

糖尿病足溃疡的影响因素

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摘 要

糖尿病足溃疡(DFU)是糖尿病常见且严重的并发症, 其发生与多种因素密切相关。本文系统综述表明, 糖尿病足溃疡(DFU)是多因素交织的结果: 高血糖、血脂异常、肥胖、吸烟饮酒、免疫失衡、高血压、长病程、高龄、运动不足和足部结构异常共同作用, 增加糖尿病足发生风险; 同时, 低知识水平、经济困难及抑郁焦虑削弱自我护理, 延长溃疡愈合时间。因此, 强化健康教育、提升知晓率与可及性、开展多学科精准干预, 是降低DFU发生率、复发率和截肢率的关键策略。

关键词

糖尿病足溃疡, 糖尿病足, 影响因素, 高血糖

Influencing Factors of Diabetic Foot Ulcer

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Abstract

Diabetic foot ulcer (DFU) is a common and serious complication of diabetes, and its occurrence is closely related to multiple factors. This systematic review indicates that diabetic foot ulcers (DFU) are the result of a combination of multiple factors: hyperglycemia, dyslipidemia, obesity, smoking and drinking, immune imbalance, hypertension, long disease course, advanced age, insufficient exercise, and abnormal foot structure all work together to increase the risk of diabetic foot. At the same time, low knowledge levels, economic difficulties and depression and anxiety weaken self-care and prolong the healing time of ulcers. Therefore, strengthening health education, enhancing

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awareness and accessibility, and conducting multi-disciplinary precise intervention are the key strategies to reduce the incidence, recurrence rate and amputation rate of DFU.

Keywords

Diabetic Foot Ulcer, Diabetic Foot, Influencing Factors, Hyperglycemia

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1. 引言

糖尿病足溃疡(DFU)是糖尿病患者因下肢远端神经异常和不同程度的血管病变导致的足部感染、溃疡和(或)深层组织破坏[1]。全球糖尿病足溃疡的发病率在不同地区和人群中存在差异[2]。据统计,全球糖尿病患者中约有 6%会发生糖尿病足溃疡[3]。糖尿病足是导致非创伤性下肢截肢的主要原因之一。在一些国家和地区,糖尿病足溃疡患者的下肢截肢率较高,给患者的生活质量和医疗系统带来了沉重负担[3]。据研究显示,美国糖尿病足溃疡的发病率和截肢率相对较高,不同种族和民族之间在糖尿病足的发病率和截肢率上也存在显著差异。糖尿病患者中约有 15%会发生足溃疡,美国黑人、西班牙裔和其他非白人组比白人成年人有更高的医疗支出,这种差异可能与社会经济地位、获得医疗保健的机会以及医疗保健系统内的种族偏见等因素有关[4]。在中国,糖尿病足的发病率和截肢率也受到普遍关注。我国糖尿病足溃疡患者的年死亡率高达 11.4%,截肢率可达 8.1% [5]。一项研究显示,中国 2 型糖尿病足溃疡患者中,男性占 68.2%,且 50~59 岁年龄段的患者截肢率较其他年龄段更高[6]。此外,男性患者中截趾或截肢的发病率也更高[4]。随着年龄的增长,DFU 发生的风险增加,当中青年成人患有 DFU 时,往往溃疡更为严重,更有可能发生足部感染、长期住院和溃疡复发[4]。综述糖尿病足发生的有关影响因素对于临床医生制定治疗方案、改善糖尿病患者预后具有重要意义。

(1) 高血糖水平: 长期高血糖状态可通过激活多元醇通路,刺激氧化应激反应,以及促进晚期糖基化终产物(AGEs)形成,诱导炎症反应和血管壁增厚,损伤血管内皮[7];另一方面高血糖可导致糖尿病神经病变,引起感觉神经、运动神经及自主神经功能受损,这有可能导致足部局部压力异常发生畸形,从而诱发糖尿病足的发生[8]。另外,高血糖微环境是细菌繁殖的培养基,免疫力低下时细菌入侵机体后可快速入血,造成伤口甚至机体感染。高血糖可通过神经病变、血管病变、免疫功能障碍和慢性炎症等多重机制,共同导致足部组织发生溃疡[9],临床上常用糖化血红蛋白(HbA1c)或糖化白蛋白(GA)来反映近 3 月或近 2~3 周血糖控制水平,若 $HbA1c \geq 7\%$, $GA \geq 17\%$ 则提示近期血糖控制不佳。因此,临床医生应向患者及家属做好糖尿病健康教育,维持血糖稳定,避免血糖过高、过低或波动过大,以期延缓并发症发生及预防 DFU 发生。

(2) 脂质代谢紊乱: 血脂异常可加速动脉粥样硬化的发展,导致下肢血管狭窄或闭塞,进而影响足部的血流灌注,增加糖尿病足溃疡的发生风险[10]。李友梅等的研究得出血清脂蛋白 $LP(\alpha)$ 水平在 2 型糖尿病足患者水平升高[11],这与 Ulloque-Badaracco 等的研究结果一致[12],且有研究认为血清脂蛋白 $LP(\alpha)$ 可能与胰岛素抵抗有关[13]。低密度脂蛋白胆固醇 LDL-C 也可能是糖尿病足发生的独立危险因素,其升高可导致胆固醇沉积,促进血小板聚集和血栓形成[14]。有研究表明,LDL-C 升高可降低中性粒细胞趋化与吞噬功能,促进感染发生,刘洋[14]的前瞻性研究证实在校正血糖、HbA1c 等因素后, sdLDL-C 每

