



doi:10.7659/j.issn.1005-6947.2021.08.012
http://dx.doi.org/10.7659/j.issn.1005-6947.2021.08.012
Chinese Journal of General Surgery, 2021, 30(8):964-970.

· 文献综述 ·

胆总管结石治疗后复发因素的研究进展

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摘要

胆总管结石是外科最常见的良性疾病之一, 随着科技的进步、医疗技术的提升以及医院硬件设施的完善, 经内镜逆行性胰胆管造影术(ERCP)及腹腔镜胆总管探查术(LCBDE)已经成为胆总管结石的主要治疗手段, 且具创伤小、恢复快的临床优势。但是, 临床多中心研究数据显示, 胆总管结石术后复发率为4%~24%, 因此, 胆总管结石术后复发是外科医生必须面对的挑战和亟待解决的问题。胆总管结石的形成是一个复杂的遗传和环境因素相互作用的过程, 其具体机制尚未完全阐明, 术后复发机制及相关因素亦成为临床研究的难点和热点。笔者通过整理归纳相关文献, 从十二指肠乳头括约肌功能、胆道微生态、胆道解剖三个维度, 阐述胆总管结石术后复发的相关机制与研究进展, 为预防胆总管结石术后复发提供新的策略和研究方向。

关键词

胆总管结石; 复发; 综述
中图分类号: R657.4

Research progress on postoperative recurrence factors of choledocholithiasis

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Abstract

Choledocholithiasis is one of the most common benign surgical diseases. With the progress of science and technology, the development of medical techniques and the improvement of hospital hardware facilities, endoscopic retrograde cholangiopancreatography (ERCP) and laparoscopic common bile duct exploration (LCBDE) have become the main treatment methods for choledocholithiasis, with the clinical advantages of less trauma and rapid recovery. However, data from multicenter clinical trials showed that the postoperative recurrence rate of common bile duct stones is 4%–24%. Therefore, the postoperative recurrence of common bile duct stones is a challenge to be faced and an urgent problem to be solved for surgeons. The formation of choledocholithiasis is a complex process of the interactions between genetic and environmental factors, and its specific mechanism has not been fully clarified. The mechanism of

基金项目: 甘肃省兰州市人才创新创业基金资助项目(2017-RC-37)。

收稿日期: 2021-03-18; 修订日期: 2021-07-24。

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postoperative recurrence and related factors have also become the challenges and hotspots of clinical research. Through literature review and extraction, the authors present the mechanism and research progress of postoperative recurrence of common bile duct stones from the three dimensionalities: duodenal papillary sphincter function, biliary microecology and biliary anatomy, so as to provide new strategies and research directions for preventing postoperative recurrence of choledocholithiasis.

Key words

Choledocholithiasis; Recurrence; Review

CLC number: R657.4

胆总管结石是全世界范围内的常见病、多发病,在消化系统疾病中占到了很大的比重,其在西方影响了超过10%的人口^[1]。除遗传因素外,年龄、性别、营养、肥胖、体质量快速增加和减少以及运动等因素都与胆总管结石的形成密切相关^[2]。而随着我国经济的飞速发展,人民生活水平的提高,人口老龄化、肥胖等问题日趋严峻,受之影响,我国胆总管结石的发病率亦呈逐年上升趋势。随着科技的进步、医疗技术的提升以及医院硬件设施的完善,经内镜逆行性胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)及腹腔镜胆总管探查术(laparoscopic common bile duct exploration, LCBDE)以“创伤小、恢复快”的临床优势,已成为临床治疗胆总管结石的主要手段。但是,临床多中心研究数据表明,胆总管结石患者接受ERCP手术后的复发率为4%~24%^[3],其高复发率已成为外科医生面临的挑战和亟待解决的问题。因此,胆总管结石的复发已成为国内外外科医生关注的焦点问题。目前,国内外学者对于胆总管结石的复发机制研究重心主要集中在胆道微生态、手术导致的十二指肠乳头括约肌功能损伤及异常以及个体胆道解剖差异等热点问题上。笔者通过整理归纳胆总管结石术后复发的相关研究,从十二指肠乳头括约肌功能、胆道微生态、胆道解剖三个维度,阐述其与胆总管结石术后复发的关系及存在的问题,拟为预防胆总管结石术后复发提供新的策略和研究方向。

