综　述

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糖尿病合并脓毒症研究进展

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【摘　要】糖尿病会造成机体系统性损伤,导致免疫功能下降,易并发严重感染。感染时宿主反应失调可导致脓毒症,其病情凶险,患者常在短时间内出现严重器官功能障碍甚至死亡。随着世界范围内糖尿病患病率的急剧上升,糖尿病合并脓毒症的患者数量也快速增加。因此,增加对这 2 种疾病之间的相互关联和影响的认识对临床救治有十分重要的意义及迫切性。本文就糖尿病与脓毒症在流行病学、总体结局、系统损害及发病机制 4 个方面的进展进行综述。

【关键词】糖尿病;严重感染;脓毒症
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Research progress of diabetes complicated with sepsis

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【Abstract】Diabetes can cause systemic damage to the body, resulting in a decline in immune function, which is prone to serious infection. Sepsis can be caused by host reaction disorder during infection, which is very dangerous, and patients often suffer from severe organ dysfunction or even death within a short period of time. With a sharp increase in the prevalence of diabetes worldwide, the number of patients with diabetes complicated with sepsis has also increased rapidly. Therefore, it is of great significance and urgency to increase the understanding of the correlation and influence between these two diseases for clinical treatment. This article reviews the progress of diabetes and sepsis in epidemiology, general outcome, systemic damage, and pathogenesis.

【Key words】diabetes; severe infection; sepsis

1　糖尿病和脓毒症流行病学

据国际糖尿病联盟最新统计,全球糖尿病患病率已达 9.3%,且在未来几十年里很有可能继续增长[1]。糖尿病患者往往年龄较大、免疫力差、并发症和伴发病多,对各种各样感染的易感性增加,发生严重感染及脓毒症的风险明显升高[2-4]。在糖尿病患病率急剧上升的背景下,糖尿病合并脓毒症的发生也更加频繁。糖尿病患者并发脓毒症的风险约为非糖尿病人群的 6 倍[2];血糖控制不佳的糖尿病患者发生脓毒症的风险比血糖控制良好患者高 3 倍多[3]。

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脓毒症是由感染引起宿主反应失调所致的严重器官功能障碍[5]。在过去几十年里,脓毒症的发生率及危重患者数量不断增加,尽管现代医疗在重症监护方面不断取得进展,但脓毒症患者住院死亡率仍接近 30%[6-7]。脓毒症常发生于免疫力低下或合并有慢性基础疾病的患者,其中糖尿病患者占 21.8%~23.9%[8-9]。部分初诊糖尿病患者可以脓毒症引起的暴发性高血糖为首发症状[10]。由此可知,脓毒症已然成为糖尿病发病率和死亡率增加的常见原因,糖尿病合并脓毒症给全球公共卫生事业带来了沉重的负担和巨大的挑战。

2　糖尿病和脓毒症总论

2.1　糖尿病对炎症反应的影响

2.1.1　靶器官损害　糖尿病患者感染风险与血糖控制情况有关,虽然感染开始多为系统性表现,但在靶器官严重感染时,高血糖加重炎症反应、抑制免疫功能、机体氧化应激增加、线粒体功能受损,导致全身中毒症状和多器官功能障碍。

虽然糖尿病合并脓毒症患者出现严重呼吸功能障碍的风险相对较低(目前具体机制尚未明确),但呼吸衰竭一旦发生,抢救成功率很低[11-12]。此外,糖尿病患者在脓毒症期间发生急性肾损伤的风险明显高于一般人群,且肾功能恢复可能性低[11,13]。糖尿病患者常有高血压、冠心病等心血管伴发病,一旦发生严重感染,出现左室射血功能受损和心脏器质性改变的风险更高。研究表明,心血管系统损害是糖尿病合并脓毒症患者短期内死亡的主要原因[14-15]。

