·综述·

DOI: 10.12449/JCH250738

远端胰腺切除术后新发糖尿病的发病机制与临床管理

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摘要: 胰源性糖尿病是一种继发于胰腺疾病的特殊类型糖尿病。胰腺切除术是导致胰源性糖尿病的主要病因之一,其中以远端胰腺切除术后发病率最高。由于胰源性糖尿病临床误诊率高,且患者较2型糖尿病患者具有更高的死亡和再入院风险,早期准确识别和诊断对改善预后至关重要。本文系统综述了远端胰腺切除术后新发糖尿病的流行病学特征、危险因素、病理生理机制、诊断标准和治疗策略的研究进展,为临床诊疗和科学研究提供参考。

关键词: 胰腺切除术; 糖尿病; 危险因素; 诊断; 治疗学

基金项目: 国家自然科学基金(82360585)

Pathogenesis and clinical management of new-onset diabetes mellitus after distal pancreatectomy

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Abstract: Pancreatogenic diabetes is a special form of diabetes secondary to pancreatic diseases. Pancreatectomy is one of the main causes of pancreatogenic diabetes, with the highest incidence rate observed after distal pancreatectomy. Due to the high misdiagnosis rate of pancreatogenic diabetes and the increased risk of death and readmission in patients with pancreatogenic diabetes compared with those with type 2 diabetes, early accurate identification and diagnosis of pancreatogenic diabetes are of great importance for improving prognosis. This article systematically reviews the research advances in new-onset diabetes after distal pancreatectomy in terms of epidemiological features, risk factors, pathophysiological mechanism, diagnostic criteria, and treatment strategies, in order to provide a reference for clinical diagnosis, treatment, and scientific research.

Key words: Pancreatectomy; Diabetes Mellitus; Risk Factors; Diagnosis; Therapeutics

Research funding: National Natural Science Foundation of China (82360585)

糖尿病是由代谢紊乱、自身免疫反应、遗传因素、环境影响以及胰腺内分泌功能障碍等多种因素共同作用,导致胰岛素分泌不足或功能异常,从而引起持续性高血糖的一类代谢性疾病[1]。根据国际糖尿病联盟预测,截至2045年,全球20~79岁糖尿病患者总数将达7.832亿[2]。在糖尿病分型中,胰源性糖尿病,即3c型糖尿病(type 3c diabetes mellitus, T3cDM),与急慢性胰腺炎、胰腺肿瘤、囊性纤维化、血色病等疾病及胰腺切除术密切相关。研究表明,欧美国家约8%~9%的糖尿病患者为T3cDM,其中2%~3%继发于胰腺切除术[3]。胰腺术后新发糖尿病(new-onset diabetes mellitus, NODM)的发病率因手术方式而异。系统综述和荟萃分析结果显示,远端胰腺切除术(distal pancreatectomy, DP)后NODM发病率最高,其次是保留十二指肠的胰头切除术、胰十二指肠切除术、胰腺中断切除术及肿瘤剜除术[4]。这种差异可能与胰岛细胞分布特征相关,胰腺体尾部胰岛细胞密度约为头部的2倍,可以解释DP对血糖调控具有更显著的影响[5]。DP是目前治疗胰腺体、尾部良恶性病变的首选

术式。随着影像学技术进步,多发于胰腺体、尾部的良性病变(如导管内乳头状黏液性肿瘤)检出率显著提高[6],DP术后患者生存期获得明显提升,但DP术后NODM也日益受到关注。因此,术前准确识别NODM高危人群并制定个体化防治策略至关重要。本文系统总结DP术后NODM的流行病学特征、危险因素、病理生理机制及诊疗进展,以提升对DP术后NODM的认识,为临床防治提供参考。

1 DP术后NODM的发病率

目前,DP术后NODM的发病率尚无确切数据,综合近年研究,其发生率在5%~50%[7],这一差异可能与随访时间、个体差异、遗传因素以及术后并发症等多种因素相关。表1汇总了近5年相关研究中报道的NODM发病率数据。

表1 近5年相关报道中的DP术后NODM发病率
Table 1 Incidence of NODM after DP in articles published in the last 5 years

第一作者	发表年份(年)	随访时间(月)	发病率	文献
Imamura S	2024	36.0	74.1%	[8]
Chen ZH	2023	42.8	29.1%	[9]
Firkins SA	2022	24.0	20.2%	[10]
Sera N	2021	48.0	28.9%	[11]
Tariq M	2020	24.0	36.0%	[12]
Maxwell DW	2020	120.0	42.9%	[13]

2 DP术后NODM的危险因素

DP术后NODM的危险因素在不同患者中表现出显著差异,这种差异可能源于个体特征和手术因素的多样性[10,14]。现有研究将危险因素分为3类:不可改变危险因素、可改变危险因素和手术相关危险因素。

