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· 文献综述 ·

胆囊切除术后远期疾病风险与“胆汁酸-肠道菌群-炎症”轴： 机制与临床证据

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摘要

胆囊切除术是治疗良性胆囊疾病的常用术式, 其术后远期健康影响近年来受到关注。流行病学研究提示, 胆囊切除术后结直肠癌、心血管疾病及代谢相关脂肪性肝病、肝硬化和肝癌等疾病的发生风险可能升高, 但胆囊切除术与上述疾病之间的因果关系尚未明确。本文以“胆汁酸-肠道菌群-炎症”轴为主线, 系统综述胆囊切除术后胆汁酸代谢改变、肠道菌群失衡及慢性低度炎症的相互作用, 并进一步分析其与结直肠癌、动脉粥样硬化以及代谢相关脂肪性肝病、肝硬化和肝癌发生发展的潜在联系。在此基础上, 结合大样本队列研究及Meta分析结果, 对现有流行病学证据与机制研究进行综合评价, 并重点讨论反向因果、混杂因素和适应证偏倚等导致因果推断困难的关键问题。同时, 总结针对胆汁酸信号、肠道菌群及代谢状态的潜在干预策略, 并提出高风险人群识别、个体化菌群重建及多组学机制验证等未来研究方向。现有证据表明, 胆囊切除术可能通过扰乱“胆汁酸-肠道菌群-炎症”轴参与多种远期疾病的发生发展, 但其独立效应及具体作用机制仍需进一步验证。临床上应在充分评估手术获益与风险的基础上, 加强术后长期代谢及微生态管理。

关键词

胆囊切除术; 胆汁酸类; 胃肠道微生物组; 炎症; 综述

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Long-term disease risks after cholecystectomy: the bile acid-gut microbiota-inflammation axis and clinical evidence

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Abstract

Cholecystectomy is a widely used surgical treatment for benign gallbladder diseases, and its potential long-term health consequences have attracted increasing attention. Epidemiological studies have suggested that cholecystectomy may be associated with increased risks of colorectal cancer, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease, cirrhosis, and hepatocellular carcinoma; however, a causal relationship between cholecystectomy and these long-term

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outcomes has not been established. In this review, we use the bile acid-gut microbiota-inflammation axis as a framework to summarize the interplay among altered bile acid metabolism, gut microbiota dysbiosis, and chronic low-grade inflammation after cholecystectomy, and further discuss their potential roles in the development of colorectal cancer, atherosclerosis, metabolic dysfunction-associated steatotic liver disease, cirrhosis, and hepatocellular carcinoma. Large population-based cohort studies and meta-analyses are integrated with mechanistic evidence to evaluate the consistency and limitations of current findings, with particular emphasis on reverse causation, residual confounding, and indication bias that may complicate causal inference. Potential interventions targeting bile acid signaling, gut microbiota, and metabolic abnormalities are also summarized, and future research priorities are proposed, including identification of high-risk populations, personalized microbiota-based interventions, and multi-omics validation of underlying mechanisms. Current evidence suggests that cholecystectomy may contribute to the development of multiple long-term diseases through disruption of the bile acid-gut microbiota-inflammation axis, but its independent effects and underlying mechanisms remain to be clarified. In clinical practice, the potential long-term metabolic and microbiota-related consequences should be considered alongside the established benefits of cholecystectomy, and appropriate long-term follow-up should be encouraged.

Key words Cholecystectomy; Bile Acid; Gastrointestinal Microbiome; Inflammation; Review
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胆囊切除术作为治疗良性胆囊疾病的标准手术,已广泛应用于临床实践^[1-2]。然而,随着腹腔镜胆囊切除术的不断普及和患者生存期延长,其术后长期影响渐受关注。有研究^[3-12]提示,胆囊切除术后患者患结直肠癌、心血管疾病(动脉粥样硬化等)及肝病(代谢相关脂肪性肝病、肝硬化、肝癌)风险上升,这提示该手术可能对机体代谢和肠-肝轴功能产生远期影响。

