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## 胆囊结石非手术治疗的研究进展

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### Non-surgical treatment of cholesterol gallstones: An update on recent developments

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### Abstract

Cholesterol gallstones (CS) are a common disease of the digestive system. The imbalance of cholesterol and bile acid metabolism tends to result in the deposition of cholesterol crystals, which is the basis of gallstone formation. Current guidelines recommend cholecystectomy for CS patients with any symptoms. Nevertheless, there are still some patients without surgical indications, surgical conditions, or surgical consent, who may benefit from non-surgical treatment. However, there are not too many tips for non-surgical treatment of CS in latest guidelines, nor sufficient attention paid from clinicians. This paper reviews the relevant recent literature on non-surgical treatment of CS, with an aim to help clinicians be familiar with non-surgical treatment of CS.

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Key Words: Cholecystectomy; Extracorporeal shock wave lithotripsy; Ezetimibe; Statins; Nuclear receptors; Cajal cells

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### 摘要

胆囊结石(gallstone, GS)是消化系统常见的疾病之一, 胆固醇、胆汁酸的代谢失衡导致胆固醇沉积与GS的发生关系密切。目前指南建议对有GS症状的患者行胆囊切除术, 但仍存在部分GS患者无手术指征、手术条件或者不接受手术治疗, 这部分人群极可能从非手术治疗中获益。目前指南对于GS的非手术治疗

并未太多提点, 临床医生对非手术治疗未予重视. 本文查阅国内外近年来发表的相关文献, 拟对GS的非手术治疗进行系统综述, 旨在让临床医生熟悉GS的非手术治疗方法, 并结合临床实际推广应用.

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关键词: 胆囊切除术; 体外冲击波碎石术; 依折麦布; 他汀类; 核受体; Cajal细胞

**核心提要:** 胆囊切除是目前有症状胆囊结石(gallstone, GS)的主要治疗方式, 但仍存在部分GS患者无手术指征、手术条件或者不接受手术治疗, 这部分人群可能从非手术疗法中获益. 本文旨在为读者介绍胆囊胆固醇结石的非手术治疗方法.

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## 0 引言

胆囊结石(gallstone, GS)在全世界广泛流行, 是消化系统最常见疾病之一. 近期的调研结果表明我国部分地区人群GS患病率约为4.2%-22.87%, 男女患病率比例约为1:1.17-1.34<sup>[1-3]</sup>. 年龄、女性、肥胖为GS的主要危险因素<sup>[1-4]</sup>. 丹麦的一项队列研究表明约80%的患者无临床症状, 每年约0.94%-1.12%的无症状患者出现GS相关症状, 最终约7.2%-8.0%的患者出现了急性胆囊炎、胆总管结石、胆源性胰腺炎等并发症<sup>[5,6]</sup>.

## 1 胆囊结石的手术治疗

目前主流的指南建议有症状的GS患者行胆囊切除术治疗, 对于无症状GS患者, 如填充型胆囊结石、无功能胆囊或合并胆囊癌高危因素患者, 建议早期行预防性胆囊切除, 首选术式为腹腔镜胆囊切除术(laparoscopic cholecystectomy, LC)<sup>[7]</sup>. 近年陆续报道经自然腔道内镜手术(natural orifice transluminal endoscopic surgery, NOTES)应用于切除胆囊, 其安全性与LC无明显差别, 但NOTES手术中转率明显高于较LC<sup>[8,9]</sup>.

## 2 手术治疗存在的问题

正常胆囊具有浓缩、储存胆汁的功能, 切除胆囊对人体正常生理状态有一定的影响. 据报道胆囊切除术后高达40%的患者出现上腹不适、消化不良、黄疸等症状, 即胆囊切除术后综合征<sup>[10]</sup>, 虽多数患者上述症状仅短期存在, 仅不到10%患者出现持续性的症状, 但这在

一定程度上仍影响了患者的生活质量. 亦有研究结果表明胆囊切除后导致机体代谢紊乱, 出现脂肪肝、胰岛素抵抗等疾病状态, 甚至增加结直肠癌、肝癌等肿瘤发生的风险<sup>[11-13]</sup>. 这些研究结果提示保留有功能的胆囊对于患者有积极的意义.

近年来有专家提出保胆取石术(gallbladder-preserving surgery, GPS)以兼顾取石及保留胆囊功能. 但GPS仅取出了胆石, 相对非手术治疗而言并未改善胆囊运动功能及胆汁的致石性, 仍有GS复发风险<sup>[14]</sup>. 另一方面GPS有切口感染、胆石遗失、胆漏、粘连等并发症风险, 而其临床效益与体外冲击波碎石术(extracorporeal shock wave lithotripsy, ESWL)联合药物治疗相比无明显优势<sup>[7]</sup>. 这些原因很大程度上限制了GPS的临床推广, 非手术方式治疗有胆囊功能的GS患者可能更为合适.