1 十二指肠乳头括约肌功能与复发性胆总管结石

十二指肠乳头括约肌即Oddi括约肌,指包绕在胆总管末端、胰管末端及壶腹部周围的环形括约肌,包括胆总管括约肌、胰腺管括约肌、壶腹

括约肌,扮演着胆汁和胰液排泄的“开关”角色,其对维持胆道系统流体压力、防止十二指肠液反流、防止胆汁和胰液之间的相互交通等发挥着重要作用^[4]。Oddi括约肌功能失调及结构受损会导致其“开关”功能不良或丧失,将导致胆汁淤积、十二指肠液反流等,临床上表现为胆道梗阻、胆道感染、胰腺炎及胆总管结石复发^[5]。

随着临床探索的深入,胆总管结石手术的改进,腹腔镜及内镜的普及,LCBDE和ERCP已成为目前胆总管结石的临床一线治疗手段^[6]。研究^[7]表明,相较ERCP治疗胆总管结石,LCBDE的创伤更大,恢复期更长,但就其长期治疗效果而言,LCBDE术后结石的复发率更低。究其原因,ERCP取石主要联合采用内镜下球囊扩张术(endoscopic papillary balloon dilation, EPBD)或十二指肠乳头括约肌切开术(endoscopic sphincterotomy, EST)两种方式,两者均伴有不同程度的Oddi括约肌功能及结构的损伤,从而导致术后Oddi括约肌“开关”不良,进而造成胆汁淤积、胆道系统感染等,应是结石复发的主要解剖学因素^[8-9]。

1.1 EST后的十二指肠乳头括约肌功能

普遍认为相较EPBD利用球囊来放松十二指肠乳头括约肌达到取石目的来说,EST对十二指肠乳头括约肌的功能有着更大的伤害^[10],其术后由于十二指肠乳头括约肌功能的丧失,使得复发胆总管结石的远期风险大大提高^[11-12],有回顾性研究^[12]结果表明,因为EST对于十二指肠乳头括约肌不可逆的损伤,所以术者应谨慎考虑对于年轻患者的术式选择以尽量保留其括约肌功能。怎样合理选择手术方式以减少十二指肠乳头括约肌功能损伤是有效预防胆总管结石术后复发的重要因素,但是,如何严格把握手术适应证,在EST与EPBD的术式选择方面缺少相应的临床指南。

1.2 EPBD后的十二指肠乳头括约肌功能

虽然EPBD相较EST更有利于保留尽量多的十二指肠乳头括约肌功能,但这种保护的效果极大程度上取决于术中使用的球囊大小。有学者^[13-14]研究发现,EPBD术中球囊大小>12 mm时术后十二指肠乳头括约肌功能几近丧失,而当球囊大小<8 mm时术后十二指肠乳头括约肌功能基本得以保留。对于十二指肠乳头括约肌功能与术后复发的关系,有研究^[15]表明,当术中球囊>15 mm时,将大大增加术后胆总管不良事件的风险,其中就包括了胆总管结石的复发,这可能与球囊过大导致十二指肠乳头括约肌功能受损有关。在一项包括了300例患者的临床研究^[16]中,通过72个月的随访结果显示,相较于单纯的EST取石,EPBD在预防胆总管结石术后复发上更具有优势。但是,不同球囊大小与不同患者的个体差异组合对于胆总管结石术后复发的影响目前尚缺少多中心、大样本前瞻性临床随机对照研究的结果及循证医学的证据,因此EPBD术后胆总管结石复发的具体数据仍有待于进一步探索。

2 胆道微生态

人类体内存在大量的微生物,即使是健康个体不同身体部位的微生物群都存在着差异,这种微生态的差异已经被证明与饮食、宿主遗传、环境及微生物接触史有关,但这些原因还远远不足以解释人体微生态的多样性^[17]。随着医学检验水平的提升,人体内的微生物群与各种疾病发生发展之间的密切联系被揭示^[18]。

2.1 胆道微生态与胆道结石的形成

胆道由于其强碱环境的存在,在以前被认为是无菌的相对封闭结构^[19],但随着人们研究的不断深入,这种认知被逐渐打破。早在20世纪60年代就有科学家证明胆道细菌的分泌产物 β -葡萄糖醛酸酶与胆结石的形成有关^[20],在80年代初期又有研究者补充证明,胆结石的形成也与细菌产生的黏液及磷脂酶有关^[21]。而80年代末随着实验技术的不断提高,科学家从结石的片状结晶层中发现了细菌,电镜下首次发现了钒红染色的胞外多糖基质包围的革兰氏阳性和革兰氏阴性细菌^[22]。进入21世纪后,有研究^[23-24]通过对胆汁的核酸提取及16s RNA高通量测序发现,胆道微生态具有强