生理状态下,胆囊具有储存和浓缩胆汁的功能,参与调节胆汁酸节律性释放及肝肠循环、维持肠道菌群平衡及脂质代谢。胆囊切除后,胆汁持续排入肠道,可致胆汁酸代谢谱改变、肠道菌群失调及肠屏障功能受损,进而诱发慢性低度炎症;“胆汁酸代谢紊乱-肠道菌群失衡-慢性炎症反应”轴线可能构成上述疾病发生发展的共同病理基础^[4, 10, 13-19]。

此外,不同术式(如传统腹腔镜、单孔腹腔镜、机器人辅助手术等)术后各种并发症(如切口疝)的发生率有差异^[2, 20-21],但对术后胆汁动力学恢复、肠道菌群结构及远期代谢的影响尚缺乏系统比较;对于部分胆囊功能尚存的患者,保胆取石术是否优于胆囊切除,目前尚无定论。术式差异对“胆汁酸-肠道菌群-炎症”轴干预程度及

远期肿瘤风险的影响,仍需更多研究验证。

但最本质的问题在于,术后远期并发症究竟是手术本身所致,还是患者术前既存的代谢紊乱(如脂质代谢异常、肠道菌群失调和慢性炎症状态)的延续,目前仍缺乏明确答案。胆石症和胆囊炎的病因学已知包括脂质代谢异常、细菌感染和胆汁排泄障碍^[1, 22],而这些因素常与不良生活方式(高脂高热量饮食、缺乏运动)、消化道菌群紊乱长期共存。因此,需要胆囊切除术的患者群体可能本身即是代谢性疾病和肿瘤的高危人群。探讨胆囊切除术与远期疾病的关系,需审慎区分“手术效应”与“患者基线特征”的混杂作用。

本文以“胆汁酸-肠道菌群-炎症”轴为主线,系统梳理胆囊切除术后各类远期疾病的发生机制,结合大样本临床研究数据,分析机制与证据间的契合与分歧,并对现有研究的局限性进行剖析,以期对临床决策和未来研究提供参考。

1 胆囊切除术后远期疾病共同病理基础:“胆汁酸-肠道菌群-炎症”轴紊乱

胆汁酸是肝脏中胆固醇经酶促反应合成的具有表面活性的类固醇分子,主要促进脂质乳化与

吸收,同时维持肠道生态平衡。正常情况下,胆汁酸通过经典和替代途径合成后储存于胆囊,进食时释放到十二指肠促进脂肪消化,其中大部分被回肠重吸收后进入肝肠循环。法尼醇X受体(farnesoid X receptor, FXR)和G蛋白偶联胆汁酸受体1(G protein-coupled bile acid receptor 1, TGR5)在调控胆汁酸合成、脂质代谢、炎症反应和肠道屏障功能中起关键作用。胆囊切除术后,由于胆囊储存功能丧失,胆汁酸持续缓慢流入肠道,致使其浓度和组成改变,影响肝肠循环以及肠道菌群组成,干扰脂质代谢与免疫稳态,此机制可能是术后相关疾病发生、发展的重要基础^[10, 23]。

研究^[4]发现,胆囊切除的机体肠道菌群多样性下降,有益菌如短双歧杆菌(*Bifidobacterium breve*, *B. breve*)显著减少,而条件致病菌如活泼瘤胃球菌(*Ruminococcus gnavus*, *R. gnavus*)增多,导致肠道微生物代谢产物发生改变。此外,肠道菌群失调表现为厚壁菌门和放线菌门类群的减少,变形菌门(*Proteobacteria*)类群的增加,这种菌群变化与肠道屏障功能受损密切相关^[24-25]。肠道菌群失调也能通过破坏肠黏膜屏障的完整性,导致内毒素,如脂多糖(lipopolysaccharide, LPS)更易穿透肠壁进入肝门静脉系统,进而引发肝脏炎症反应^[26]。

同样,胆囊切除术后胆汁酸及肠道菌群的失衡,也逐渐显示出对肠-肝轴的长远影响,是诱发肠-肝轴慢性低度炎症的关键因素,这种失衡不仅诱发肠道屏障功能受损,还促进肿瘤坏死因子 α (tumor necrosis factor α , TNF- α)、白细胞介素6(interleukin 6, IL-6)等炎症因子持续表达,形成肠-肝轴上的慢性低度炎症反应^[27-31]。此外,胆囊切除术患者常伴有代谢异常^[32],如高血糖、高脂血症及肥胖等,这些代谢紊乱与炎症反应相互促进,形成恶性循环。研究^[33-35]表明,肥胖相关的慢性炎症可促使脂肪组织巨噬细胞极化成促炎型,胆汁酸代谢产物如27-羟基胆固醇也能诱发全身性及局部炎症反应。慢性炎症的持续存在,不仅促进了细胞增殖和基因不稳定,还可能通过肠-肝轴的交互作用,促进结直肠癌及肝脏相关疾病的发生发展^[4, 36]。