2.1 *不可改变危险因素* 年龄是NODM重要的不可改变危险因素之一。研究显示,DP术后NODM患者的年龄显著高于未发生NODM患者(OR=1.03,P<0.001)[9]。在≥38岁的患者中,术后6个月的NODM发生率为13.0%,1年时为19.9%,2年时为24.6%,3年时为30.2%,5年时为35.9%,10年时达到44.8%(P<0.001)[15]。老年人群中NODM的发生率较高的原因可能与胰腺储备减少导致胰腺功能减退,术后恢复较差等有关[9,16-17]。性别与NODM的关联性尚存争议,有报道显示男性患者具有较高的NODM风险(OR=1.32,P<0.001)[18],也有研究显示女性患者更可能发展为NODM(OR=5.19,P<0.003)[19]。

2.2 *可改变危险因素* 术前的饮食习惯、吸烟和饮酒行为以及体质量指数被认为是NODM的可改变危险因素[19-22]。肥胖作为糖尿病的明确危险因素,其机制与糖耐量受损及胰岛素抵抗密切相关[23]。术前体质量指数较高的患者,在DP术后更易出现内分泌功能损伤,提示肥胖患者术后发生NODM的风险更高。

2.3 *手术相关危险因素* 目前公认的手术相关危险因素包括胰腺切除范围、术中出血量、脾切除、术中低血压及术后胰瘘等[15,24-26]。其中,胰腺切除体积与NODM发生率呈正相关,多数研究支持胰腺切除体积越大、NODM发病率越高的观点。但最近一项研究指出,虽然DP术后残余胰腺体积减少将导致胰岛素分泌功能下降,但这种变化与糖耐量异常及NODM的发生并无直接因果关系[10]。

3 DP术后NODM的发病机制

DP术后NODM的病理生理机制尚未完全明确,但主要涉及胰岛β细胞和α细胞功能异常、胰岛素分泌障碍及残余胰腺功能损伤等方面(图1)。

3.1 *胰岛β细胞数量减少,胰岛素分泌量下降* 胰岛素由分布于全胰腺的β细胞分泌,通过抑制肝糖异生和糖原分解、促进肝糖原合成,调节血糖水平[27]。由于β细胞主要富集于胰腺体尾部,DP术后即使非糖尿病患者也可能出现空腹胰岛素和C肽水平降低[28]。研究发现,DP术后胰岛β细胞数量减少的同时,其面积增大且ALDH1A3(乙醛脱氢酶1家族成员A3)表达上调。ALDH1A3在胰岛中的高表达通常被视为β细胞功能衰竭的标志,这些改变共同促进了NODM的发生[29-30]。

3.2 *胰岛α细胞数量减少* 胰高血糖素主要由分布在胰腺体、尾部的α细胞分泌[31]。在生理状态下,胰高血糖素通过促进肝糖原分解和糖异生作用维持血糖稳态,构成重要的低血糖防御机制[27]。正常情况下,葡萄糖摄入可抑制胰高血糖素分泌以预防高血糖[32-33]。然而,DP术后患者对葡萄糖刺激的胰高血糖素抑制反应受损[34]。这种抑制缺陷联合术后肝脏对胰高血糖素敏感性增强,可能在胰岛素分泌不足的情况下协同导致高血糖状态。

3.3 *残余胰腺损伤* 研究表明,DP术中出血量增加及联合脾切除术与NODM风险显著相关。手术出血量与胰腺质地及病变区域血供密切相关,大量失血可诱发全身应激反应并导致残余胰腺组织炎症损伤[9]。此外,术中过量补液可能引起胰腺水肿和再灌注损伤[35],这些因素均可损害残余胰腺的内分泌功能。动物实验显示,脾脏$Hox11^{+}$干细胞具有分化为胰岛细胞的潜能[36-37]。发

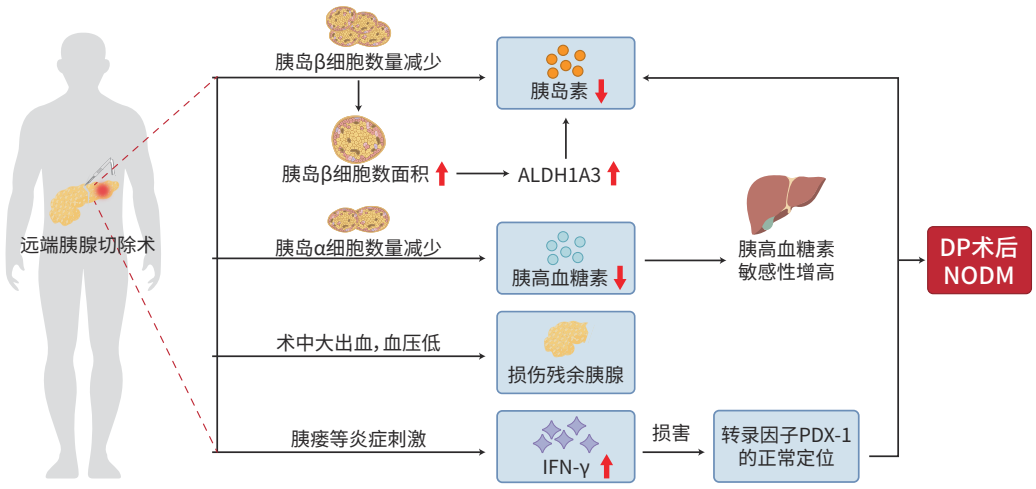

图1　DP术后NODM的发病机制示意图

Figure 1　Schematic diagram of the pathogenesis of NODM after DP

育生物学研究发现，脾脏间质组织源自胰腺间质，PTF1-p48基因敲除小鼠虽缺乏外分泌胰腺，但其脾脏中存在功能性胰岛并能维持正常血糖水平[38]。临床研究证实，联合脾切除的胰腺切除术患者较单纯胰腺切除患者更易发生NODM[12,14,39]。

