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全身因素影响角膜生物力学的研究进展

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摘　要

作为眼的重要组成部分，角膜不仅具有屈光特性，还有着独特的生物力学特性。既往角膜生物力学特性主要用于排除角膜手术相关禁忌症，预测角膜手术疗效和预后、扩张性角膜疾病的发生和发展，协助诊治青光眼及近视等眼科疾病，随着国内外团队的研究不断深入，研究者们将角膜生物力学与临床相结合，发现全身因素的改变也可能影响角膜的生物力学特性，如年龄、糖尿病、甲状腺疾病、性激素、结缔组织疾病等。本文将已发表的关于角膜生物力学与全身因素改变的研究结果进行了综述。

关键词

角膜生物力学，年龄，糖尿病，甲状腺疾病，结缔组织疾病

Advances in the Study of Systemic Factors Affecting Corneal Biomechanics

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Abstract

As an important part of the eye, the cornea has not only refractive properties but also unique biomechanical properties. Previously, corneal biomechanical properties were mainly used to rule out contraindications related to corneal surgery, predict the efficacy and prognosis of corneal surgery, the occurrence and development of dilated corneal disease, and assist in the diagnosis and treatment of ophthalmic diseases such as glaucoma and myopia, etc. As the research of the domestic and international teams continues to deepen, researchers have combined corneal biomechanics

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with clinical, and found that the changes in the systemic factors may also affect the cornea's biomechanical properties, such as age, diabetes mellitus, thyroid disease, connective tissue disease, and so on. This article summarizes the results of published studies on corneal biomechanics and systemic changes.

Keywords

Corneal Biomechanics, Age, Diabetes, Thyroid Disease, Connective Tissue Disease

1. 引言

作为眼的重要组成部分，角膜不仅具有屈光特性，还有着独特的生物力学特性。任何改变角膜结构的因素都可能影响角膜的生物力学特性[1]。角膜生物力学不仅在近视[2]、青光眼[3] [4] [5]、圆锥角膜[6]等眼科疾病患者中存在显著差异，在许多全身疾病患者中也存在差异。本文围绕年龄、糖尿病、甲状腺疾病、性激素、结缔组织疾病等全身因素对角膜生物力学的影响进行综述。

2. 角膜生物力学的临床测量方式

临床上，角膜生物力学常通过眼反应分析仪(Ocular Response Analyzer, ORA)及可视化角膜生物力学分析仪(Corneal Visualization Scheimpflug Technology, Corvis ST)进行在体测量[7] [8] [9]。ORA 通过喷气式压平角膜后，测量及记录了角膜的变形及恢复，使用角膜两次压平时的眼内压计算出两个独立参数—角膜滞后量(Corneal Hysteresis, CH)及角膜阻力因子(Corneal Resistance Factor, CRF)，具有良好的精确性及一致性，其中 CH 被认为是与角膜黏性阻力有关，代表了角膜吸收及消散能量的能力；CRF 是一个衡量角膜黏弹性的参数，代表了整体角膜抵抗外力的能力。Corvis ST 喷出恒定脉冲气流，运用高速 Scheimpflg 技术完整记录角膜变形过程，获得动态反应参数，从而计算和获得了生物力学参数，其中基于初代的参数(第 1/2 压平时间、第 1/2 压平长度、第 1/2 压平速率、最大压陷时间、最大压陷曲率半径、最大压陷屈膝峰间距、最大形变幅度、眼压、中央角膜厚度)研发得出的新参数(如角膜形变幅度比值(Deformation Amplitude Ratio at 2 mm, DAR)、综合半径(Integrated Radius, IR)、硬度指数(Applanation 1 Stiffness Parameter, SP-A1)、Corvis 生物力学指数(Corvis Biomechanical Index, CBI)目前得到更为广泛的应用。

3. 年龄

随着年龄的增长，角膜结构发生改变，可能引起了硬度的增加，从而角膜滞后降低[10] [11]。Ahmed Abdel Karim El Massry 等人开展了一项针对大型横断面研究，利用 ORA 对 20 至 70 岁及以上正常人不同年龄组的角膜生物力学特性进行测量，得出年龄与 CH 和 CRF 均呈显著负相关[12]。动物实验研究结果与上述结果相一致[13]年龄与圆锥角膜发生、发展的风险及 LASIK 术后角膜扩张症的风险增加也呈负相关[14]。

4. 糖尿病

糖尿病以高血糖为特征，而长期高血糖会导致各个器官功能紊乱和衰竭，就眼部而言，其角膜生物

力学会显著改变。一项共纳入 15 项研究的大型荟萃分析研究，综合了糖尿病组 1506 只眼及对照健康组 2190 只眼的临床数据，结果显示糖尿病组的 CH、CRF 值均显著高于对照健康组[15]，这提示着糖尿病眼可能具有更高的角膜硬度，与临床上糖尿病患者发生圆锥角膜、角膜扩张性疾病的风险较低相一致。Bing Zhang 等研究者使用英国数据库的相关数据，进行大型队列研究，结果示糖尿病患者的 CH 较高[16]。也有研究结果显示控制不佳(HbA1c ≥ 7%)的糖尿病患者其 CH 及 CRF 显著高于健康对照组及控制良好的糖尿病患者，且健康对照组及控制良好的糖尿病患者之间的角膜生物力学特性没有明显差异，这提示着血糖水平的稳定性可能在糖尿病患者的角膜生物力学特性的改变中起着关键作用[17]。