2.1.2 临床结局 糖尿病患者可能因免疫力下降、代谢紊乱或血管病变而携带更高侵袭性的病原体,从而对脓毒症患者临床结局产生不利影响。已有一些研究证实,糖尿病合并脓毒症患者死亡率升高[12,16]。但另一些研究发现,在糖尿病患者中脓毒症的死亡率反而更低[17-20]。为什么不同的研究会出现截然相反的结论呢？通过对文献进一步解析,发现这种现象或与糖尿病的治疗方法有关。研究表明,胰岛素和胰岛素增敏剂可通过改善中性粒细胞功能发挥抗炎作用[17-18],接受强化胰岛素治疗的重症患者血清中促炎性介质水平明显降低[19]。另外,还有一部分研究显示糖尿病和脓毒症死亡率之间缺乏直接关联。更有趣的是,这部分研究发现伴有入院高血糖的非糖尿病脓毒症患者死亡风险增加[8,13]。由此可知,患者感染时的高血糖状态可能是死亡的独立危险因素,而非直接与糖尿病相关。综上,目前糖尿病对脓毒症死亡率的影响仍未确定,可能与实验设计、选择偏倚有一定关系,未来还需要大样本量的前瞻性研究深入探讨。

2.2 脓毒症对糖代谢的影响

2.2.1 短期影响 机体发生脓毒症时,炎性介质过度释放和神经内分泌系统激活会对血糖控制产生不利影响导致血糖暴发性升高。高血糖不仅标志着代谢紊乱,还可反映疾病严重程度。在我国,感染是糖尿病酮症酸中毒及高渗性高血糖状态常见诱发因素和主要死亡原因[21-22]。国外也有研究提示脓毒症与高血糖危象死亡率升高密切相关[23]。

2.2.2 远期影响 Gornik I 等[24]提出,炎症反应引起的代谢损伤是持续的,对脓毒症期间发生高血糖的患者来说,即使感染得到控制,代谢障碍依然存在。这些患者在脓毒症发生后的 5 年内,发生 2 型糖尿病的风险是血糖正常患者的 4 倍。因此,脓毒症期间发生急性高血糖的患者作为糖尿病高危人群,应予以密切随访。

3 糖尿病对各系统感染的影响

3.1 神经系统

中枢神经系统感染的患者常出现昏迷、瘫痪、感觉异常等症状,患者无法自主咳嗽、翻身,易并发肺炎、压疮甚至脓毒症。由于免疫功能缺陷,糖尿病患者脑膜炎发生率和死亡率增加[25-26]。由于胰岛素缺乏,糖尿病加重了创伤性脑损伤患者的认知损伤、神经变性和神经炎症,增加了脓毒症发病率,使患者病情加重、病程延长、死亡风险升高[27]。

3.2 心血管系统

过去二十几年,感染性心内膜炎患病率和死亡率不断攀升,在糖尿病人群中这一趋势更为明显。脓毒症时病原体随血流播散并侵袭心内膜导致心血管系统感染。研究显示,糖尿病患者感染风险约为普通人群的 2 倍,且常因临床表现不典型而难以确诊、错过黄金治疗时间，住院死亡率高达 83%[15,28]。

3.3 呼吸系统

糖尿病增加肺部感染的风险和治疗难度,感染若未及时控制,细菌可通过淋巴或血液播散到不同器官引起脓毒症[29]。糖尿病合并活动性肺结核患者治疗失败概率是非糖尿病患者的 9 倍[30]。据不完全统计,武汉大学中南医院确诊的新型冠状病毒肺炎危重病例中 22.2%有糖尿病基础病史,糖尿病合并新型冠状病毒肺炎的粗病死率约为非糖尿病患者的 8 倍[31-32]。

3.4 消化系统

糖尿病代谢紊乱,可影响胃酸分泌、抑制十二指肠黏膜血液循环,并发消化性溃疡;糖尿病血管功能不全,增加了溃疡穿孔和消化道出血的风险,还可引起胆囊动脉病变,诱发坏疽性胆囊炎;糖尿病患者持续高血糖浓度促进细菌生长,增加胰腺炎、化脓性肝脓肿及结肠癌术后腹腔感染的风险;组织氧合差和代谢紊乱使感染快速播散为全身脓毒症;自主神经病变患者腹部症状不典型常导致诊疗延误;糖尿病并发症和伴发病进一步损害预后甚至危及患者生命[33-37]。