此外, 是否有症状GS患者均需行胆囊切除仍存在争议. 国外两项队列研究针对有症状但未手术治疗的患者进行随访观察, 随访14年最终仅45%-50.7%的随诊患者需接受胆囊切除术手术治疗, 观察期间仅2-4%的患者出现GS并发症, 相比手术治疗的患者, 其平均经济支出显著减少<sup>[15-17]</sup>. 综上, 选择长期随诊并在随诊过程中接受非手术治疗似乎也是安全可行的方案<sup>[18]</sup>.

## 3 GS的非手术治疗

**3.1 危险因素的控制** 控制危险因素是GS非手术治疗的基础. 限制胆固醇的摄入、适当体力活动、科学减重等生活方式的改变以及高脂血症、胰岛素抵抗、慢性肝病、克罗恩病等疾病状态的改善可在一定程度上可预防GS发生并限制GS的进一步发展<sup>[4]</sup>.

**3.2 ESWL** ESWL是一种相对无创、快速碎石的治疗方法, 目前主要用于泌尿系结石、胆系结石以及胰管结石的治疗. 据报道ESWL治疗后GS的完全清除率达到80%以上, 结石的钙化程度及胆囊功能为影响结石清除率的重要原因, 是术前评估的关键<sup>[19]</sup>. 葡萄牙的一项研究证实ESWL与LC对比两者同样安全有效, LC的经济-效应比更高, 而接受ESWL患者生活治疗质量更好<sup>[18]</sup>. 但是相比LC, ESWL术后的GS复发率限制了ESWL在临床中应用<sup>[20]</sup>. 国外的报道ESWL治疗后的患者发生大多数为轻度的胰腺炎(1%-2%), 严重的胆源性胰腺炎比较罕见, 未见死亡病例报道<sup>[19]</sup>, 1994年上海中山医院报道的1089例ESWL碎石患者中, 出现胰腺炎的比率也只有0.8%<sup>[21]</sup>. 日本胃肠镜协会2016年推出的胆石症诊治指南将ESWL再次推出, 作为有无胆囊切除术条件或者不愿接受手术的GS患者的备选治疗方案<sup>[7]</sup>.

### 3.3 药物治疗

**3.3.1 熊去氧胆酸:** 熊去氧胆酸(ursodeoxycholic acid,



UDCA)是一种亲水、非细胞毒性的胆汁酸,参与调解体内胆固醇稳态。UDCA抑制胆固醇在肠内吸收及肝脏排泄,并能诱导调节肝细胞分泌胆汁酸,这两种方式改善胆固醇/胆盐成分比例降低胆固醇饱和指数(cholesterol saturation index, CSI),促使GS溶解。此外UDCA亦可抑制疏水性胆汁酸的分泌,避免其对胆囊壁的损伤,一方面这改善了胆囊上皮的选择性吸收功能,对胆汁成分的选择性吸收可稳定胆汁成分,另一方面这可以协助恢复胆囊动力及时排出胆固醇结石结晶<sup>[22]</sup>。目前报道UDCA的总体溶石有效率约为50%<sup>[23,24]</sup>。GS大小及钙化程度是影响溶石后结石清除率的重要原因,意大利的研究者报道UDCA治疗6 mo后大部分直径小于5 mm的GS可完全清除<sup>[22]</sup>。对于体积较大的结石,亦有报道结合ESWL碎石使用UDCA治疗6 mo后GS完全清除率可达87%<sup>[7]</sup>。不同种类的GS对于UDCA的反应也不一样,据报道CT提示等密度GS病例中,UDCA治疗6 mo后结石完全溶解率达85.38%,泥沙样胆结石中更高,达92.65%<sup>[24]</sup>。

由法国开展的一项研究对比了减肥手术后是否使UDCA对于胆结石发生的影响,结果发现UDCA可降低减肥手术后GS的发生率以及无症状GS患者的症状化转变风险<sup>[25]</sup>。对于有症状的GS患者,无论溶石是否成功,UDCA治疗均可缓解患者的胆绞痛症状<sup>[23]</sup>。UDCA不仅能提高GS患者的生活质量,而且显著减少GS患者并发症的发生率<sup>[26]</sup>。对于GS发生高风险人群(如快速减肥、使用生长抑素及其类似物者),建议使用UDCA预防GS的形成<sup>[27]</sup>。

