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肝内胆管结石术后复发的研究进展*

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[摘要]　肝内胆管结石(IBDS)是临床肝胆外科常见疾病,是我国良性胆道疾病重要的致死原因。其治疗方式以外科手术为主,随着现代医疗技术的发展,手术方式呈现多样化,腹腔镜、胆肠吻合术、精准肝部分切除术、肝脏移植、微创取石等各种技术的飞速发展,极大地降低了患者痛苦,但因其术后高复发率、多并发症,严重影响患者的生活质量。目前肝内胆管结石术后复发机制尚未完全清楚,与胆道感染、胆汁淤积、饮食结构等多种因素密切相关。该文就肝内胆管结石术后复发的病因及其危险因素的研究进展进行综述,以期为临床治疗肝内胆管结石及预防术后复发提供一定的帮助。

[关键词]　肝内胆管结石;复发;病因;危险因素;综述
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Research progress of postoperative recurrence of intrahepatic cholelithiasis*

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[**Abstract**]　Intrahepatic bile duct stones (IBDS) is a common disease in clinical hepatobiliary surgery, which is an important cause of death for benign biliary diseases in our country. Its treatment method is dominated by operation, with the development of modern medical technology, the surgical methods are diversified. The rapid development of laparoscopy, choledochojejunostomy, precise partial hepatectomy, liver transplantation, minimally invasive stone extraction and other technologies greatly reduce the pain of the patients. However, due to its postoperative high recurrence rate and multiple complications, the quality of life of the patients is seriously affected. At present, the recurrence mechanism of intrahepatic cholelithiasis has not been fully understood, and is closely related to many factors such as biliary tract infection, cholestasis and dietary structure. In this paper, the etiology and risk factors of recurrence of intrahepatic cholelithiasis are reviewed in order to provide some help for clinical treatment of intrahepatic cholelithiasis and prevention of postoperative recurrence.

[**Key words**]　intrahepatic bile duct stones; recurrence; etiology; risk factors; reviewed

肝内胆管结石(IBDS)是指发生在肝右、左胆管的近端胆管内,无论胆囊或胆总管中是否有结石的一种常见的肝胆外科疾病[1]。IBDS 多发于中国、日本、韩国等亚太地区,其发病率为 3.1%～21.2%[2]。IBDS 临床治疗以外科手术治疗为主,随着医疗水平的提高及腹腔内镜技术的不断更新,肝内胆管结石的治疗有了一定成效。但术后高复发率、多并发症仍是亟须解决的问题。为解决这个问题,首先需要弄清楚 IBDS

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术后复发的病因及危险因素。

1 手术现状

IBDS 注重第 1 次治疗，如果处理不当，术后残石率高达 20%，复发率高达 70%，严重者需要反复多次手术。IBDS 手术方式以胆管切开取石、胆肠吻合术、肝脏移植手术、精准肝切除术为主。胆道镜下胆管切开取石是肝内胆管最基本的手术方式，该手术切口大、残石率高，不利于患者恢复。胆肠吻合术因彻底废除了 Oddi 括约肌功能，肠液易反流继发胆管炎症致使结石复发，目前胆肠吻合术的使用存在争议。对于分布全脏各处的结石，肝脏移植能够极大地降低结石复发；然而在国内，因肝脏移植手术成本和风险较高、肝源稀少，临床上难以广泛使用。近年来，精准肝切除术成为最有效治疗 IBDS 的一线治疗手段，结合术中超声准确定位胆管病变及结石范围，能有效清除病灶，结石清除率达 95%，然术后复发率仍高达 3%～15%[3-5]。因此，IBDS 术后高残石率、高复发率、多并发症一直是困扰临床医师的重要问题。