3.4　*其他因素*　研究表明，炎症相关细胞因子如IL-1β、TNF-α和IFN-γ可抑制葡萄糖刺激的胰岛素分泌[40]。高表达IL-1R和IL-1β的胰岛细胞可促进β细胞凋亡[41]。临床研究显示，IL-1R、IL-1β和TNF-α拮抗剂对2型糖尿病具有一定治疗效果[42]。在DP术后胰瘘等慢性炎症状态下，升高会破坏胰岛细胞中PDX-1（胰十二指肠同源框转录因子1）的正常定位[43]，而特异性抑制IFN-γ可恢复PDX-1的核定位。此外，炎症反应中表达的肾上腺髓质素和vanin-1可能在DP术后NODM的胰岛功能调节中发挥重要作用[44]。

4　DP术后NODM的诊断

DP术后NODM的诊断目前尚未形成国际统一标准，但基于最新研究和临床实践可归纳以下核心诊断要素[45]。（1）血糖标准：需符合现行糖尿病诊断指南，基于术后血糖异常（空腹血糖≥7.0 mmol/L或随机血糖≥11.1 mmol/L等）；（2）胰腺外分泌功能评估：通过粪便弹性蛋白酶-1检测或直接功能试验确认外分泌胰腺功能不全[46]；（3）影像学检查：采用超声内镜、MRI或CT评估胰腺结构及残余功能；（4）自身免疫标志物排除：需检测谷氨酸脱羧酶抗体等以排除1型糖尿病；（5）辅助指标：包括β细胞功能受损（如C肽水平降低）、肠促胰岛素效应减弱、脂溶性维生素（A/D/E/K）缺乏等[19,47]；（6）临床特征整合：需综合评估年龄、体质量指数、胰腺切除范围、术中失血量及脾切除史等手术相关因素。由于缺乏特异性生物学标志物，NODM的确诊需结合胰腺严重损伤或切除病史，并排除其他糖尿病类型。诊断过程应整合动态血糖监测、胰腺功能检测及影像学结果，以实现精准识别和个体化管理。

5　DP术后NODM的治疗

DP术后NODM的治疗需采取多学科协作模式，重点解决胰腺外分泌功能不全和营养管理等关键问题[48]。虽然T3cDM被归类为继发性糖尿病，但其治疗方案应基于个体病理生理特征进行优化[49]。胰岛素治疗目前仍是T3cDM的标准疗法，其优势在于对营养不良患者的合成代谢作用。然而，针对存在外周胰岛素抵抗的患者，需精细调整剂量以预防低血糖。值得注意的是，近期研究提示胰岛素治疗可能增加胰腺导管腺癌风险，对已有胰腺炎性病变的T3cDM患者应谨慎评估风险获益比[50]。已有研究显示口服降糖药疗效有限，多数患者最终需转为胰岛素治疗[51]。但部分证据支持二甲双胍在轻度高血糖患者中的应用价值，其可通过改善外周胰岛素敏感性和抑制肝糖输出发挥作用[52]。目前仍需更多临床研究来优化T3cDM的药物治疗策略。

6　展望

随着DP术后患者生存期的延长，长期并发症管理日益受到重视。当前研究主要聚焦于NODM危险因素和预测模型，但对胰腺纤维化、脂肪浸润等关键病理变化的关注不足，且现有预测模型多缺乏影像学客观指

标。剪切波弹性成像技术已在肝纤维化评估中广泛应用,其在胰腺组织密度和脂肪浸润定量分析中亦展现出良好应用前景。未来研究可将剪切波弹性成像等无创影像学技术整合至术前NODM风险评估体系。在治疗领域,DP术后NODM的药物干预、生活方式管理及患者教育等综合治疗方案正成为研究热点。通过优化治疗策略,有望实现更好的血糖控制、生活质量改善及生存期延长。同时,降低相关并发症发生率、减轻患者经济负担也具有重要的临床价值和社会意义。

利益冲突声明: 本文不存在任何利益冲突。

作者贡献声明: 阿拉帕提·外力负责课题设计,资料分析,撰写论文及修改论文;韩玮负责拟定写作思路,指导撰写文章,提供基金支持并最后定稿。

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收稿日期：2024-11-10；**录用日期：**2024-12-11
本文编辑：邢翔宇

引证本文：ALAPATI WL, HAN W. Pathogenesis and clinical management of new-onset diabetes mellitus after distal pancreatectomy[J]. J Clin Hepatol, 2025, 41(7): 1476-1480. 阿拉帕提·外力, 韩玮. 远端胰腺切除术后新发糖尿病的发病机制与临床管理[J]. 临床肝胆病杂志, 2025, 41(7): 1476-1480.