**3.3.2 依折麦布及他汀类药物:**肠道内吸收和细胞内生物合成为体内胆固醇的主要来源,与胆固醇的肝脏转化及排泄共同维持体内胆固醇稳态,胆汁中胆固醇过饱和为GS形成的基础。NPC1L1为肠内的胆固醇转运体,其基因多态性可影响个体胆固醇吸收效率导致人群GS分布差异,以NPC1L1为靶点进行临床干预降胆固醇治疗具有重要的临床价值<sup>[28]</sup>。依折麦布为选择性NPC1L1活性抑制剂,可减少胆固醇的肠道内吸收并增加胆汁中的分泌,促进体内胆固醇外排。长期限制肠道胆固醇吸收可诱导HMG-CoA还原酶的活性导致细胞内胆固醇从头合成增加<sup>[29,30]</sup>,他汀类药物能够抑制HMG-CoA还原酶活性,限制胆固醇的从头合成,两者可协同减少胆汁中胆固醇的来源<sup>[31]</sup>。

胆固醇为胆汁酸合成原料,理论上原料的缩减可能造成胆汁中胆酸含量减少,导致胆固醇/胆盐比增高,但目前的研究并未观察到依折麦布以及他汀类药物减少胆汁酸排泄,这可能是机体维持胆汁酸稳态诱导胆汁酸合成酶、转运蛋白活性表达后的代偿效应<sup>[29,30,32]</sup>。此外,

研究发现胆囊切除后的患者使用依折麦布后胆汁致石性增加,而胆囊健全的患者胆汁致石性正常,这也说明胆囊对于维持胆汁稳定性有重要意义<sup>[33]</sup>。

目前的一些研究结果表明依折麦布与他汀对于胆囊胆固醇结石的治疗有治疗作用。已有研究证实他汀及依折麦布有利于减少胆汁CSI<sup>[34,35]</sup>,甚至在动物实验中观察到他汀及依折麦布治疗后GS溶解<sup>[36,37]</sup>。另外也有研究表明长期服用中-大剂量他汀可预防GS,显著降低GS并发症所致的胆囊切除术发生率,并倾向于减少胆囊切除术的操作时间<sup>[38,39]</sup>。

**3.3.3 LXR/FXR的靶向治疗:**肝脏X受体(liver X receptor, LXR)可诱导肠道、肝脏中的ABCG5/8、ABCA1等胆固醇转运体活化抑制肠道胆固醇的吸收并促进外周胆固醇向肝脏转运,是参与胆固醇代谢平衡的重要受体<sup>[40,41]</sup>。研究发现LXR的活化可增加胆汁中胆固醇的分泌,相对而言降低了胆汁酸与胆固醇的比例,增加胆汁CSI,促进GS形成<sup>[42]</sup>。我国的非肥胖型、血脂正常胆石病患者均伴随LXR及其ABCG5/8等靶基因过表达<sup>[43]</sup>,这些研究结果充分指明LXR在GS形成中的重要性,抑制LXR的活性对于GS的预防有积极意义。

目前已证实LXR受体拮抗剂胡椒碱可调节小鼠血脂水平、改善肝细胞脂肪变性、减少肝胆管细胞氧化损伤并能降低胰岛素抵抗,这在一定程度上控制了GS的危险因素<sup>[44,45]</sup>。此外,胡椒碱可下调ABCG5/8的表达,有效控制了小鼠胆汁中的胆固醇含量及胆固醇磷脂比,降低CSI并减少胆固醇结晶形成<sup>[45,46]</sup>。

法尼醇X受体(farnesoid X receptor, FXR)通过调控胆汁酸合成、摄取及分泌调节体内胆汁酸代谢。FXR激活BACS、BAT等基因促进结合型胆汁酸的生成增加胆汁中结合型胆汁酸的比例减少其细胞毒性,FXR亦能调节BSEP、MDR2等肝细胞内的胆汁酸转运体,促进胆汁分泌<sup>[47,48]</sup>。目前研究表明FXR激动剂治疗易发生GS的野生型小鼠后促进ABCB11和ABCB4转运体的表达,提升小鼠胆汁中胆盐、磷脂的浓度并降低胆汁CSI,而敲除FXR基因导致ABCG5/8等胆固醇转运体表,并增加疏水性胆汁酸分泌,导致胆汁毒性、致石性增加<sup>[49]</sup>。

胆酸成分如UDCA、鹅去氧胆酸等胆汁酸是FXR的天然激动剂,半合成的鹅去氧胆酸衍生物奥贝胆酸(Obeticholic acid, OCA)对FXR有更强的激动效能。2016年美国食品药品监督管理局批准OCA用于治疗UDCA应答不佳或者不耐受的原发性胆汁性胆管炎<sup>[50]</sup>。OCA对于改善脂代谢、降低胰岛素抵抗以及缓解肝脏纤维化效果显著,在治疗非病毒性肝脏疾病方面前景很好<sup>[51]</sup>。此外,OCA对促胆汁排泄及降低胆汁毒性亦有显著的效果,



在GS治疗方面潜力巨大<sup>[50]</sup>, 目前奥贝胆酸应用于GS的临床实验正在进行中(NCT01625026).