综上,胆囊切除术通过改变胆汁酸循环和肠道环境,诱导肠道菌群失调,引发慢性低度炎症,因此导致的“胆汁酸-肠道菌群-炎症”轴紊乱可为后续相关疾病的发生奠定基础。

2 结直肠癌:次级胆汁酸的促癌作用与临床证据

在“胆汁酸-肠道菌群-炎症”轴紊乱的背景下,胆囊切除术后结直肠癌风险升高可能涉及胆汁酸信号异常、肠道菌群失衡及慢性炎症等多重机制。

胆囊切除术后次级胆汁酸通过激活FXR和TGR5调控肠道免疫反应、细胞凋亡和微环境形成。胆汁酸信号通路失衡导致炎症微环境的形成、肠道屏障功能受损及肠道菌群失调,共同促进肿瘤微环境的塑造和肿瘤的进展。研究^[37-38]显示,胆汁酸代谢异常与结直肠癌患者的肠道微环境紊乱密切相关,且干预胆汁酸代谢及其受体信号通路具有潜在的防治价值。

另外,胆囊切除术后肠道菌群失衡通过产生致癌物质、诱导肠黏膜炎症、促进基因突变以及免疫调节紊乱促进结直肠癌的发生发展。首先,失调的菌群产生多种致癌物质,如细菌毒素和脱氧胆酸(deoxycholic acid, DCA),这些物质能诱导肠黏膜炎症反应及DNA损伤,促进基因突变积累^[4, 39]。如具核梭杆菌(*Fusobacterium nucleatum*, *F. nucleatum*)和脆弱拟杆菌(*Bacteroides fragilis*, *B. fragilis*)分泌的毒素可直接损伤肠上皮细胞DNA,促进癌变^[40]。其次,菌群失调可导致免疫调节功能紊乱,一方面增强肿瘤的免疫逃逸能力,促使肿瘤微环境恶化;另一方面促进促炎因子释放,加剧免疫抑制细胞浸润^[41]。菌群代谢产物如短链脂肪酸和三甲胺N-氧化物(trimethylamine N-oxide, TMAO)等也参与调节免疫反应和肿瘤细胞信号通路^[42-44]。肠道菌群失衡也会影响肠屏障完整性,使致癌物质更易渗透至肠壁深层,加剧局部炎症和肿瘤形成^[45-47]。

此外,慢性炎症作为结直肠癌发生的重要推动力,其分子机制主要涉及炎症介导的氧化应激反应和信号通路激活。慢性炎症状态下会产生大量活性氧和活性氮,引发DNA的氧化损伤,促进基因突变和基因组不稳定,成为肿瘤启动的重要因素^[48-49]。研究^[49]中检测到结直肠癌患者血清及肿瘤组织中氧化应激标志物和DNA损伤水平显著高于正常对照,且与病情进展相关。信号通路方面,炎症因子如TNF- α 、IL-6等通过激活核因子 κ B(nuclear factor κ B, NF- κ B)和信号转导与转录激活

因子3信号通路(signal transducer and activator of transcription 3 signaling pathway, STAT3),增强肿瘤细胞增殖、抗凋亡及侵袭能力^[50-52]。此外,microRNA-146a等非编码RNA与肠道菌群的失衡不仅直接影响肿瘤细胞,也改变肿瘤微环境中免疫细胞的功能,导致免疫逃逸^[33, 53-55]。临床数据^[56-58]表明,结直肠癌患者中炎症标志物如C-反应蛋白(C-reactive protein, CRP)、IL-6、TNF- α 水平升高,且与疾病预后相关。