升高 0.3 mmol/L, DFU 风险增加 1.42 倍。而鞠炜仙[15]等的回顾性研究也能证实这一点, 其需截趾/肢组 LDL-C 基线值显著高于未截趾组。综上所述, 定期监测血脂功能是有必要的。

(3) 肥胖: 肥胖患者的甘油三酯 TG、低密度脂蛋白胆固醇 LDL-C 常升高, 导致血小板聚集、纤维蛋白原升高, 且因机体各种激素水平的变化, 其发生心肌梗死、外周动脉疾病的风险增加约 3~4 倍, 而且更容易合并高血压、睡眠暂停呼吸综合征等疾病[16][17], 进一步降低机体抵抗外界疾病的能力。脂肪组织肥大增生后可抑制 IRS-1 丝氨酸磷酸化胰岛素信号通路, 导致高胰岛素血症, 长期胰岛素抵抗后 β 细胞代偿性耗竭最终会导致高血糖发生[18]。肥胖和高血糖互相作用下, 机体保护性痛觉降低, 抗炎能力下降; 较高的 BMI 值使下肢承重增加, 足部血液循环受阻, 足底压力改变, 易形成胼胝, 多种因素作用下增加糖尿病足发生风险[17]。而肥胖患者糖尿病足溃疡清创或截肢(趾)后, 术后感染率是非肥胖者的 1.9 倍, 伤口愈合时间延迟[19]。有研究表明, 减重 5%~15%即可改善足底压力、恢复血流并降低炎症因子[20][21]。因此, 保持正常的体质指数, 对预防 DFU 的发生有重要意义。

(4) 吸烟与饮酒: 吸烟会损害血管内皮细胞, 促进动脉粥样硬化的发展, 同时还会导致血管收缩, 减少足部的血液供应, 增加糖尿病足溃疡的发生风险[22]。尼古丁可短暂兴奋副交感神经引起心动过缓, 继而兴奋交感神经, 心率变快, 血压升高, 增加心脏负荷[23]; 也可通过诱导内皮素-1ET-1 释放, 使一氧化氮 NO 氧化, 减少 NO 表达与活性, 降低 NO 生物利用度; 同时, 尼古丁刺激细胞外基质迁移增殖, 促进胶原纤维连接蛋白沉积, 诱导血管中膜肥厚、内膜增生, 进而损伤血管[24][25]。而血管内皮功能障碍以及血栓前状态可使神经内膜毛细血管逐渐狭窄、闭塞, 引发周围神经病变。动物实验证实长期吸烟大鼠坐骨神经 Na^+K^+ -ATP 酶活性下降, 神经传导速度减慢[26]。长期大量饮酒可导致营养不良, 影响足部组织的修复能力, 同时酒精还会对神经系统造成损害, 加重糖尿病神经病变[27]。一项韩国队列研究表明大量饮酒(≥ 30 g 乙醇/日)使 DFU 截肢风险升高 8.2% (HR = 1.082; 95% CI 1.011~1.158) [28]。长期大量饮酒(乙醇摄入量 ≥ 40 g/日)也可抑制肝脏糖原异生, 导致胰岛素抵抗, 进而血糖异常[29]。由此得出, 养成良好的生活习惯对健康是有益的。

(5) 免疫功能异常: 长期高血糖状态可破坏机体先天性免疫和适应性免疫平衡状态。中性粒细胞、巨噬细胞功能障碍, 导致细菌清除时间延长, 感染风险增高; T 细胞亚群及自身免疫失衡, 促炎微环境持续存在, 炎症因子分泌不足, 可导致微血管及神经损伤[30][31]。糖尿病患者体内往往存在慢性炎症状态, 炎症因子水平升高, 可加重血管病变和神经病变, 影响足部组织的修复和再生, 增加糖尿病足溃疡的发生风险[32]。预防感冒、发热以及上呼吸道感染、结核等其他原因所致感染是一项有效预防措施。

(6) 高血压: 高血压可加重血管病变, 导致下肢血管狭窄或闭塞, 影响足部的血液循环, 增加糖尿病足的风险[33]。高血压可导致血管壁增厚、管腔狭窄, 增加下肢血管病变的风险, 进而影响下肢血液循环, 使糖尿病足的溃疡愈合缓慢, 增加感染和坏疽的风险, 从而导致再次住院[34]。一项研究对 2012 至 2014 年间因糖尿病足并发症住院的患者进行了 3 年随访, 发现高血压是糖尿病足反复发作的相关因素之一, 而反复发作的糖尿病足溃疡会增加再次住院的风险[35]。因此, 预防高血压以及控制高血压变得尤为重要。