3.5 泌尿系统

糖尿病肾病引起泌尿生殖系统损害导致尿路感染难以控制或反复发生,尿液中的高葡萄糖浓度为病原菌生长代谢提供热量,进而引起防御机制紊乱并发严重感染和脓毒症[38]。产气性肾盂肾炎、产气性膀胱炎及富尼埃坏疽最初表现为泌尿系统局部组织急性坏死性感染,最常影响糖尿病患者,糖代谢紊乱可加重患者全身中毒症状,加速疾病恶化和患者死亡[38-40]。

3.6 风湿免疫系统

由于免疫系统功能紊乱,风湿免疫病患者发生脓毒症的风险极高;由于大剂量糖皮质激素治疗及自身免疫反应对胰腺 β 细胞功能的损害,加重胰岛素抵抗和糖代谢紊乱;因此,有糖尿病基础的风湿免疫病患者一旦感染,病程急骤凶险,易出现高血糖危象和脓毒性休克,使得治疗难度和费用都明显增加[14,41]。

3.7 皮肤与骨关节感染

高血糖增加了蜂窝组织炎及坏死性筋膜炎的发生风险[42],糖尿病周围神经病变患者常由于感觉丧失导致神经性溃疡。患者对炎症反应失调,加上皮肤缺乏弹性,易导致足部皮肤溃烂。久治不愈的糖尿病足溃疡感染易扩散至全身并发脓毒症,最终导致患者截肢或死亡[43]。

4 糖尿病与脓毒症发病机制的相互影响

4.1 糖尿病对炎症反应的影响

脓毒症早期,糖尿病损害内皮细胞活化,影响中性粒细胞黏附,中性粒细胞到感染部位的迁移失败,血液中细菌含

量高；高血糖损害中性粒细胞的吞噬作用和细胞内杀伤力，先天免疫系统受损，感染部位宿主反应失调，全身中毒症状进一步加重[17,44]。脓毒症晚期，糖尿病促进成纤维细胞增殖，导致细胞外基质和Ⅰ型胶原蛋白在胰腺组织沉积，加重胰岛β细胞功能障碍；C 反应蛋白、肿瘤坏死因子、白介素-6 和白介素-8 升高，淋巴细胞活化增强，适应性免疫反应不堪重负，脓毒症进一步恶化[45-46]。

4.2 脓毒症对糖代谢的影响

脓毒症发生时，机体处于应激状态，为保证重要器官的能量供应，交感神经兴奋、肾上腺皮质激素等升糖激素分泌增加[10,47]、趋化蛋白增加，加重糖代谢紊乱[48]；血浆中白介素-6 水平升高，胰岛素基因表达受限，血糖难以控制[49]。糖尿病患者β细胞功能障碍影响胰岛素分泌，高血糖不能及时得到纠正，病情进一步加重。非糖尿病患者虽然可通过分泌胰岛素纠正高血糖状态，但在严重脓毒症时，微循环障碍及氧化应激增加等病理生理过程会引起调节糖代谢的器官出现功能障碍，目前已有一些研究证明这些损害是不可逆的，应激性高血糖可能增加危重患者糖尿病患病率[24,50]。

5 结论和未来方向

根据目前的文献，虽然糖尿病对脓毒症死亡率的影响还未有定论，但可以确定的是糖尿病的代谢紊乱会影响宿主对脓毒症的反应，脓毒症增加了糖尿病患者相关治疗和护理费用，高血糖与脓毒症预后之间存在很强的因果关系。糖尿病合并脓毒症已给全球公共卫生系统造成了重大的人口负担和经济负担，未来的研究应将其作为一种综合征，充分考虑混杂因素（如代谢控制和治疗方式的差异、血管并发症与慢性伴发病的影响，肥胖、高龄、血糖控制差以及有重大传染病病史的特殊群体），以便更深刻地认识糖尿病与脓毒症之间的复杂相互作用，并针对如何有效降低感染风险、改善不良结局加以探讨。

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