**3.3.4 促胆囊运动药物:** 胆囊收缩素(Cholecystokinin, CCK)主要由小肠黏膜I细胞产生, 作用于胆囊平滑肌上的胆囊收缩素受体(Cholecystokinin receptor, CCKR)刺激胆囊收缩, 是刺激胆囊收缩能力最强的物质. Cajal间质细胞广泛分布于肠道中, 可自发产生慢波电位调节肠道收缩节律. 研究发现Cajal间质细胞亦存在于胆囊壁中, 维持胆囊平滑肌基础慢波电位调节胆囊收缩<sup>[52]</sup>. 胆囊规律及有效的收缩是维持胆汁正常流动及避免胆汁过度浓缩的重要保障. 研究发现GS患者胆囊壁平滑肌中CCKR数量较低, 胆囊对CCK刺激的敏感性下降<sup>[52]</sup>. 胆囊壁内Cajal间质细胞的数量显著减少, 胆囊平滑肌慢波电位发生异常干扰平滑肌运动-肌电耦合过程抑制胆囊运动<sup>[53,54]</sup>. 此外, 胆固醇过饱和以及毒性疏水性胆汁酸盐渗入胆囊壁中损伤CCKR、Cajal间质细胞并直接抑制平滑肌细胞电活动亦是胆囊运动功能减退的主要原因<sup>[52]</sup>.

红霉素及其类似物、西沙比利等药物可通过刺激肠蠕动促进小肠黏膜I细胞产生CCK, 并调节迁移性肌电活动及胆碱通路介导的肌电活动改善胆囊动力<sup>[52,55]</sup>, 可应用于合并长期肠道动力不足的患者中. 通过其他药物降低胆汁CSI以及改善疏水性/亲水性胆酸的比例降低胆汁毒性亦是改善胆囊动力的主要治疗手段.

**3.3.5 其他药物:** 胆汁成分的化学损伤及GS的机械刺激及慢性炎症反应促进黏蛋白形成保护胆囊上皮细胞. 然而, 过度分泌的黏蛋白可作为胆固醇成核的中心蛋白, 为GS的形成的必备条件<sup>[52]</sup>. 动物实验中观察到阿司匹林等非甾体抗炎药可抑制胆囊黏蛋白分泌, 降低胆固醇结晶的成核预防GS形成<sup>[56]</sup>. 亦有报道阿米洛利通过抑制胆囊吸收限制胆汁浓缩实现预防GS<sup>[57]</sup>, 但这些方法一定程度上干扰了机体自我保护机制及正常代谢机制, 近年来的跟踪研究趋于冷淡.

## 4 非手术治疗的局限性

GS的非手术治疗后复发为常见的问题, 据报道ESWL完全清除GS的患者在随访的10年中50.7%的患者结石复发, 其中位复发时间为6.7年<sup>[20]</sup>. UDCA治疗后12年GS复发率为50%-70%<sup>[22]</sup>. GS复发决定了非手术治疗的长期性而长期服药必定带来患者依从性相关的问题. 疾病的科学宣教、药物制剂的改进以及综合慢病管理体系可提高患者依从性<sup>[26]</sup>. 此外, 长期非手术治疗所面对的药物临床效益-经济支出比不容忽视, 未来生产工艺的改进及生产能力的提高可在一定程度上减少经济支出, 值得寄予厚望.

## 5 小结与展望

胆囊切除术是大部分有症状GS患者的首选治疗方案, 但保留有功能的胆囊更利于维持消化吸收生理功能及正常代谢状态, 对于保障患者生活质量有积极意义. GS是消化系统疾病以及代谢性疾病的局部体现, 也是心血管疾病常见伴随疾病, 其治疗药物也有共同的作用靶点. 非手术治疗兼有对原发疾病及GS的共同作用. 目前的研究结果提示非手术治疗安全、有效, 可作为GS一级、二级预防. 随着GS形成关键作用机制的阐明, 新型靶向药物将不断涌出并应用于临床, 未来GS非手术治疗的地位将进一步提升.