多项队列研究及Meta分析^[3, 5, 59-60]提示,胆囊切除术与结直肠癌风险升高存在统计学关联,部分研究报道总体风险增加约20%,且这种关联可能具有结肠部位特异性。Mu等^[59]纳入超过30万例患者的Meta分析显示,胆囊切除术与结直肠癌的关联呈部位特异性,右半结肠癌相对危险度(relative risk, RR)为1.20(95% CI=1.04~1.38),而与横结肠、降结肠及乙状结肠癌均无显著关联($P>0.05$)。这种部位差异与次级胆汁酸在右半结肠浓度更高、停留时间更长的药代动力学特征一致,为机制假说提供了间接支持。

3 动脉粥样硬化:从代谢紊乱到斑块形成

胆囊切除术后动脉粥样硬化风险的增加可能与“胆汁酸-肠道菌群-炎症”轴紊乱所致的代谢异常、肠屏障损伤及慢性炎症密切相关。

胆囊切除术后胆汁酸代谢紊乱可能影响FXR和TGR5等胆汁酸受体介导的信号通路,并进一步干扰血管舒缩、脂质代谢及能量稳态。FXR信号异常可能导致一氧化氮(nitric oxide, NO)释放减少及载脂蛋白C-II(apolipoprotein C-II, ApoC-II)表达改变,进而影响血管舒缩功能以及极低密度脂蛋白(very low density lipoprotein, VLDL)和高密度脂蛋白(high-density lipoprotein, HDL)的代谢^[61]。同时,FXR对胆固醇7 α -羟化酶的负反馈调控发生改变,可影响胆汁酸合成及胆固醇向胆汁酸的转化,进而影响胆固醇清除和体内蓄积,并可能促进动脉粥样硬化斑块形成。另一方面,TGR5信号参与肥胖、能量代谢及胰岛素敏感性的调节,其信号减弱可能促进肥胖和胰岛素抵抗,从而间接增加动脉粥样硬化风险^[62-63]。

肠道菌群失衡主要通过肠屏障破坏、免疫调

控及慢性炎症等共性机制,促进动脉粥样硬化的发生与发展。首先,肠道菌群失衡导致肠道屏障功能受损,LPS移位增加,并通过激活Toll样受体4(toll-like receptor 4, TLR4)信号通路,诱导炎症因子(如IL-6、TNF- α)释放,促进动脉粥样硬化和血栓形成^[64-66]。其次,菌群代谢产物如TMAO进一步促进TNF- α 、白细胞介素1 β (interleukin 1 β , IL-1 β)的释放,诱导血小板的高反应性,加剧血栓风险与动脉粥样硬化^[65]。临床研究^[67]发现,肠道真菌如白色念珠菌还可通过激活肠道缺氧诱导因子2 α -神经酰胺途径影响血脂代谢,促进动脉粥样硬化发生与发展。

慢性、无症状的低度炎症是动脉粥样硬化斑块形成、进展、破裂及血栓形成的关键驱动力。动脉粥样硬化也是一种慢性炎症性疾病,全身性和局部炎症在其发生、发展中起到关键作用。炎症诱导内皮功能障碍,抑制NO产生并促进内皮素产生,影响血管扩张及其通透性。其次,血管内皮细胞黏附分子表达增加,低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)在内皮下间隙聚集,同时白细胞介素1 α (interleukin 1 α , IL-1 α)、IL-1 β 、IL-6等促炎性细胞因子和TNF- α 分泌增加,这些都与动脉粥样硬化进展有密切关系^[68]。此外,IL-1 α 、TNF- α 诱导巨噬细胞分泌基质金属蛋白酶,催化斑块胶原蛋白的分解,加剧疾病风险^[69]。

动脉粥样硬化是多数心血管疾病的核心病理基础,多项大样本研究支持胆囊切除术与心血管疾病风险的关联。Song等^[7]的Meta分析显示,胆囊切除术后心血管病风险增加19%(RR=1.19),心血管病死率增加24%(RR=1.24)。Park等^[70]的韩国队列研究发现,术后2年内心血管风险显著升高,校正风险比(adjusted hazard ratio, aHR)为1.35,冠心病发生风险尤为明显(aHR=1.77)。Jung等^[71]针对2型糖尿病患者的队列研究显示,50岁以下患者术后心血管事件风险增加24%(aHR=1.24)。Emilsson等^[72]研究提示,年轻患者(20~39岁)术后全因死亡率显著高于对照,而老年患者因手术筛选偏倚可能呈现“保护性”关联。TMAO作为关键代谢产物,其水平与心血管事件风险呈剂量-反应关系^[73],为菌群机制提供了间接支持。