烈的个体特色,而这种个体化与胆汁酸对细菌细胞的毒性有关,胆汁酸对细菌细胞的毒性作用选择性的筛选了人体胆道微生态的构成组分。在没有任何胆道疾病的健康个体中,胆道微生物群主要以肠杆菌为主,这与肠道菌群的优势菌种相一致^[21],与健康对照组相比,胆结石患者的胆汁中虽然还是以肠杆菌为主,但病理情况下胆汁中的变形菌数量增多,菌种多样性减低^[25-26]。关于变形菌对人体胆道系统的影响,有研究者^[27]认为变形菌破坏了上皮细胞的正常功能,导致组织上皮功能障碍,虽然此学说仅仅在人肠道上皮的功能障碍上得到了印证,尚未明确变形菌的增加是否与胆道上皮功能障碍有关,但也为胆总管结石反复发作的原因提供了合理猜想。尽管对组成胆道微生态的微生物菌落和其来源缺乏进一步了解,但在实验中已经证实了胆道微生态与胆结石疾病存在密切的关系^[28-29],且胆汁中细菌毒素的含量与肠杆菌的数量密切相关^[26]。在体外实验中,模拟的含菌胆汁环境更有利于胆结石的形成及发展^[30]。也有研究^[31]通过试验证明,小鼠肠道微生态的改变与胆结石疾病的发生有关,这为我们猜想胆道微生态的潜在来源提供了证据,可能是由于肠内容物的返流,导致了胆道微生态的改变^[32],由此推测,ERCP造成的十二指肠乳头括约肌结构、功能受损,一方面,Oddi括约肌关闭不全导致十二指肠液返流,通过菌群植入、影响胆道环境以及胆汁组分;另一方面,Oddi括约肌开放功能障碍或炎性狭窄导致胆汁排泄动力学发生改变,两方面原因共同作用导致胆汁组分变化、胆道环境变化、分泌功能异常,进而影响胆道内菌群变化,打破原有胆道微生态平衡导致结石形成。

2.2 胆道微生态紊乱与胆总管结石复发

相较于初发胆结石疾病,复发性胆总管结石患者的胆道微生态中的微生物多样性降低^[33]。有实验证明应用质子泵抑制剂可能增加胆总管结石复发的风险,其机制可能与质子泵抑制剂的给药改变了胆汁中的细菌混合物有关^[34],也从侧面印证了胆总管结石的复发与胆汁微生态的紊乱有关。有学者^[32]也同意胆汁微生态的紊乱创造了更容易致石的环境,从而诱导胆总管结石的复发。在近期的实验中,有研究者^[35]通过分析胆结石患者的胆汁微生态构成,明确了胆道结石患者的胆汁中,存在更多与炎症反应、氧化应激等相关的微生物

群,梁廷波团队^[36]的一项囊括202例患者的前瞻性研究也验证了这一点,研究结果显示十二指肠括约肌的松弛明显改变了胆道微生态的构成,大大增加了胆道系统中梭状芽胞杆菌的丰度,使得患者胆总管结石复发率更高,复发时间更短。Deng等^[37]也通过大样本回顾性分析验证了术前未使用抗生素或合并胆道感染是原发性胆总管结石复发的独立危险因素。

上述研究结果均能直接或间接地证实胆道微生态的存在,且胆道微生态与胆总管结石的复发关系密切,改善胆道微生态可降低胆总管结石复发的风险亦得到证实,但是,如何恢复胆道微生态平衡,应提高或降低何种细菌的丰度,使用何种抗生素或微生态制剂,目前都缺少相应的基础及临床研究的证据,因此,通过改善胆道微生态平衡来预防结石的产生和术后复发还有很多问题亟待揭示,这些薄弱区或盲区都应是我们未来关注的热点和研究方向

3 胆道解剖

在胆总管结石手术后,结石复发的危险因素尚未明确,但学者们都普遍认为结石的复发与胆汁淤积相关^[38-39]。而胆总管结石的复发也可能与胆汁淤积造成的胆汁排泄过程中动力学改变有关。对于胆总管结石合并异常胆道解剖的患者,我们应在术后对其进行长期随访,以便做到对胆总管结石复发的早发现、早治疗,尽量减轻疾病造成的负面影响。

3.1 胆总管成角

由于胆总管下端向十二指肠开口,所以其形态上会形成一个向右偏移的解剖位置,这个偏移角度通常被称为胆总管成角^[40],而胆汁淤积的程度与术后胆总管成角有着密切关系^[41]。通过多个学者团队随访ERCP术后患者复发胆总管结石的调查结果得出,尖锐的胆总管成角($<145^\circ$)可能更容易造成胆总管结石的复发^[38-39, 41]。