糖尿病患者角膜力学特性改变的潜在机制主要为以下几个假说：① 持续的高血糖引起的氧化应激导致高级糖化终末产物(Advanced Glycation End-products, AGEs)的形成，角膜基质、基底膜、弹力层中可能存在 AGEs 的积聚；② 基质的蛋白多糖和糖胺多糖的糖基化，可能会改变角膜的粘度，增加角膜吸收及消散能量的能力；③ 角膜上皮细胞和内皮细胞的功能障碍会改变对角膜水化的控制，引起亚临床水肿症，但这可能会通过导致角膜生物力学特性的改变[15]。

5. 性激素

既往研究证明角膜存在性类固醇激素受体，性激素通过血液循环进入组织，通过受体对角膜发挥作用并产生影响[18]。性激素包括雌激素、孕激素和雄激素，其中雌激素被认为是影响角膜生物力学的重要因素。Walter E 对比了猪角膜在不同培养条件(雌激素、孕激素、对照组)下的拉伸试验结果，认为雌激素对猪角膜有降低组织硬度的作用，而孕激素无明显影响[19]，这与 Spoerl E 得出的结果相似[20]。

在女性群体中，性激素虽然随月经周期、妊娠、绝经而波动，其生物力学特性的改变尚不明确[21]，也有可能是因为多种激素的平衡作用。Goldich 等研究者通过用 ORA 检测 22 名女性月经周期期间卵泡期、排卵期、黄体期的 CH 和 CRH，其中排卵时 CH 和 CRF 暂时降低[22]，而 Bahadir 等研究者分析了 21 名女性在月经周期的不同阶段的角膜生物力学特性，结果在统计学上没有显著变化[23]。屈光手术后继发性圆锥角膜以及原发性圆锥角膜进展可能与妊娠状态有关[24] [25] [26]然而 Bujor IA 等研究者通过荟萃分析对比晚期妊娠妇女与非妊娠女性的角膜生物力学特性，CH、CRF 均未观察到统计学显著性变化[27]。

6. 甲状腺疾病

在发育过程中，甲状腺激素对眼睛的发育起着重要作用，而在成年人中，一些病理性甲状腺疾病会影响眼睛的正常功能。甲状腺眼病是常见的由病理性甲状腺疾病引起的眼部病变。甲状腺眼病患者生物力学的改变被认为与角膜基质的微结构变化、胶原排列、炎症因子(如 IL-1、IL-6、TNF-α)的表达、白细胞的激活有关。Zhang 等研究者对甲状腺眼部的患者角膜生物力学使用 Corvis ST 进行评估，发现了角膜硬度的降低以及角膜扩张的易感性，同时根据活动性及疾病严重程度进行分组，发现中重度甲状腺眼病患者组的角膜生物力学稳定性低于轻度组，这可能与疾病后期软组织纤维化有关[28]。而 Comert MC 等研究者虽然研究认为甲状腺眼病患者与健康对照组患者的 CH、CRF 组间无明显差异性，但仍发现其临床严重度评分与 CRF 呈负相关[29]。

7. 结缔组织病

结缔组织病是一种累及多系统、多脏器的自身免疫性疾病，其发病机制一般认为是在遗传、免疫、环境等多因素共同作用下，多种炎症介质和细胞因子导致的免疫损伤。就眼部而言，临床工作中多关注结缔组织病相关的葡萄膜炎、巩膜炎等疾病，而对角膜结构的影响也会引起生物力学的改变，也被视作屈光手术的相对禁忌症。

Bing Zhang 等人进行的英国生物库内的横断面研究中分析了角膜滞后量与多种自我报告的系统性疾病(如系统性红斑狼疮、干燥综合症、类风湿性关节炎等)的相关性，其中仅系统性红斑狼疮与 CH 显著相关，且 CH 显著升高，然而这与病例对照研究中报告的结缔组织病患者的角膜力学特性改变相矛盾[16]。Yazici 等人研究了系统性红斑狼疮(SLE)患者的角膜生物力学，并与相同年龄组的对照组进行了比较，结果显示 SLE 组的 CH 和 CRF 值显著降低[30]。干燥综合征患者可能因局部的抗原抗体反应引起胶原溶解及角膜水合作用受到影响从而影响其生物力学[31]。

Qin Long 等研究者通过 CorVis ST 比较了干燥综合征和非干燥综合征干眼患者的角膜生物力学，发现干燥综合征干眼患者的刚度较低[32]。类风湿关节炎患者的角膜病变可分为基质炎症、胶原溶解、边缘沟和溃疡性角膜炎等阶段。促炎细胞因子的上调，触发角膜细胞产生蛋白水解酶，导致细胞外基质的分解，继而胶原溶解，使 CH、CRF 降低，且无论疾病的炎症期、缓解期，其角膜生物力学特性都可能受到影响[33]。成骨不全和 Ehlers Danlos 综合征都通过影响胶原合成，继而影响角膜生物力学，其中成骨不全是与 I 型前胶原的原发性缺陷和 I 型前胶原生物合成的失调有关，而 Ehlers Danlos 综合征是特定胶原蛋白突变(I 型、III 型或 V 型)或参与胶原蛋白产生或加工的基因中的其他突变引起[34] [35]。黏多糖贮积症(MPS)的患者除了进行性的角膜混浊外，与健康对照组相比，MPS 组的生物力学测量值 CH 和 CRF 显著较高。该疾病主要是由于负责糖胺聚糖分解的酶缺乏或功能障碍，而在病理检查中也发现了角膜基质中糖胺聚糖的积聚，这可能使该疾病患者角膜力学特性改变的原因[36]。

8. 小结

总之，角膜生物力学可能受到各种全身因素的影响，了解这些影响对于眼睛健康和疾病管理至关重要，这些因素会影响角膜的结构完整性和对外力的反应，使其成为眼科诊断和治疗，以及全身疾病筛查的重要考虑因素。

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