## 6 参考文献

- Xu Q, Tao LY, Wu Q, Gao F, Zhang FL, Yuan L, He XD. Prevalences of and risk factors for biliary stones and gallbladder polyps in a large Chinese population. *HPB (Oxford)* 2012; 14: 373-381 [PMID: 22568413 DOI: 10.1111/j.1477-2574.2012.00457.x]
- Zhu L, Aili A, Zhang C, Saiding A, Abudureyimu K. Prevalence of and risk factors for gallstones in Uighur and Han Chinese. *World J Gastroenterol* 2014; 20: 14942-14949 [PMID: 25356055 DOI: 10.3748/wjg.v20.i40.14942]
- Chen CH, Huang MH, Yang JC, Nien CK, Etheredge GD, Yang CC, Yeh YH, Wu HS, Chou DA, Yueh SK. Prevalence and risk factors of gallstone disease in an adult population of Taiwan: an epidemiological survey. *J Gastroenterol Hepatol* 2006; 21: 1737-1743 [PMID: 16984599 DOI: 10.1111/j.1440-1746.2006.04381.x]
- Pak M, Lindseth G. Risk Factors for Cholelithiasis. *Gastroenterol Nurs* 2016; 39: 297-309 [PMID: 27467059 DOI: 10.1097/sga.0000000000000235]
- Shabanzadeh DM, Sørensen LT, Jørgensen T. A Prediction Rule for Risk Stratification of Incidentally Discovered Gallstones: Results From a Large Cohort Study. *Gastroenterology* 2016; 150: 156-167.e1 [PMID: 26375367 DOI: 10.1053/j.gastro.2015.09.002]
- Shabanzadeh DM, Sørensen LT, Jørgensen T. Determinants for clinical events in gallstone carriers unaware of their gallstones. *J Gastroenterol Hepatol* 2017; 32: 721-726 [PMID: 27521335 DOI: 10.1111/jgh.13531]
- Tazuma S, Unno M, Igarashi Y, Inui K, Uchiyama K, Kai M, Tsuyuguchi T, Maguchi H, Mori T, Yamaguchi K, Ryozaawa S, Nimura Y, Fujita N, Kubota K, Shoda J, Tabata M, Mine T, Sugano K, Watanabe M, Shimosegawa T. Evidence-based clinical practice guidelines for cholelithiasis 2016. *J Gastroenterol* 2017; 52: 276-300 [PMID: 27942871 DOI: 10.1007/s00535-016-1289-7]
- Federlein M, Müller VA, Fritze-Büttner F, Burghardt J, Gräber S, Gellert K, Borchert DH. Transvaginal cholecystectomy: results of a randomized study. *Chirurg* 2014; 85: 825-832 [PMID: 25139479 DOI: 10.1007/s00104-014-2852-5]
- Peng C, Ling Y, Ma C, Ma X, Fan W, Niu W, Niu J. Safety Outcomes of NOTES Cholecystectomy Versus Laparoscopic Cholecystectomy: A Systematic Review and Meta-Analysis. *Surg Laparosc Endosc Percutan Tech* 2016; 26: 347-353 [PMID: 27557339 DOI: 10.1097/sle.0000000000000284]
- Jaunoo SS, Mohandas S, Almond LM. Postcholecystectomy syndrome (PCS). *Int J Surg* 2010; 8: 15-17 [PMID: 19857610 DOI: 10.1016/j.ijsu.2009.10.008]