(7) 病程: 糖尿病病程越长, 血糖控制越差, 更易发生周围血管病变及周围神经病变, 发生糖尿病足的风险越高[36]。一项 Meta 分析显示: 糖尿病病程每延长 1 年, DFU 复发风险增加 6%, 当病程 ≥ 10 年时, 复发风险可升高 4.4 倍[37]。

(8) 年龄: 随着年龄的增长, 血管和神经的退行性变加重, 机体的修复能力下降, 糖尿病足的发生风险也会相应增加[38]。高龄人群周围神经纤维密度下降, 足底压力感知较年轻患者弱; 老龄化加速动脉粥样硬化进程, 下肢血流灌注下降, 足溃疡更易演变为缺血型, 且老年人机体免疫能力下降, 对外界抵抗力弱[39]。老年患者易出现胃排空障碍、食欲不佳、低蛋白血症等情况, 从而影响血糖控制效果[40]; 同

时老年患者血管弹性降低, 血液黏稠度增加, 易发生血管阻塞, 导致肢端血液运行障碍而引起糖尿病足[41]。Rosinha 等[42]的研究显示高龄组(≥ 65 岁)神经-缺血性溃疡比例显著高于中青年组, 提示老年患者血管病变更为严重。陈方等人[41]的研究也证实年龄 ≥ 65 岁是老年 2 型糖尿病患者易发生糖尿病足的危险因素之一。对于高龄患者的糖尿病健康教育是必不可缺的, 同时患者家属的陪伴与监督也能适当预防 DFU 发生。

(9) 运动: 适量运动和适宜运动方式及强度可改善血糖控制水平。指南推荐初发糖尿病患者首选饮食运动疗法控制血糖, 必要时加用二甲双胍, 这说明了运动的重要性, 也突出了饮食和运动是控制血糖的基础。同时建议行有氧运动每周 ≥ 3 天, 快走、骑车等中等强度 ≥ 150 min/周或高强度 ≥ 75 min; 建议每周间断抗阻运动 2~3 天[43]。适量运动可改善心肺耐力, 降低糖尿病全因死亡率[44]。Joseph 等[45]单盲 RCT 研究显示自行车有氧运动联合恒定足压运动 12 周创面缩小面积较对照组多, 其缩小速度较对照组快。运动不足可能导致下肢血液循环不良, 增加糖尿病足发生风险。因此, 对于糖尿病人群, 推荐每周适度进行体育锻炼。

(10) 足部结构和功能异常: 足部畸形、肌肉萎缩和关节活动受限可能导致足部压力分布异常, 增加溃疡风险。运动神经病变使足内在肌(骨间肌、蚓状肌)萎缩, 趾伸肌腱相对挛缩, 形成锤状趾/爪形趾等, 跖骨头向足底突出; 跟腱缩短形成马蹄足。自主神经病变可致汗腺、皮脂腺萎缩, 出汗减少, 皮肤干燥、皲裂, 细菌较易侵入[7]。这些足部畸形不但影响足底正常生理结构, 还会使局部压力负荷过大, 长期的高压状态会阻碍局部血液循环, 引发缺血性改变, 更易形成足部溃疡, 甚至导致严重的 Charcot 神经骨关节病[7] [46]。定制个体化鞋具或减压鞋垫可有效预防 DFU 发生。

(11) 其他因素: 家庭经济水平可能限制患者医疗条件, 目前有些治疗方法比如血管内造影或血运重建以评估和改善下肢血管狭窄或闭塞情况, 经济困难者无法定期评估血运情况[47], 定制合适的鞋具或减压鞋垫对他们来说更是遥不可及。教育水平低的患者可能缺乏糖尿病足预防知识, 影响自我管理。沙特阿拉伯的一项研究[48]发现, 高中以上受教育者足部护理知识得分中位数显著高于低学历组, 每日足部自检率 95.7%, 正确穿鞋检查率 75.6%。提升糖尿病知识知晓率可显著改善自我护理行为, 减少足部创伤, 最终降低糖尿病足溃疡和截肢发生率。另外, 负性情绪可能影响患者自我管理行为, 增加糖尿病足发生风险。糖尿病足患者因为不能下地活动而减少劳动, 更易发生抑郁、焦虑等心理问题, 这也反过来降低了患者的治疗依从性, 延长了伤口愈合时间, 造成恶性循环[49] [50]。

2. 结论

目前糖尿病足患病率较高, 如何有效预防其发生及恶化成为临床医生苦恼的一重大问题, 本文主要综合分析 DFU 发生发展的有关影响因素, 为临床应用做出部分贡献。糖尿病足溃疡的发生发展是多因素、多方面作用的结果, 病程, 年龄, 吸烟、饮酒、运动等生活方式, 肥胖、脂质代谢紊乱、高血压等疾病, 机体所参与的免疫功能异常等均可直接或间接增加糖尿病足发生风险。但研究证据多基于回顾性数据, 缺乏高质量随机对照(RCT)试验验证, 未来需开展多中心、长期随访的 RCT 研究补充其外部有效性, 为精准干预提供一级证据[51]。通过多学科交叉与数字化整合, 希望早期干预和预防糖尿病足发生, 显著降低其发生率和截肢率, 减轻全球糖尿病足负担。

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