4 胆囊切除术后肝脏疾病风险:代谢进展与胆汁酸/炎症介导的多重打击

胆囊切除术后肝脏疾病风险的增加具有明显的连续谱特征,其潜在机制既可能表现为由代谢异常驱动的疾病逐级进展,也可能表现为胆汁酸及菌群代谢产物介导的直接损伤。

第一,经典递进路径(代谢驱动):胆汁酸代谢紊乱致肝细胞脂质沉积,脂毒性与炎症激活肝星状细胞,推动纤维化进展至肝硬化,最终诱发肝癌。该路径中,脂质沉积为起始环节:胆囊切除后胆汁持续流入肠道,导致FXR、TGR5信号通路失衡,促进肝细胞脂肪蓄积;同时肠道菌群失衡致肠黏膜屏障受损,LPS入肝激活库普弗细胞(Kupffer cell, KC)诱发炎症^[26, 74],菌群代谢产物进一步加剧脂肪变性^[75-76]。临床研究显示,术后5年内代谢相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)发生率显著升高,与术前体质量指数(body mass index, BMI)及血脂无关^[77],持续脂肪变性与局部炎症是其向肝硬化进展的关键。代谢相关单纯性肝脂肪变性(metabolic dysfunction-associated steatotic liver, MASL)持续进展可致肝硬化:慢性炎症与脂肪毒性损伤肝细胞,胆汁酸代谢紊乱加剧,未结合型胆汁酸蓄积激活TGR5诱导肝星状细胞活化,加速纤维化^[78-80];肠道菌群失衡促进MASL向代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)及肝硬化进展^[11, 81],DCA升高也会加速肝纤维化。长期炎症刺激下,肝纤维化持续进展至肝硬化^[82],而肝纤维化加重、肝细胞损伤及免疫稳态破坏是肝硬化向肝癌进展的关键。肝硬化阶段,次级胆汁酸增加直接促进肝细胞癌发生^[83],肠道菌群失衡通过激活KCs、调控肿瘤信号通路加速癌变^[26, 74, 84];分子层面,NF- κ B、STAT3等信号通路及氧化应激、线粒体功能障碍促进基因突变,最终诱发肝癌^[85-88]。

第二,直接损伤路径(毒性/炎症驱动):DCA及菌群LPS移位可直接诱导肝细胞DNA损伤(启动癌变)或激活肝星状细胞(启动纤维化),可无需经过显著MASLD阶段。胆囊切除后胆汁持续流入肠道致DCA升高,肠道菌群失衡加剧肠黏膜屏障受损,使DCA及LPS易移位至肝脏。其中,DCA直接诱导肝细胞DNA损伤启动癌变,LPS激活KC

诱发炎症并激活肝星状细胞启动纤维化,二者共同推动肝脏病变进展。相关研究证实,LPS移位可诱发肝脏炎症^[26, 74],DCA升高加速肝纤维化^[11],亦直接促进肝细胞癌发生^[83]。同时肝细胞持续受损和坏死,激活肝星状细胞和免疫细胞,释放大促炎细胞因子如TNF- α 、IL-1 β 、IL-6,促进纤维化及肝癌的微环境形成^[85-86]。代谢异常引发的脂质过载导致脂肪毒性、线粒体功能障碍及氧化应激,进一步加剧炎症反应和肝细胞损伤^[87]。转化生长因子 β (transforming growth factor β , TGF- β)、NF- κ B、STAT3、核转录因子红系2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)等信号通路在炎症与肝癌发生中起调控作用^[82, 88]。