- 11 Cortés V, Quezada N, Uribe S, Arrese M, Nervi F. Effect of cholecystectomy on hepatic fat accumulation and insulin resistance in non-obese Hispanic patients: a pilot study. *Lipids Health Dis* 2017; 16: 129 [PMID: 28666456 DOI: 10.1186/s12944-017-0525-3]
- 12 Guo L, Mao J, Li Y, Jiao Z, Guo J, Zhang J, Zhao J. Cholelithiasis, cholecystectomy and risk of hepatocellular carcinoma: a meta-analysis. *J Cancer Res Ther* 2014; 10: 834-838 [PMID: 25579515 DOI: 10.4103/0973-1482.135992]
- 13 Zhang Y, Liu H, Li L, Ai M, Gong Z, He Y, Dong Y, Xu S, Wang J, Jin B, Liu J, Teng Z. Cholecystectomy can increase the risk of colorectal cancer: A meta-analysis of 10 cohort studies. *PLoS One* 2017; 12: e0181852 [PMID: 28771518 DOI: 10.1371/journal.pone.0181852]
- 14 Tan YY, Zhao G, Wang D, Wang JM, Tang JR, Ji ZL. A new strategy of minimally invasive surgery for cholelithiasis: calculi removal and gallbladder preservation. *Dig Surg* 2013; 30: 466-471 [PMID: 24481280 DOI: 10.1159/000357823]
- 15 Schmidt M, Søndena K, Vetthus M, Berhane T, Eide GE. A randomized controlled study of uncomplicated gallstone disease with a 14-year follow-up showed that operation was the preferred treatment. *Dig Surg* 2011; 28: 270-276 [PMID: 21757915 DOI: 10.1159/000329464]
- 16 Brazzelli M, Cruickshank M, Kilonzo M, Ahmed I, Stewart F, McNamee P, Elders A, Fraser C, Avenell A, Ramsay C. Systematic review of the clinical and cost effectiveness of cholecystectomy versus observation/conservative management for uncomplicated symptomatic gallstones or cholecystitis. *Surg Endosc* 2015; 29: 637-647 [PMID: 25119541 DOI: 10.1007/s00464-014-3712-6]
- 17 Vetthus M, Søreide O, Solhaug JH, Nesvik I, Søndena K. Symptomatic, non-complicated gallbladder stone disease. Operation or observation? A randomized clinical study. *Scand J Gastroenterol* 2002; 37: 834-839 [PMID: 12190099]
- 18 Carrilho-Ribeiro L, Serra D, Pinto-Correia A, Velosa J, De Moura MC. Quality of life after cholecystectomy and after successful lithotripsy for gallbladder stones: a matched-pairs comparison. *Eur J Gastroenterol Hepatol* 2002; 14: 741-744 [PMID: 12169982]
- 19 Paumgartner G, Sauter GH. Extracorporeal shock wave lithotripsy of gallstones: 20th anniversary of the first treatment. *Eur J Gastroenterol Hepatol* 2005; 17: 525-527 [PMID: 15827443]
- 20 Carrilho-Ribeiro L, Pinto-Correia A, Velosa J, Carneiro De Moura M. A ten-year prospective study on gallbladder stone recurrence after successful extracorporeal shock-wave lithotripsy. *Scand J Gastroenterol* 2006; 41: 338-342 [PMID: 16497623 DOI: 10.1080/00365520500483256]
- 21 何连齐, 王炳生, 林守诚, 孟承伟. 体外冲击波碎石治疗胆囊结石1089例报道. *上海医科大学学报* 1994; 6: 471-473
- 22 Guarino MP, Cocca S, Altomare A, Emerenziani S, Cicala M. Ursodeoxycholic acid therapy in gallbladder disease, a story not yet completed. *World J Gastroenterol* 2013; 19: 5029-5034 [PMID: 23964136 DOI: 10.3748/wjg.v19.i31.5029]
- 23 Hyun JJ, Lee HS, Kim CD, Dong SH, Lee SO, Ryu JK, Lee DH, Jeong S, Kim TN, Lee J, Koh DH, Park ET, Lee IS, Yoo BM, Kim JH. Efficacy of Magnesium Trihydrate of Ursodeoxycholic Acid and Chenodeoxycholic Acid for Gallstone Dissolution: A Prospective Multicenter Trial. *Gut Liver* 2015; 9: 547-555 [PMID: 26087862 DOI: 10.5009/gnl15015]
- 24 Lee JM, Hyun JJ, Choi IY, Yeom SK, Kim SY, Jung SW, Jung YK, Koo JS, Yim HJ, Lee HS, Lee SW, Kim CD. Comparison on Response and Dissolution Rates Between Ursodeoxycholic Acid Alone or in Combination With Chenodeoxycholic Acid for Gallstone Dissolution According to Stone Density on CT Scan: Strobe Compliant Observation Study. *Medicine (Baltimore)* 2015; 94: e2037 [PMID: 26683912 DOI: 10.1097/md.0000000000002037]
