

基于病理分级的代谢相关脂肪性肝病严重程度对袖状胃切除术后疗效的影响

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摘要

随着肥胖及其合并症的全球大流行, SG手术因其安全有效, 操作简单而成为主要的减重手术之一。代谢性脂肪性肝病(MASLD)是与代谢功能障碍相关的慢性肝病, MASLD分为四个等级: 无MASLD、轻度、中度和重度脂肪变性。随着全球肥胖和代谢疾病的流行, MASLD的患病率上升, 尤其在肥胖和2型糖尿病患者中较为常见。研究表明, 袖状胃切除术(SG)对MASLD患者有效, 但术后体重减轻效果因病情严重程度而异。重度MASLD患者通常因胰岛素抵抗、肝脏炎症和代谢紊乱, 术后体重减轻较慢且效果差。慢性炎症和肝纤维化进一步加剧这一问题。精准的术前评估和个体化治疗策略对优化术后效果至关重要。未来的研究应深入探讨MASLD分级与SG术后疗效的关系, 优化治疗方案, 提高长期代谢获益。

关键词

肥胖, 代谢相关脂肪性肝病, 袖状胃切除术

Impact of Severity of Metabolism-Related Fatty Liver Disease Based on Pathologic Grading on Outcomes after Sleeve Gastrectomy

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Abstract

With the global epidemic of obesity and its complications, SG surgery has become one of the main weight-loss operations because of its safety, effectiveness and simple operation. Metabolic fatty liver disease (MASLD) is a chronic liver disease related to metabolic dysfunction. MASLD is divided into four grades: no MASLD, mild, moderate and severe steatosis. With the prevalence of obesity and metabolic diseases in the world, the prevalence of MASLD is increasing, especially in obese and type 2 diabetic patients. Studies have shown that sleeve gastrectomy (SG) is effective for patients with MASLD, but the effect of weight loss after operation varies with the severity of the disease. Patients with severe MASLD usually lose weight slowly after operation due to insulin resistance, liver inflammation and metabolic disorder, and the effect is poor. Chronic inflammation and liver fibrosis further aggravate this problem. Accurate preoperative evaluation and individualized treatment strategy are very important to optimize postoperative results. Future research should further explore the relationship between MASLD grading and postoperative curative effect of SG, optimize the treatment plan and improve the long-term metabolic benefit.

Keywords

Obesity, Metabolic Dysfunction-Associated Steatotic Liver Disease, Sleeve Gastrectomy

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1. 引言

代谢相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)是一种以肝细胞脂肪变性为特征的代谢相关慢性肝病,其定义由2023年国际共识更新确立,取代了既往“非酒精性脂肪性肝病(NAFLD)”的命名,以更精准地反映其与代谢功能障碍的紧密关联[1]。MASLD的病理分级基于肝细胞脂肪变性比例,分为无MASLD(脂肪变性<5%);轻度(5%~33%);中度(34%~66%)及重度(脂肪变性>66%)四组。值得注意的是,约20%~40%的MASLD患者可能进展为代谢功能障碍相关脂肪性肝炎(MASH),其特征性病理改变包括肝细胞气球样变、小叶炎症及纤维化,最终增加肝硬化及肝细胞癌(HCC)风险[2]-[4]。

在全球肥胖大流行的背景下, MASLD在全球范围内的发病率持续上升。流行病学数据显示, MASLD在肥胖个体中的患病率可高达50%~90% [5]-[8]。肥胖不仅是MASLD的主要危险因素,还与2型糖尿病(T2DM)、胰岛素抵抗(IR)、高血压和血脂紊乱等代谢异常密切相关,这些因素在MASLD进展过程中起关键作用[6] [9]。此外, MASLD还与心血管疾病(CVD)高度相关,研究表明MASLD患者的心血管事件发生率显著高于无MASLD个体,即使在调整了传统的心血管危险因素后,这种风险仍然存在[10] [11]。研究表明, MASLD不仅影响肝脏,还通过改变全身能量代谢和炎症状态,对肥胖相关疾病的进展产生重要影响[12]-[15]。因此, MASLD的管理应当纳入整体代谢健康的考量,以优化肥胖及其并发症的治疗策略。

基于最新的系统性综述和长期随访研究,生活方式干预在BMI ≥ 35 kg/m²或BMI ≥ 30 kg/m²伴代谢

合并症患者中的长期减重效果确实不佳, 而代谢减重手术在长期体重维持、代谢改善和糖尿病缓解等方面均显著优于生活方式干预。这一结论已被多个前瞻性随机对照试验及大型回顾性研究所验证[16]-[18]。此外, 与 RYGB 相比, SG 具有手术风险更低、术后并发症较少的优势, 因此成为许多肥胖合并代谢疾病患者的首选手术方案[19] [20]。