上述“多重打击”模型得到流行病学数据的支持。Luo等^[9]的Meta分析显示,胆囊切除术后MASLD[比值比(odds ratio, OR)=1.54]、肝硬化(OR=2.73)及肝癌(OR=1.46)风险均显著升高,且效应量呈梯度增强,提示手术可能在整个肝病谱系中发挥“多点驱动”作用。韩国全国性队列研究^[89]显示,胆囊切除术后肝内胆管癌的发病率比(incidence rate ratio, IRR)=1.78(95% CI=1.65~1.92)高于肝细胞癌[IRR=1.22(95% CI=1.15~1.30)],支持胆汁酸直接损伤胆管上皮的独立致癌路径。动物实验^[90]证实,胆囊切除可加剧高脂饮食诱导的肝脏脂质沉积,同时DCA可直接诱导肝细胞DNA损伤的标志物磷酸化组蛋白H2AX(phosphorylated H2A histone family member X, γ -H2AX)表达上调^[91-92],为两种路径并存提供了实验依据。

5 讨论

本文以“胆汁酸-肠道菌群-炎症”轴为主线,系统梳理了胆囊切除术后上述疾病的共同病理基础。各疾病在分子机制层面高度重叠:大多为胆汁酸受体(FXR/TGR5)信号失衡启动,经肠道菌群结构改变放大,最后通过慢性炎症驱动靶器官病变。这一框架为理解术后远期风险的“多病共存”现象提供了可行性的解释。同时也提示术后患者的管理或许不应仅停留在手术恢复层面,还需关注代谢与微生态的远期变化。

5.1 临床数据的支持与分歧及局限性分析

上述的大样本队列研究和Meta分析虽为上述

机制提供了间接支持,即上述疾病的总体风险均呈轻度至中度升高,且存在解剖部位和病理类型的特异性(如右半结肠、肝内胆管)。但上述引用的临床研究间异质性明显,以肝癌风险为例,部分亚洲人群的队列研究并未发现胆囊切除术后的显著关联,提示遗传背景、生活方式(饮食、运动、吸烟)、代谢指标(如血脂、血糖、炎症因子)等因素可能在其中起到修饰作用^[93]。虽机制研究和流行病学数据日趋丰富,但胆囊切除术与远期疾病之间的因果关系仍未确立,后续研究可聚焦以下问题,或能推动临床转化。

第一,反向因果的可能。胆结石、胆囊炎的发病原因本身即包括脂质代谢异常、肠道菌群紊乱和胆汁排泄障碍。换言之,需要接受胆囊切除术的患者,在术前可能已处于代谢异常和慢性炎症状态,这些因素既是胆囊疾病的病因,也是结直肠癌、动脉粥样硬化、MASLD的危险因素。在此背景下,术后观察到的远期风险可能是患者基线特征的延续,或非手术本身所致。

第二,中介效应的界定。即手术可能只增加风险,非诱发风险,其效应可能是通过加重术前已有的代谢紊乱实现,此时手术可被视为“加速器”而非“始动因素”。区分“手术独立效应”与“术前状态放大效应”可能是未来研究方向。

第三,适应证偏倚。行胆囊切除术者与保守治疗者的基线特征本身不同(症状更重、合并症更多),直接比较两组可能存在适应证偏倚。

此外,手术方式(腹腔镜 *vs.* 开腹,如传统腹腔镜、单孔腹腔镜、机器人辅助手术等)、随访时间以及术后是否使用他汀类或益生菌等药物,也可能导致结论的差异。因此,胆囊切除术亦可能是揭示或加重患者术术前已存在的代谢-菌群-炎症紊乱的“压力测试”,其远期风险亦可能是患者自身因素与手术干预交互作用的结果。所以,现有证据尚不足以证明“胆囊切除术”与“远期疾病”是因果关系,即在解读现有证据时仍需保持审慎,未来应鼓励开展多中心、标准化设计的前瞻性研究,以厘清不同亚组人群的真实风险。

5.2 潜在干预策略及转化前景

针对胆囊切除术后“胆汁酸-肠道菌群-炎症”轴的紊乱,目前已有多项干预策略进入临床前或临床研究阶段,但整体而言,证据质量参差不齐,尚未形成明确的临床路径。目前针对胆囊切除术

后“胆汁酸-肠道菌群-炎症”轴的特异性干预证据十分有限,现有研究主要来源于MASLD、代谢性疾病、肠道菌群紊乱及动脉粥样硬化等相关疾病领域,因此以下策略更多属于具有潜在转化价值的探索方向,而非已经建立的临床治疗方案。