- 25 Coupaye M, Calabrese D, Sami O, Msika S, Ledoux S. Evaluation of incidence of cholelithiasis after bariatric surgery in subjects treated or not treated with ursodeoxycholic acid. *Surg Obes Relat Dis* 2017; 13: 681-685 [PMID: 28089591 DOI: 10.1016/j.soard.2016.11.022]
- 26 Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Chatedaki C, Sioka E, Zacharoulis D. Ursodeoxycholic Acid in the Prevention of Gallstone Formation After Bariatric Surgery: an Updated Systematic Review and Meta-analysis. *Obes Surg* 2017; 27: 3021-3030 [PMID: 28889240 DOI: 10.1007/s11695-017-2924-y]
- 27 Portincasa P, Di Ciaula A, Grattagliano I. Preventing a Mass Disease: The Case of Gallstones Disease: Role and Competence for Family Physicians. *Korean J Fam Med* 2016; 37: 205-213 [PMID: 27468338 DOI: 10.4082/kjfm.2016.37.4.205]
- 28 Lauridsen BK, Stender S, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Genetic variation in the cholesterol transporter NPC1L1, ischaemic vascular disease, and gallstone disease. *Eur Heart J* 2015; 36: 1601-1608 [PMID: 25841872 DOI: 10.1093/eurheartj/ehv108]
- 29 Lin X, Racette SB, Ma L, Wallendorf M, Ostlund RE Jr. Ezetimibe Increases Endogenous Cholesterol Excretion in Humans. *Arterioscler Thromb Vasc Biol* 2017; 37: 990-996 [PMID: 28279967 DOI: 10.1161/atvbaha.117.309119]
- 30 Davidson MH, Voogt J, Luchomun J, Decaris J, Killion S, Boban D, Glass A, Mohammad H, Lu Y, Villegas D, Neese R, Hellerstein M, Neff D, Musliner T, Tomassini JE, Turner S. Inhibition of intestinal cholesterol absorption with ezetimibe increases components of reverse cholesterol transport in humans. *Atherosclerosis* 2013; 230: 322-329 [PMID: 24075764 DOI: 10.1016/j.atherosclerosis.2013.08.006]
- 31 Husain NE, Hassan AT, Elmadhoun WM, Ahmed MH. Evaluating the safety of Liptruzet (ezetimibe and atorvastatin): what are the potential benefits beyond low-density lipoprotein cholesterol-lowering effect? *Expert Opin Drug Saf* 2015; 14: 1445-1455 [PMID: 26134926 DOI: 10.1517/14740338.2015.1063613]
- 32 Fu ZD, Cui JY, Klaassen CD. Atorvastatin induces bile acid-synthetic enzyme Cyp7a1 by suppressing FXR signaling in both liver and intestine in mice. *J Lipid Res* 2014; 55: 2576-2586 [PMID: 25278499 DOI: 10.1194/jlr.M053124]
- 33 Kishikawa N, Kanno K, Sugiyama A, Yokobayashi K, Mizooka M, Tazuma S. Long-term administration of a Niemann-Pick C1-like 1 inhibitor, ezetimibe, does not worsen bile lithogenicity in dyslipidemic patients with hepatobiliary diseases. *J Hepatobiliary Pancreat Sci* 2016; 23: 125-131 [PMID: 26692575 DOI: 10.1002/jhbp.313]
- 34 Smith JL, Roach PD, Wittenberg LN, Riottot M, Pillay SP, Nestel PJ, Nathanson LK. Effects of simvastatin on hepatic cholesterol metabolism, bile lithogenicity and bile acid hydrophobicity in patients with gallstones. *J Gastroenterol Hepatol* 2000; 15: 871-879 [PMID: 11022827]
- 35 Kishikawa N, Kanno K, Sugiyama A, Yokobayashi K, Mizooka M, Tazuma S. Clinical evaluation of ezetimibe on bile lithogenicity in humans: Use of transnasal endoscopy for bile sampling. *Hepatol Res* 2015; 45: 693-697 [PMID: 25132425 DOI: 10.1111/hepr.12402]
- 36 Abedin MZ, Narins SC, Park EH, Smith PR, Kirkwood KS. Lovastatin alters biliary lipid composition and dissolves gallstones: a long-term study in prairie dogs. *Dig Dis Sci* 2002; 47: 2192-2210 [PMID: 12395892]
- 37 Wang HH, Portincasa P, Mendez-Sanchez N, Uribe M, Wang DQ. Effect of ezetimibe on the prevention and dissolution of