尽管 SG 对肥胖及其相关代谢疾病具有显著疗效, 但在临床工作中我们发现术后个体间的体重减轻效果仍然存在较大差异[21]; 且目前针对术前 MAFLD 对 SG 术后减重效果存在影响的研究非常少, 仅有少量相关研究报道。2023 年 Abu-Rumaleh M 等人的研究指出 SG 术后两年内 MASLD 组体重减轻显著低于非 MASLD 组[22]。2024 年 11 月发表的一项最新的 meta 分析观察到与没有 MASLD 的患者相比, 先前存在 MASLD 的个体的总体重减轻和超重减轻明显减少, 且 MASH 患者在 SG 术后 1 年的体重减轻效果(%EWL)显著低于无 MASLD 和轻度 MASLD 患者, 提示 MASLD 可能影响手术后的体重管理[23]。但围绕肝脏脂肪肝变性程度分组的研究暂无相关报道。

对于 MASLD 影响 SG 术后体重减轻的可能猜测是: 重度的肝脏脂肪变性可能导致更加严重的肝脏和外周组织(如肌肉、脂肪)的 IR; 同时, 重度肝脏脂肪变性常伴随较为严重的肝脏炎症和氧化应激, 导致炎症因子(如 TNF- α 、IL-6)的释放及炎症信号的激活, 进一步加剧脂肪组织的胰岛素抵抗和功能异常, 形成肝脏脂肪堆积-IR-全身代谢紊乱的恶性循环, 其次, 肝脏脂肪变性可能导致线粒体功能障碍, 降低基础代谢率和脂肪氧化效率[24]-[27]; 最后, 肠道-肝脏轴紊乱-中枢系统调控异常的交互作用, 肝脏作为代谢中枢的功能失调是其核心驱动力[28] [29]。因此, 明确 MASLD 患者的肝脏脂肪变性程度与 SG 术后体重减轻的关系, 对于优化术前评估和制定个体化治疗方案具有重要的临床意义, 这有助于预测术后效果并采取相应的管理策略。

2. MASLD 与全身代谢紊乱

2.1. 病理分级

MASLD 的分级主要依据肝细胞脂肪变性的程度, 通常采用病理学评分体系, 如 Brunt 分级和 Kleiner 分级。根据肝细胞内脂肪累积的比例, 可将 MASLD 分为以下四个等级: 无 MASLD (脂肪变性 < 5%); 无明显肝细胞脂肪浸润。轻度脂肪变性(5%~33%): 肝小叶内部分肝细胞含有脂滴, 累积范围较小。中度脂肪变性(34%~66%): 脂肪累积在较大范围的肝细胞中, 可能伴有轻微的肝脏炎症反应。重度脂肪变性组(>66%): 超过三分之二的肝细胞存在明显的脂肪浸润, 可能合并炎症及纤维化。这一分级系统广泛应用于临床研究和病理评估, 以指导 MASLD 患者的分层管理和预后判断[30] [31]。

2.2. MASLD 与全身代谢紊乱密切相关

MASLD 不仅是单纯的肝脏疾病, 还与全身代谢异常密切相关。以下几种代谢因素在 MASLD 的不同分级中呈现不同的病理变化。

2.2.1. 胰岛素抵抗

胰岛素抵抗(Insulin resistance, IR)是 MASLD 发展的核心机制之一[32]。研究表明, MASLD 患者的胰岛素抵抗程度随着肝脂肪变性加重而显著增加, HOMA-IR (胰岛素抵抗指数)在中重度 MASLD 患者中显著高于轻度或无 MASLD 组。胰岛素抵抗可促进肝脏异常脂质积累, 主要机制包括: 促进肝脏葡萄糖生成, 抑制肝细胞脂肪酸氧化。增加脂肪组织的脂解作用, 使更多游离脂肪酸(FFA)进入肝脏, 促进肝脂肪变性, 减少胰岛素介导的肝糖原合成, 加重脂肪沉积; 此外, 胰岛素抵抗还通过激活炎症信号通路(如 NF- κ B 通路)和氧化应激通路, 促进肝脏炎症反应和氧化损伤, 形成恶性循环, 加剧 MASLD 的病理进程[26]

[27] [33]。

2.2.2. II 型糖尿病(T2DM)

MASLD 与 T2DM 呈现双向关系, MASLD 患者发生 T2DM 的风险是无 MASLD 个体的 2~3 倍[34]。此外, T2DM 可加速 MASLD 进展至 MASH 甚至肝纤维化。研究显示, 在 MASLD 患者中, 伴 T2DM 者比无 T2DM 者的肝脂肪变性程度更严重, 且术后体重减轻(%EWL)相对较低, 提示 T2DM 可能影响代谢手术的疗效[4] [35]。