第一,FXR激动剂是目前研究较为深入的干预靶点之一。FXR激动剂奥贝胆酸(obeticholic acid, OCA)在MASLD的II期临床试验^[94]中确实显示出改善肝脂肪变性和炎症指标的作用(如降低丙氨酸氨基转移酶、改善胰岛素抵抗),但专门针对胆囊切除术后人群的研究仍属空白。需注意的是,OCA的瘙痒和HDL下降等副作用,使其在低风险人群中的应用受限^[95-96]。

第二,益生菌干预在改善肠道屏障功能方面显示出潜在价值。一项系统综述^[97]提示益生菌可调节肠道通透性指标(如连蛋白)。针对结直肠癌术后患者的Meta分析^[98]证实,益生菌可显著降低腹泻发生率($OR=0.42$)。动物实验^[99]证实含长双歧杆菌(*Bifidobacterium longum*, *B. longum*)和嗜酸乳杆菌(*Lactobacillus acidophilus*, *L. acidophilus*)的制剂可维持肠屏障完整性。目前尚缺乏针对胆囊切除术后人群的肿瘤预防证据。

第三,饮食干预在MASLD预防中具有潜在价值。UK Biobank研究^[100]提示地中海饮食依从性筛查(mediterranean diet adherence screener, MEDAS)高评分者MASLD风险降低24%($HR=0.76$, 95% $CI=0.62\sim0.94$)。最新Meta分析^[101]进一步确认地中海饮食与慢性肝病风险呈负相关($OR=0.65$, 95% $CI=0.56\sim0.75$)。但上述研究均非专门针对胆囊切除术后人群,且饮食干预的长期依从性和文化差异仍是临床实施的挑战。

至于TGR5激动剂6 α -乙基-23(S)-甲基胆酸(INT-777),虽有动物实验显示其可改善胰岛素抵抗、减轻肝脏炎症和动脉粥样硬化^[102],但距离临床应用尚有距离^[103]。总体而言,现有干预研究多集中于中间指标(如丙氨酸氨基转移酶、LPS、菌群组成),以肿瘤或心血管事件为终点的长期随访数据仍匮乏。

5.3 未来研究方向

基于上述现状,笔者认为后续研究可聚焦以下问题:第一,高风险人群的筛选标志物待明确。借助多组学技术(胆汁酸谱、宏基因组、代谢组等;上述提到的胆汁酸、菌群多样性、炎症指标

等或许可成为筛选标志物),有望构建术后结直肠癌或 MASLD 的风险预测模型,真正实现从“一刀切”到“分层管理”的跨越。第二,FXR/TGR5 双靶点激动剂的开发。考虑到二者在胆汁酸代谢与炎症调控中的协同作用,双靶点策略可能在疗效和安全性之间取得更好平衡,但需先在胆囊切除动物模型中验证其对肠-肝轴的重塑能力。第三,益生菌干预的临床随机对照试验(randomized controlled trial, RCT)升级。应设计以结直肠癌发生率为终点的多中心 RCT,明确特定菌株(如 *B. longum*) 在术后人群中的长期干预效果,回答“能否防癌”这一临床最关心的问题。第四,术后菌群重建应走向个体化。结合术前菌群特征,探索个体化饮食与益生菌联合干预方案,并通过连续采样评估其动态调控效果,或许能打破目前“千人一方”的困局。第五,术后代谢综合征的早期预警体系尚待建立。借助可穿戴设备与数字健康技术,建立术后代谢随访体系,有望实现对代谢异常的早期识别与干预。

综上所述,胆囊切除术通过扰乱“胆汁酸-肠道菌群-炎症”轴,可能在一定程度上参与上述远期疾病的发生发展。当前机制研究与流行病学证据虽初步支持胆囊切除术与远期疾病发生有关联,但因果关系仍受制于混杂偏倚、适应证选择及术前代谢状态等因素,尚难明确手术本身的独立效应。因此,临床决策应审慎权衡胆囊切除的必要性,术后管理亦应从短期恢复延伸至长期代谢与微生态监测。未来研究应聚焦于高风险人群的早期识别、个体化干预策略的构建,以及基于多组学技术的机制验证,以期实现从机制探索到临床转化的突破,为胆囊切除术后患者的精准管理提供科学依据。

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