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胆总管结石复发因素的研究进展

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摘　要

胆总管结石是外科消化系统的一种常见的慢性复发性肝胆疾病，可引起多种并发症，严重影响患者的生活质量和健康。胆道解剖，动力学和代谢异常是胆总管结石复发的基本危险因素，通过对相关复发因素的了解，可以为疾病复发的预防和治疗提供更多参考。

关键词

胆总管结石，复发，危险因素

Research Progress on Recurrence Factors of Choledocholithiasis

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Abstract

Choledocholithiasis is a common hepatobiliary disease of the surgical digestive system, which can cause a variety of complications and seriously affect the quality of life and health of patients. Biliary anatomy, kinetic and metabolic abnormalities are the basic risk factors of choledocholithia-

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sis recurrence, and by understanding the related recurrence factors, we can provide more reference for the prevention and treatment of disease recurrence.

Keywords

Choledocholithiasis, Recurrence, Risk Factor

1. 引言

胆总管结石是外科消化系统一种常见的慢性复发性肝胆疾病，可引起急性化脓性胆管炎、胰腺炎、胆道穿孔等疾病，严重影响患者的生活质量，甚至威胁生命。胆道解剖，动力学和代谢异常是胆总管结石复发的基本危险因素。这些因素都会导致胆汁引流不足和胆汁淤积，是形成胆总管结石的前提。研究数据表明，胆总管结石患者接受经内镜逆行性胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)手术后的复发率为4%~24% [1]，腹腔镜胆总管探查术(laparoscopic common bile duct exploration, LCBDE)术后也有14%左右的结石复发率[2]。通常胆总管结石的复发定义为原发性结石完全清除后6个月[3]，结石复发因素较为复杂，不能完全归结于单一因素，本文就胆总管结石复发的危险因素进行以下方面论述。

2. 复发因素

2.1. 异常解剖和动力学

2.1.1. 壶腹周围憩室(Peripapillary Diverticulum, PAD)

PAD被分为三种类型：I型，憩室内的乳头；II型，位于憩室边缘；III型，距憩室2 cm以内[4]。有研究认为PAD患者患胆总管结石的可能性是无PAD的2.6倍。多变量分析证实憩室类型(I和II)是胆总管结石复发的独立危险因素[5]。Oak等人也认为胆囊切除术后胆总管结石复发的危险因素是PAD (I型或II型) [4]。PAD导致功能性胆道淤积，可能是由于PAD反复扩张压迫远端胆总管，引起乳头周围炎症，由于炎症的长期刺激Oddi括约肌功能受到影响其紧张力、收缩力、节律明显减弱，胆道内压力也相应改变，使胆汁排空受阻和/或肠胆返流，易致细菌繁殖导致胆道感染，从而形成结石[6] [7]。

2.1.2. 胆总管直径

胆总管直径(≥15 mm)被认为是胆囊切除术后6个月以上胆总管结石复发的独立危险因素[6]。Kim等人报告称，在移除结石后，持续的胆管扩张可能会导致胆汁引流延迟，是结石复发的潜在风险因素[5]。如果胆道壁的弹性因慢性炎症和纤维化而降低，在乳头括约肌切开术或胆囊切除术后胆管将保持扩张，这可能导致胆汁淤积从而形成胆总管结石。

2.1.3. 胆总管成角

在先前的研究中，胆总管成角与结石的复发有关[8] [9] [10]。理论上，成角度的胆总管可能会干扰胆汁的流动，容易发生胆汁淤积，导致胆汁浓度升高和胆固醇饱和度增加，这可能促进结石的形成和复发[11]。Yoo等人报道，胆管锐角(<145˚)与胆总管结石复发有关[12]，一项meta分析也显示，胆总管成角≤145˚可能会增加结石复发的风险[13]。但Rong等人认为≤135˚ [10]，Chong等人发现130˚是一个特殊的角度[11]。

角度的差异可能与术前/术后平片读数有关[14]，这需要进一步的大数据研究。

2.1.4. 胆囊管低插入

胆道系统的解剖变异是常见的，由于其发育的复杂性，可能会影响其功能。胆囊管通常在中三分之一位置插入肝总管，大约 10%的病例中出现胆囊管低插入[15] [16]。Tsitoridis 等人报道，低胆囊管插入患者的胆总管结石明显更多[17]。最近的一项研究显示[18]，胆囊管的低插入增加了胆总管结石复发的风险，这可能与急性胆总管远端成角或壶腹周围憩室的机制类似，通过干扰胆管的正常生理，容易发生结石复发，因为在胆总管远端三分之一处形成汇流，导致胆汁淤积和反流[18]。