2.2.3. 血脂异常

MASLD 患者普遍存在血脂紊乱, 尤其是甘油三酯(TG)升高、高密度脂蛋白胆固醇(HDL-C)降低。中重度 MASLD 患者的血浆甘油三酯水平较轻度 MASLD 和无 MASLD 组更高。这一现象可能与: 肝脏极低密度脂蛋白(VLDL)合成增加, 导致循环系统 TG 水平升高。HDL-C 清除率增加, 影响胆固醇的逆向转运, 进而加重肝脂肪沉积[36] [37]。此外, 这一过程与胰岛素抵抗(IR)密切相关, IR 通过激活 SREBP-1c 通路促进 VLDL 的合成和分泌[32]。

2.2.4. 炎症水平

慢性低度炎症在 MASLD 发展过程中起关键作用。MASLD 患者的 C 反应蛋白(CRP)、白细胞介素-6(IL-6)和肿瘤坏死因子- α (TNF- α)水平显著升高, 且在中重度 MASLD 患者中炎症水平更高。这些炎症因子不仅加重肝细胞损伤, 还可能影响胃肠道激素(GLP-1, PYY)的调控[38], 降低袖状胃切除术的长期代谢效应[39]。

3. SG 对 MASLD 患者的影响

目前, 袖状胃切除术(SG)已成为全球范围内最常实施的减重代谢手术, 其占比已超过 50%, 超过了 Roux-en-Y 胃旁路手术(RYGB) [16]。

3.1. SG 手术机制与体重减轻

SG 是一种限制性手术, 其主要作用机制包括减少胃容量、改变胃肠激素(如 GLP-1、PYY、Ghrelin)的分泌模式[38], 以及改善胰岛素敏感性及调节能量代谢, 实现体重减轻和代谢改善[40] [41]。已有大量研究证实, SG 能显著改善 T2DM、高血压、血脂异常及 MASLD, 并可使部分 MASH 患者的肝脏病理学指标得到逆转[18] [19] [42] [43]。

3.1.1. 限制性手术的体重减轻原理

SG 通过切除大部分胃体, 减少胃容量约三分之二, 从而限制食物摄入量[20]。此外, SG 对胃肠激素的调节作用是其减重和代谢改善的关键机制之一: 如 SG 后, 胰高血糖素样肽-1 (GLP-1)分泌显著增加, GLP-1 能促进胰岛素分泌、抑制胃排空, 并增强饱腹感。肽 YY (PYY)是一种抑制食欲的激素, 术后其水平升高, 可减少食物摄入量。生长素释放肽(Ghrelin)由胃底部产生, 是已知的主要饥饿激素。SG 术后, 由于胃底的切除, Ghrelin 水平显著降低, 从而减少饥饿感[38]。

3.1.2. 代谢改善效应

SG 不仅通过减少食物摄入促进体重减轻, 还能改善胰岛素敏感性和脂肪组织功能: 研究表明, SG 术后, 胰岛素抵抗指数(HOMA-IR)显著下降, 表明胰岛素敏感性增强; SG 减少了内脏脂肪组织的积累, 从而降低了脂肪因子(如 TNF- α 、IL-6)的分泌, 这些因子与 MASLD 进展密切相关; SG 术后, 肝糖原生成能力下降, 同时肝脏糖原储存增加, 表明 SG 可改善肝脏糖代谢异常[44]-[46]。

3.2. SG 对 MASLD 的影响

近年来, 多项研究通过影像学、病理学和代谢指标评估 SG 对 MASLD 的影响, 结果显示 SG 可显著改善肝脂肪变性, 并在一定程度上逆转肝纤维化, 2022 年 JAMA 杂志报道的一篇基于肝活检的研究发现, SG 术后 84% (95% CI: 73%~92%) 的 NASH 消退, 70% 的纤维化分期降低 (95% CI: 57%~82%), 56% 的纤维化消失 (95% CI: 42%~69%), 肝脏疾病进展率下降 88%; 同时, 术后肥胖、NASH 相关的主要心血管不良事件 (MACE) 发生率降至最低 [11]。且术后体重减轻幅度越大, 肝纤维化逆转的可能性越高, 但部分研究显示, 即使术后体重减轻有限, SG 仍然能够改善肝纤维化 [47]。

4. MASLD 对 SG 手术的影响

4.1. 术前 MASLD 严重程度及有无 MASH 和纤维化对 SG 术后疗效的影响

研究发现, 术前 MASLD 的严重程度, 以及术前有无 MASH 与术后体重减轻 (%EWL) 呈负相关, 即 MASLD 越严重的患者, 术后体重减轻程度可能越有限 [48]。