3.2 壶腹周围憩室

除了尖锐的胆总管成角外,存在壶腹周围憩室也是胆总管结石复发的危险因素之一,壶腹周围憩室指的是邻近或包含壶腹的十二指肠黏膜和黏膜肌层的腔外突出物^[42],其影响胆总管结石的复发具体机制可能也与胆汁淤积相关^[39]。根据内

镜下憩室与十二指肠乳头的位置,壶腹周围憩室可分为I、II、III型,而I型的壶腹周围憩室更易造成胆道结石的复发,即十二指肠乳头开口位置位于憩室内^[42]。其机制可能与胆汁在憩室处的动力学发生改变,从而导致胆汁淤积有关。由于壶腹周围憩室常见于中老年人群,在40岁以下人群中很少见^[43],而年龄又是胆总管结石复发的独立危险因素,所以壶腹周围憩室与胆总管结石复发关系的具体机制还有待于进一步研究。但不可否认的是,壶腹周围憩室的存在使胆总管结石发生率提高了1.8~2.4倍^[44]。对于这类疾病的术后管理,可以考虑对存在高复发风险的壶腹周围憩室患者进行长期随访,或有赖于治疗壶腹周围憩室的新疗法问世。

3.3 胆总管直径

也有学者表示胆总管的远端直径与胆总管结石的短期复发有关,胆总管的远端直径越大,短期复发胆总管结石的风险也越大,虽然不同研究者对于复发患者胆总管直径的随访数据稍有差距,但他们的数据都表明了随着远端胆总管直径的增大,患者复发胆总管结石的风险也随之上升这一趋势^[45-46],韩国学者的一项多中心的回顾性研究^[47]表明,胆总管直径 $>10\text{ mm}$,既往胆囊切除史是胆总管结石术后复发的危险因素,这可能与胆囊切除术后胆总管代偿性增粗有关。

3.4 胆总管结石的残留

除了胆道自身的原因,初发胆总管结石的数量与最大结石的直径似乎也与术后复发的风险息息相关^[48]。有研究表明,取石术后的胆管冲洗处理可以显著减少胆总管结石的复发,其机制可能与冲洗帮助去除较小直径的结石有关,当胆总管结石数量多而直径小时,更容易在术中遗漏细小的胆结石,而这些细小结石会作为复发结石的内核,在短期内造成术后复发^[49-50],Ahm等^[51]的一项关于ERCP术后盐水冲洗胆管的前瞻性、随机研究也证实了术后常规运用生理盐水冲洗胆道可以减少结石残留,在不增加术后并发症发生率的条件下降低胆总管结石复发率。这也为预防胆总管结石复发提供了一个新的思路。

4 小结

胆总管结石是一种常见的胆道良性疾病,它

的复发常常被认为是多因素共同作用的结果,目前所取得的研究结果表明这些因素多与胆总管结石术式选择、术中操作、十二指肠乳头括约肌功能的保留、胆道微生态紊乱、尖锐的胆总管成角、远端胆总管直径、壶腹周围憩室、胆总管结石的大小和数量等因素有关。上述这些因素共同导致了肠内容物经由功能减弱的十二指肠乳头括约肌反流至胆道,从而影响胆道微生物群的构成,破坏了稳定的胆道环境,造成胆总管结石复发。遗憾的是,关于多种胆道因素影响胆总管结石复发的研究多停留在回顾性研究阶段,更多的详细机制还有待于进一步的实验结果来证明。但目前已知的研究结果已经为围术期管理提供了新的思路,是否可以通过长期随访高复发风险患者、围术期运用抗生素、ERCP术中胆道冲洗等措施来改善胆总管结石患者预后,降低复发风险呢?具体证据还有赖于更多的临床试验来进行挖掘。

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(本文编辑 宋涛)

本文引用格式: 黄瑶, 易剑锋, 周文策. 胆总管结石治疗后复发因素的研究进展[J]. 中国普通外科杂志, 2021, 30(8): 964–970. doi: 10.7659/j.issn.1005-6947.2021.08.012

Cite this article as: Huang Y, Yi JF, Zhou WC. Research progress on postoperative recurrence factors of choledocholithiasis[J]. Chin J Gen Surg, 2021, 30(8): 964–970. doi: 10.7659/j.issn.1005-6947.2021.08.012



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