2.1.5. 胆十二指肠瘘

有研究报道胆十二指肠瘘的存在是胆总管结石复发的危险因素[19]，推测可能由于胆管－十二指肠瘘长期存在，反流的肠液刺激胆道粘膜，最终导致慢性炎症。

2.2. 结石情况

2.2.1. 结石性质

相较于胆囊结石多为胆固醇结石和黑色素结石，胆总管结石多为棕色素结石，其病理基础是胆固醇，胆红素和胆汁酸代谢受损[20]。有研究表明棕色素结石主要来自于胆汁淤积和胆道感染[21]，然而，Yoo 等人认为，胆固醇结石是胆总管结石复发的独立危险因素[22]。因为胆固醇过饱和胆汁在胆囊中的滞留时间足以为胆固醇晶体的成核和沉淀以及晶体的滞留提供时间，使其生长为结石。

2.2.2. 石头数量

Oak 等[4]证实了多个胆总管结石的存在是结石复发的独立因素。也有研究也认为有多个胆总管结石(≥2)被认为是结石复发的不显著危险因素[6]。多发 CBD 结石在取出结石后可能更容易导致胆汁淤积[22]，这可能是引起结石复发的原因。

2.2.3. 结石大小

一项 Mata 分析表明结石直径越大，复发风险越高，术前结石直径 ≥ 1 cm 与复发相关[23]，韩国的一项研究也表明，结石直径 ≥ 1 cm 与结石复发有关[24]。较大的结石通常需要碎石，这可能会增加术后结石复发的风险。且较大的结石会引起胆管扩张，造成胆管功能受损，导致胆汁排出困难，引起胆汁淤积和细菌感染[25] [26]。

2.2.4. 术前胆囊结石

术前胆囊结石是结石复发得危险因素之一。一项回顾性研究显示，根据多变量分析，术前胆囊结石增加了复发的风险[27]。

2.3. 患者自身情况

2.3.1. 高龄

年龄 65 岁以上患者的胆总管结石复发率高达 30% [27]。Parra 发现年龄是唯一的独立危险因素，86.4%的复发患者在 65 岁以上[2]。Peng 等人也认为年龄≥65 岁是胆总管结石术后复发的重要独立危险因素[28]，也有研究认为 65 岁以上，合并心血管疾病和呼吸系统疾病被确定为胆总管结石复发的危险因素，但这些因素是不可改变的。胆总管结石首次复发后，在多种因素作用下，多次复发的概率增加[29]。

2.3.2. 甲状腺功能减退

Laukkarinn 等人[30] [31]在实验和临床研究中验证了甲状腺素对人体 Oddi 括约肌具有直接的促舒张

作用，可能导致胆道排空延迟[32]。甲状腺素缺乏可能解释甲状腺功能减退患者胆总管结石患病率增加的原因。

2.3.3. 胆道感染

Choe J 等人在对胆总管结石治疗后复发和未复发的胆总管结石患者胆汁的微生物特征和成分调查中发现，胆管内微生物菌群失调、细菌群落组合改变和胆汁液中胆汁酸降低与胆管结石复发有关[33]。奥迪括约肌是肠道和胆管之间的先天屏障，在对胆总管结石患者进行 ERCP 的过程中，可能需要进行括约肌切除术以实现结石的完全清除，所以细菌可能从肠道回流到胆管，从而造成胆道感染[34]。研究表明，超过 94.6%的色素结石患者的胆汁标本细菌培养阳性[35]，原因包括胆道解剖异常、壶腹周围憩室等，胆管细菌产生的 β-葡糖苷酸酶使胆红素水解成非共轭胆红素，易与钙结合形成胆红素钙，促进胆结石形成。而术前不使用抗生素可能增加胆道感染的风险，促进结石复发[19]。

