视的是，角膜的增厚变硬还可能导致眼压测量误差，从而影响对糖尿病患者并发青光眼的准确评估[24,32]。

高血糖引起角膜上皮损伤，破坏了正常角膜上皮细胞的增殖和迁移能力，同时使角膜缘上皮干细胞标志物表达下降及其数量降低[33-34]，这些因素影响了手术后或损伤后伤口的愈合，导致角膜出现损伤延迟愈合甚至持续的上皮缺损，并破坏了角膜上皮的屏障功能，使角膜抵御外界刺激的能力下降，更容易发生角膜感染[20,33,35]。

3 糖尿病角膜病变治疗进展

目前，临床上治疗糖尿病角膜病变的措施主要包括胰岛素治疗、局部应用眼表润滑剂、抗炎药物和角膜绷带镜等，此外，越来越多的生长因子被证明有助于角膜神经和上皮的再生，干细胞疗法也可能成为新的治疗手段。

3.1 内科治疗

胰岛素是治疗糖尿病及其并发症的首选方法。研究[36]显示：皮下注射胰岛素可以模拟生理胰岛素的释放与分泌，维持正常血糖，恢复上皮细胞有丝分裂的昼夜节律，从而改善高血糖导致的角膜上皮损伤延迟愈合。

3.2 眼部治疗

3.2.1 干眼的缓解治疗

人工泪液、局部的抗炎药物和角膜绷带镜通过润滑眼表、减轻炎症保护角膜上皮，是目前临床常用的缓解干眼的治疗手段[37-38]。此外，局部应用胰岛素也能促进泪液分泌，改善糖尿病患者的干眼症状[39]。但这些治疗方法对于角膜组织损伤的修复能力有限。

3.2.2 促再生治疗

促进角膜再生的治疗方法是恢复正常角膜形态结构，应对糖尿病角膜神经和上皮组织受损的有效手段。

自体血清中含有丰富的生长因子，有助于促进角膜神经再生以及上皮细胞增殖和迁移[37,40]。此外，Gao等[41]发现结膜下注射重组睫状神经营养因子(ciliary neurotrophic factor，CNTF)可促进糖尿病小鼠角膜感觉神经的再生。同样，Di等[8]发现血管内皮生长因子-β(vascular endothelial growth factor，VEGF-β)加快了角膜中央和周围区域基底神经纤维再生的速度。色素上皮衍生因子(pigment epithelial-derived factor，PEDF)与二十二碳六烯酸(docosahexaenoic acid，DHA)合用则被证实有助于恢复糖尿病小鼠角膜上皮神经纤维的密度，并恢复角膜敏感性及正常的泪液量[7]。最近，中脑星形胶质细胞源性神经营养因子(mesencephalic

astrocyte-derived neurotrophic factor，MANF)也被发现具有改善糖尿病角膜伤口延迟愈合的作用，其机制与减轻内质网应激诱导的细胞凋亡相关[42]。除营养因子外，DNase I滴眼液和神经导向因子Netrin 1也能够抑制糖尿病小鼠角膜中性粒细胞浸润，加快炎症消退，发挥促上皮和神经再生作用[43-44]。

3.3 干细胞治疗

干细胞强大的分化能力、组织修复能力和免疫抑制作用使其具有广泛的应用前景[45]，目前，许多临床试验正在使用不同类型的干细胞治疗神经系统疾病和严重的免疫炎症性疾病[46-47]。间充质干细胞(mesenchymal stem cells，MSCs)已被证明可以减轻泪腺炎症，恢复正常泪液量，缓解非肥胖糖尿病小鼠的干燥综合征样疾病[48]，同时，MSCs分泌CNTF以促进糖尿病小鼠角膜神经的再生[35]，干细胞移植还将修复高血糖引起的角膜缘干细胞功能障碍，促进角膜创面愈合[34]。未来，干细胞治疗也将有望成为糖尿病角膜病变的可行治疗手段之一。

4 结语

糖尿病角膜病变是糖尿病眼部并发症中不可忽视的一部分。目前研究者已对糖尿病角膜病变有了初步认识，但仍需深入了解其发病机制，以更好地解决糖尿病患者的角膜并发症。糖尿病角膜病变的治疗目的已从最初的缓解症状，转向促进角膜神经和上皮再生以及维持包括泪膜在内的眼表稳态，角膜营养治疗和干细胞疗法将成为糖尿病角膜病变更加有效的治疗选择。

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