2 胆道感染

胆道感染是结石形成及术后复发的重要原因，引起胆道感染的微生物主要包括细菌和寄生虫。几乎所有的 IBDS 患者胆汁都能培养出细菌，SHEN 等[6]在胆汁培养出约 173 种细菌，其中革兰阳性球菌以大肠埃希菌、肺炎克雷伯菌为主，革兰阴性球菌以粪肠球菌和屎肠球菌为主。最近也相继报道了幽门螺杆菌也与 IBDS 有关[7-10]。细菌入侵主要是经过 Oddi 括约肌胆道逆行感染或者是门静脉血行感染，进入胆道后可能凭借以下方式参与结石的形成：(1)细菌产生的外源性 β-葡萄糖醛酸酶(β-GD)和磷脂酶，前者催化结合胆红素(CB)分解游离胆红素(UCB)，促使 UCB 与 Ga^{+} 结合形成胆色素结石；后者降解卵磷脂为不溶于水的游离软脂酸和溶血磷脂，发生软脂肪酸沉淀[11-12]。(2)细菌感染会介导内皮细胞、白细胞、成纤维细胞等释放炎症因子，促进胆道炎症并诱导胆管上皮细胞发生上皮-间叶样表型转化，继发胆道纤维化，最终形成结石[13]。(3)感染导致的胆管炎使上皮细胞分泌的黏性蛋白增多，产生结石，同时还可造成胆管狭窄、胆汁淤积、肠液返流等病理改变，加速结石形成。寄生虫感染也是 IBDS 形成和复发的原因，在高达 30%的 IBDS 患者中都检测到寄生虫[14]。华枝睾吸虫、胆道蛔虫、血吸虫等寄生虫经 Oddi 括约肌上线感染，引起机械和化学损伤，导致肝内外胆管炎症、梗阻和癌变，同时易造成 Oddi 括约肌痉致使胆管狭窄、胆汁淤积、肠液返流等间接促进结石的形成[15]。此外，被困的在胆管内的虫体及虫卵，死亡后可直接成为胆泥和棕色色素胆管结石的病灶和来源[16]。

3 胆汁瘀滞

胆汁瘀滞是形成结石的必要条件，是胆汁分泌和排泄障碍造成的一种生理病理过程。由于胆汁分泌及排泄受阻，胆汁在胆管内淤积，胆盐和胆红素颗粒不能及时排除胆管，易沉积发生聚集而梗阻。同时胆汁瘀滞与胆道感染关系密不可分，胆汁瘀滞的过饱和成分促进细菌定植于胆道内，诱发胆道感染，促进结石形成。由于梗阻、感染，胆汁中的酸性黏蛋白增多降低了胆汁的 pH 值，导致胆红素钙的沉淀。黏性蛋白同时捕获 Ga^{+} 和脂质而形成胆泥，加重胆道梗阻[17]。反复的梗阻和感染进一步影响胆管中胆汁流动的机械或功能障碍，加重胆汁瘀滞，最终导致结石的形成。

4 饮食结构

相关研究表明，饮食结构与肝内胆管结石的形成有着密切相关。长期食用低蛋白低脂高碳水化合物可能使 β-GD 抑制物葡萄糖二酸 1-4 内酯的含量减少，内源性 β-GD 和胆红素 β-GD 活性增强，使游离未结合的胆红素不溶于水，加速与 Ca^{2+} 结合，发生沉淀，是形成结石的基础[18-19]。长期低蛋白低脂饮食还会导致胆囊收缩素释放减少和 Oddi 括约肌功能减退，继发肠液反流和胆汁淤积而感染，致使结石形成[20]。与之相反，ISABEL 等[21]在临床观察中发现高蛋白高脂饮食能增加胆汁酸的分泌，促进胆红素形成结合胆红素进入肠道，并显示出了高抗菌活性。MISCIAGNA 等[22]还发现饮食过于油腻、高糖、高热量的习惯会增加胆汁中的饱和度，促使胆固醇结石的形成。相反，ZHANG 等[23]在实验中发现膳食纤维可以通过增加胆汁酸排泄量和降低胆固醇的肝合成来降低总胆固醇和低密度脂蛋白胆固醇。此外，长期不食用早餐也是结石形成原因之一，这可能和空腹时胆汁分泌减少，胆酸含量减少，胆固醇因此在胆管中沉积有关。

5 医源性及术后危险因素

IBDS 的治疗以外科手术方式为主，虽然现代医疗水平提高了，但由于各种局限性原因也是造成结石术后复发的原因。有研究报道手术方式的错误、手术创伤胆道损伤和狭窄、胆道感染、胆汁淤积也是 IBDS 术后复发的原因[24]。特别是结石分布位置造成术后残石、手术损伤引起的胆道解剖异常及手术损害 Oddi 括约肌功能也是 IBDS 术后复发的危险因素。