2.3.4. 白细胞增多症

研究发现，术前白细胞增多(WBC ≥ 11,000/μL)，与胆总管结石复发显著相关。白细胞增多的结石复发风险是正常白细胞水平的 3.43 倍。其中白细胞计数为 11,000/μL 或更高，是一个独特的因素。炎症对胆总管结石的形成有显著影响。在胆总管结石形成过程中，氧化应激促进肝细胞线粒体功能障碍，导致坏死。丙二醛是氧化应激的产物，具有极强的细胞毒性，对细胞膜和细胞内大分子造成损害。此外，内分泌细胞(endocrine cells, ECs)的存在可能与胆汁低破坏和结石形成有关。EC 增生可能与慢性胆囊炎等长期炎症有关，所有 EC 分泌的激素都可以支持胆总管的病理过程[36]。

2.3.5. 胆汁酸

Choe JW 等人的研究发现，胆汁成分非复发组的胆汁酸浓度高于复发组[33]。先前的研究表明，胆汁中胆盐浓度降低会减少胆红素和胆固醇的胶束增溶，有利于形成棕色色素结石[36]。胆汁酸通常作为肠道微生物群的主要调节器抑制小肠中的细菌生长，并防止胆总管中的细菌逆行感染[37]。胆汁酸自身也可通过激活先天免疫系统直接或间接调节胆管中微生物群的组成[38]。肠道微生物组的改变可以通过减弱回肠 FXR 抑制，调节次级胆汁酸代谢和抑制胆汁酸合成[39]。

2.3.6. 基因

一项瑞典的研究发现，25%的胆结石病是由基因决定的[40]，WV 等[41]研究发现，编码肝胆胆固醇转运蛋白 5/8 (ABCG5/8)等位基因与胆总管结石的复发相关，其变异基因 ABCGD19H 目前被认为是胆总管结石形成的遗传危险因素[42]。而来自冰岛的一项 GWAS 研究报告了高达 2%的人群中 ABCB4 的致病性变异[43]。Dröge 等人也报道了与胆汁淤积症相关的常见 ABCB4 多态性[44]。ABCB4 基因变异的低磷脂相关胆石症患者可能会增加患胆总管结石、慢性胆汁淤积症和肝胆癌个人或者家族的风险[45]。熊去氧胆酸对 70%的 ABCB4 缺陷相关的胆汁淤积症和复发性胆结石病例有作用，所以，该药物目前代表一线治疗[46]。

2.4. 手术情况

2.4.1. 内镜下取石

ERCP 内镜下取石的主要方法有乳头括约肌切开术(endoscopic sphincteroto-my, EST)、球囊扩张术(endoscopic papillary balloon dilatation, EPBD)、小切开联合球囊扩张(EST-EPBD)。一项 11 个中心的研究显示 EST 是复发的危险因素[46]。EST 会永久性的损伤奥迪括约肌，还有可能引起胆管炎、十二指肠乳头狭窄及乳头旁憩室、胆总管扩张、十二指肠内容物反流等并发症，这些并发症都可能导致胆总管结石

的复发[47]。EPBD 可以保持十二指肠乳头功能而无出血，有望更好地保护括约肌的解剖结构和功能，它适用于那些服用抗凝剂的人[5]。但 meta 分析显示 EPBD 的胰腺炎发生高于 EST 和 EST-EPBD，而 EST-EPBD 在成功去除结石方面较其他二者排名最高[48]。

2.4.2. 腹腔镜胆总管探查

尽管 LCBDE 被认为是 ERCP 失败患者安全有效的治疗方法，但它也是胆囊切除术中疑似胆总管结石的有效治疗方法，且大型结石也应进行 LCBDE，保持奥迪括约肌完整。然而，LCBDE 的长期结果显示高结石复发，因为它没有改变胆管结构和致石环境[49]。且他可能造成以下医源性损伤：1) T 管相关粘连和胆总管成角(肘征)；2) 残余缝合线，用作结石形成的核心；3) 碎石相关损伤[5]。

2.4.3. 胆总管切开术及 T 管引流

胆总管切开术会破坏胆总管的解剖结构，增大结石复发的风险；而引流的 T 管长期压迫胆道可能会导致胆道上皮细胞坏死和结痂，从而引起细菌聚集和胆道内部结构破坏，导致胆道狭窄和胆汁排泄障碍，从而促进胆总管结石的形成[34]。