- cholesterol gallstones. *Gastroenterology* 2008; 134: 2101-2110 [PMID: 18442485 DOI: 10.1053/j.gastro.2008.03.011]
- 38 Kan HP, Guo WB, Tan YF, Zhou J, Liu CD, Huang YQ. Statin use and risk of gallstone disease: A meta-analysis. *Hepatol Res* 2015; 45: 942-948 [PMID: 25297889 DOI: 10.1111/hepr.12433]
- 39 Pulkkinen J, Eskelinen M, Kiviniemi V, Kotilainen T, Pöyhönen M, Kilpeläinen L, Käkälä P, Kastarinen H, Paajanen H. Effect of statin use on outcome of symptomatic cholelithiasis: a case-control study. *BMC Gastroenterol* 2014; 14: 119 [PMID: 24993977 DOI: 10.1186/1471-230x-14-119]
- 40 Sato K, Kamada T. Regulation of bile acid, cholesterol, and fatty acid synthesis in chicken primary hepatocytes by different concentrations of T0901317, an agonist of liver X receptors. *Comp Biochem Physiol A Mol Integr Physiol* 2011; 158: 201-206 [PMID: 21056113 DOI: 10.1016/j.cbpa.2010.10.028]
- 41 Korach-André M, Gustafsson JÅ. Liver X receptors as regulators of metabolism. *Biomol Concepts* 2015; 6: 177-190 [PMID: 25945723 DOI: 10.1515/bmc-2015-0007]
- 42 Uppal H, Zhai Y, Gangopadhyay A, Khadem S, Ren S, Moser JA, Xie W. Activation of liver X receptor sensitizes mice to gallbladder cholesterol crystallization. *Hepatology* 2008; 47: 1331-1342 [PMID: 18318438 DOI: 10.1002/hep.22175]
- 43 Jiang ZY, Parini P, Eggertsen G, Davis MA, Hu H, Suo GJ, Zhang SD, Rudel LL, Han TQ, Einarsson C. Increased expression of LXR alpha, ABCG5, ABCG8, and SR-BI in the liver from normolipidemic, nonobese Chinese gallstone patients. *J Lipid Res* 2008; 49: 464-472 [PMID: 18007013 DOI: 10.1194/jlr.M700295-JLR200]
- 44 Jwa H, Choi Y, Park UH, Um SJ, Yoon SK, Park T. Piperine, an LXRα antagonist, protects against hepatic steatosis and improves insulin signaling in mice fed a high-fat diet. *Biochem Pharmacol* 2012; 84: 1501-1510 [PMID: 23000915 DOI: 10.1016/j.bcp.2012.09.009]
- 45 Song XY, Xu S, Hu JF, Tang J, Chu SF, Liu H, Han N, Li JW, Zhang DM, Li YT, Chen NH. Piperine prevents cholesterol gallstones formation in mice. *Eur J Pharmacol* 2015; 751: 112-117 [PMID: 25645812 DOI: 10.1016/j.ejphar.2015.01.038]
- 46 Li Y, Li M, Wu S, Tian Y. Combination of curcumin and piperine prevents formation of gallstones in C57BL6 mice fed on lithogenic diet: whether NPCIL1/SREBP2 participates in this process? *Lipids Health Dis* 2015; 14: 100 [PMID: 26335572 DOI: 10.1186/s12944-015-0106-2]
- 47 Chiang JY. Bile acids: regulation of synthesis. *J Lipid Res* 2009; 50: 1955-1966 [PMID: 19346330 DOI: 10.1194/jlr.R900010-JLR200]
- 48 Yuan ZQ, Li KW. Role of farnesoid X receptor in cholestasis. *J Dig Dis* 2016; 17: 501-509 [PMID: 27383832 DOI: 10.1111/1751-2980.12378]
- 49 Moschetta A, Bookout AL, Mangelsdorf DJ. Prevention of cholesterol gallstone disease by FXR agonists in a mouse model. *Nat Med* 2004; 10: 1352-1358 [PMID: 15558057 DOI: 10.1038/nm1138]
- 50 Jhaveri MA, Kowdley KV. New developments in the treatment of primary biliary cholangitis - role of obeticholic acid. *Ther Clin Risk Manag* 2017; 13: 1053-1060 [PMID: 28860789 DOI: 10.2147/TCRM.S113052]
- 51 Gitto S, Guarneri V, Sartini A, Andreone P. The use of obeticholic acid for the management of non-viral liver disease: current clinical practice and future perspectives. *Expert Rev Gastroenterol Hepatol* 2018; 12: 165-171 [PMID: 29082798 DOI: 10.1080/17474124.2018.1399060]
- 52 Chen Y, Kong J, Wu S. Cholesterol gallstone disease: focusing on the role of gallbladder. *Lab Invest* 2015; 95: 124-131 [PMID: 25502177 DOI: 10.1038/labinvest.2014.140]
- 53 Pasternak A, Gil K, Matyja A, Gajda M, Sztéfko K, Walocha JA, Kulig J, Thor P. Loss of gallbladder interstitial Cajal-like cells in patients with cholelithiasis. *Neurogastroenterol Motil* 2013; 25: e17-e24 [PMID: 23121223 DOI: 10.1111/nmo.12037]
- 54 Fan Y, Wu S, Fu B, Weng C, Wang X. The role of interstitial Cajal-like cells in the formation of cholesterol stones in guinea pig gallbladder. *Hepatol Int* 2015; 9: 612-620 [PMID: 25788205 DOI: 10.1007/s12072-015-9623-3]
- 55 Sengupta S, Modak P, McCauley N, O'Donnell LJ. Effect of oral clarithromycin on gall-bladder motility in normal subjects and those with gall-stones. *Aliment Pharmacol Ther* 2006; 24: 95-99 [PMID: 16803607 DOI: 10.1111/j.1365-2036.2006.02962.x]
- 56 Cariati A, Piromalli E. Limits and perspective of oral therapy with statins and aspirin for the prevention of symptomatic cholesterol gallstone disease. *Expert Opin Pharmacother* 2012; 13: 1223-1227 [PMID: 22607008 DOI: 10.1517/14656566.2012.685161]
- 57 Strichartz SD, Abedin MZ, Abdou MS, Roslyn JJ. The effects of amiloride on biliary calcium and cholesterol gallstone formation. *Ann Surg* 1989; 209: 152-156 [PMID: 2916859]

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