5.1 术后残石

IBDS 的病情是复杂的，结石往往是多发的。很多患者结石分布于双侧肝叶，甚至呈弥漫性的，复杂的肝内胆管结石易导致胆道梗阻、反复感染等[25-26]。

要彻底清除病灶，势必切除大量肝脏组织，这不仅增加了手术难度，同时增加了术后肝功能衰竭的风险[27-28]。故在手术中往往只行一侧或者部分切除术，然而肝切除术主要运用于肝一侧或肝段有萎缩、纤维化或肝硬化的结石患者，当肝内胆管结石存在两个肝叶中，会造成病灶清除不彻底、结石残留，也是术后复发的重要原因[29]。此外，IBDS 常伴有肝外胆管结石和胆囊结石，由于手术操作者操作不当，挤压进入肝内胆管，也是结石复发的重要原因。

5.2 胆道解剖异常

先天因素和后天因素均可导致胆道解剖异常，而造成胆汁排泄障碍和胆汁淤积问题，最终诱发结石的形成。据文献报道，胆道解剖异常的比例为 28%～43%[30]。先天异常主要包括吻合口狭窄、先天性胆总管囊肿、Caroli 及硬化性胆管炎等。后天异常是由侵入性的探查、胆道手术等医源性胆管损伤、反复的胆管炎刺激造成的。结石沿着病变的胆管树呈区域性分布，近端发生胆管狭窄而远端发生胆管扩张是 IBDS 最为显著的解剖特点；胆管狭窄造成胆汁引流不畅、胆汁瘀滞，继发胆道感染，促进结石的形成，同时胆管狭窄易使手术结石残留，术后胆道狭窄的患者复发率明显高于无狭窄患者[31-32]。此外，若是手术时没有及时纠正胆管狭窄，或者术后在原来的狭窄部位出现新的狭窄，都增加了术后结石复发的风险。

5.3 Oddi 括约肌功能障碍

Oddi 括约肌作为一道生理门阀，有着调节胆汁流动、胰液流动、防止十二指肠内容物及肠道细菌返流的作用[33]。Oddi 括约肌功能一旦障碍，易致肠液返流而胆管炎复发。此外，伴有 Oddi 括约肌障碍的 IBDS 患者，特别是多次胆道手术者，易继发胆道感染。临床医师对于合并有 Oddi 括约肌障碍的 IBDS 患者，为减少胆肠返流预防术后胆管炎及结石的复发，常选择胆肠 Roux-en-Y 吻合术，但胆肠吻合术破坏了胆道的正常解剖生理，永久性的失去 Oddi 括约肌这一生理阀门，目前欧洲肝病学会已经不推荐使用胆肠吻合术[34]。ZHANG 等[35]发现因 Oddi 括约肌功能障碍引起十二指肠胆管反流的发病率高达 35.9%，是细菌感染和结石复发的重要原因。ZHOU 等[36]发现因 Oddis 括约肌松弛的患者更容易患上胆管结石，并且经常需要再次手术，这可能是和 Oddi 括约肌松弛时，胆囊过度充盈，胆汁流入十二指肠的流量减少，而继发生胆道胆汁淤积有关。

6 小　结

随着医疗技术的进步，根据 IBDS 患者病情可选择的手术方式越来越多，精准肝切除术已成为最有效治疗 IBDS 的一线治疗手段，随之被治愈的患者也越来越多，但仍有很多患者术后出现结石复发的情况。IBDS 的术后复发是多因素引起的，与胆道感染、胆汁淤滞、饮食结构有着密切的关系。由于结石分布位置造成术后残石、手术损伤引起的胆道解剖异常及损害 Oddi 括约肌功能也是术后复发的危险因素。此外，与性别、年龄、肥胖、药物、遗传及高血压、糖尿病、肝硬化等代谢异常均有着密切关系[37-38]。虽然 IBDS 术后复发病因尚未完全清楚，但可以肯定的是 IBDS 的形成和复发都是极其复杂的过程，期待进一步相关的动物实验和临床试验来明确其发病机制。

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