2.4.4. 胆道支架植入术

Choi 发现 ERCP 术后短期(肝功能恢复一个月)植入支架可以降低结石复发的风险[50]。然而，Kaneko 等人[51]发现(≥301 天)放置塑料支架和支架植入期间胆管扩张是支架结石复合体形成的独立因素。短期使用胆道支架可以缓解胆汁淤积，减少小残留结石，从而降低胆总管结石复发的风险[21]，但长期胆管支架置入会影响胆道动力学，使患者发生胆汁淤积有利于细菌繁殖。并且胆汁淤积刺激胆管粘膜的炎症变化，导致胆汁细菌、脱落细胞和炎性细胞沉淀，从而促进结石的复发[52]。笔者认为患者定期复查，不适随诊，医院定期回访可以及时发现并治疗可能的结石复发。

2.4.5. 胆囊切除术

胆囊切除术后会导致胆总管代偿增宽，进而促进胆总管结石的形成，同时，当胆囊切除后，奥迪括约肌的压力降低，细菌逆行感染机会增加，也增加了结石复发的风险[53]。多数文献认为胆囊切除术史是胆总管结石复发的危险因素[21] [54]，但也有研究发现，内镜下取石后，与原位胆囊患者相比，接受胆囊切除术的患者胆道复发的累积发生率显著降低($p < 0.001$) [33]。然而，也有研究认为手术适合的患者通常在初次出现胆总管结石时进行胆囊切除术，不适合胆囊切除术的患者即使在多次继发胆总管结石复发后也不一定要进行胆囊切除[55]。

2.4.6. 内镜下机械碎石术

内镜下机械碎石术会产生碎石片，这些碎石片会使胆管梗阻，导致胆总管结石的形成，且碎石术还会增加术后胰腺炎的风险[56]。

2.4.7. 术后残留结石

碎石后留下的小结石碎片可能会成为结石复发的病灶[57]。使用导管内超声检查的研究表明，胆道造影阴性残余小结石可能是结石生长的原因，完全清除结石会降低胆总管结石的复发率[58]。一项研究显示，胆道冲洗在清除小残留结石方面非常有用，100 ml 盐水冲洗的清除率为 92.4%。胆管盐水冲洗减少了胆总管结石的复发[59]。

2.5. 药物

2.5.1. 质子泵抑制剂

研究发现口服质子泵抑制剂是增加胆总管结石复发风险的独立危险因素，质子泵抑制剂可以促进小

肠细菌的生长并且改变胆汁中的细菌混合物，从而增加胆总管结石复发的风险[60]。

2.5.2. 熊去氧胆酸

熊去氧胆酸可以促进胆固醇结石溶解，减少胆汁淤积，从而有效的防止胆总管结石复发[61]。Yamamoto 等人[62]报道，在内镜治疗胆总管结石后，不接受熊去氧胆酸是结石复发的独立危险因素。然而，Akiyama 等人报道了反复胆总管结石与熊去氧胆酸治疗相关，并表明该药物通过未知机制导致结石形成[62]。

3. 结语

胆总管结石目前不管是哪种手术治疗，术后复发率较高，机制尚未完全明确，总体来说，胆总管结石的复发因素较为复杂，是多因素共同作用的结果，本文从异常解剖与动力学、结石情况、患者自身情况、手术及药物方面对这些可能的危险因素进行了阐述，目前的研究表明，在异常解剖动力学方面，胆总管结石的复发多与壶腹周围憩室、尖锐的胆总管成角、胆囊管的低插入、结石的性质、数量、大小以及术前的胆囊结石，以及患者的高龄、甲状腺功能减退、胆道感染、白细胞增多、胆汁酸的成分及微生物组成改变以及基因的变异和缺陷、手术情况，药物的使用有关，这些因素之间相互联系，共同造成了胆管阻塞、奥迪括约肌损伤、胆管损伤、结石残留、胆汁淤积等一系列后果，从而导致肠内容物通过奥迪括约肌反流至胆道，破坏了胆道环境的稳定，造成胆总管结石的复发。我们建议有以上复发危险因素的胆总管取石术后患者定期复查，不适随诊，在日常生活中保持营养清淡的饮食，适度锻炼，保持良好的生活作息，而围术期使用抗生素，ERCP 术中盐水冲洗胆道、定期回访也从医者的角度给出了降低结石复发的参考。目前对于复发因素相关的研究多为回顾性研究，我们期待更多前瞻性的高质量研究对可能的胆总管结石复发因素进行证实和开拓。

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