研究表明, MASH 患者 SG 术后 %EWL 显著低于无 MASLD 和 MASL 患者。在一项基于 163 名 SG 患者的研究中, 1 年随访数据显示: 无 MASLD 组 %TWL 为 30.9 ± 8.8 , %EWL 为 69.4 ± 21.8 ; MASL 组 %TWL 为 30.3 ± 9.3 , %EWL 为 67.8 ± 23.1 ; MASH 组 %TWL 为 27.3 ± 9.9 , %EWL 为 57.4 ± 20.1 ($p = 0.004$)。这些数据表明, MASH 患者术后体重减轻效果较差, 尤其是 %EWL 的下降更为显著, 提示 MASH 可能影响 SG 的短期减重效果。调整混杂因素 (年龄、性别、术前 BMI 和 HbA1c) 后, MASH 仍然与较低的 %EWL 显著相关 (Beta: -7.1 ; 95% CI: $-13.6 \sim -0.5$; $p = 0.035$), 但对 %TWL 的影响在调整后不再显著 (Beta: -2.7 ; 95% CI: $-5.7 \sim -0.2$; $p = 0.069$)。这意味着 MASLD 的影响主要体现在超重减少率 (%EWL), 而对总的体重减轻 (%TWL) 影响相对较小 [48]。

上述研究充分证实术前有无 MAFLD 及有无 MASH 对 SG 术后体重减轻和肝脏代谢存在显著负相关, 但并未阐明 MAFLD 脂肪变性程度对术后患者疗效的影响。但是, 关于术前肝纤维化对袖状胃切除术 (SG) 后体重减轻百分比 (%EWL) 的直接影响仍缺乏明确证据。

MASLD 的严重程度可能影响患者在 SG 术后体重减轻的效果, 尤其是对超重减少率 (%EWL) 和总体重减少率 (%TWL) 的影响已在多个研究中被探讨。

4.2. MASLD 对 SG 术后体重减轻效果影响的可能机制

4.2.1. 胰岛素抵抗及代谢异常

重度 MASLD 患者的 HOMA-IR 指数通常较高, 意味着更严重的胰岛素抵抗。有证据显示, 术前 HOMA-IR 较高的患者, 术后 %EWL 显著较低 ($p < 0.05$) [49]。其可能机制包括: (1) 高 HOMA-IR 患者术后脂肪氧化能力下降, 导致术后能量消耗受限; (2) 术后胰岛素敏感性改善不足削弱代谢适应, 降低体重减轻幅度。 (3) IR 可能通过 GLP-1 和 Ghrelin 水平的变化而影响术后体重减轻; (4) 术前 HbA1c 水平较高的患者术后 %EWL 较低 ($p < 0.05$)。2 型糖尿病的存在和术后 2 型糖尿病的不缓解对术后 %EWL 较低显著相关, 而脂肪肝严重程度与 2 型糖尿病发病显著相关, 这证实了重度 MAFLD 影响术后体重减轻与糖代谢紊乱和 IR 严重程度密切相关 [50] [51]。

4.2.2. 炎症及纤维化程度

严重的 MASLD 往往与肝脏炎症, 肝纤维化密切相关术前 CRP、IL-6 水平较高的患者术后 %EWL 和 %TWL 均较低, 提示慢性炎症可能抑制术后代谢适应性。高炎症状态可能导致脂肪组织持续释放促炎因子, 干扰胰岛素信号通路, 降低体重减轻效果 [52] [53]。

研究指出, 肝纤维化程度越严重(F2 及以上), 术后体重减轻可能更低。其可能机制是通过减少肝脏葡萄糖摄取能力和降低胰岛素敏感性, 影响 SG 术后的代谢改善[54]。Umemura *et al.* (2024)研究了 SG 对严重肥胖患者肝脏功能的影响, 并发现术后代谢改善与术前肝脏炎症程度相关。这可能表明, 较严重的术前肝纤维化可能会限制 SG 在改善代谢方面的效果[55]。

4.2.3. 胃肠道激素及食欲调节

研究发现, MASLD 患者术后 GLP-1 和 PYY 水平升高较少, 可能导致术后饱腹感下降, 从而影响体重管理。重度 MASLD 患者术后 Ghrelin 水平下降不及无 MASLD, 可能影响长期食欲调控[56]。

5. 未来研究方向

未来需要更大样本量和长期随访的前瞻性研究, 进一步验证 MASLD 分级与 SG 术后疗效的关系。对于肥胖、MASLD 以及 T2DM 等慢病患者制定安全有效且复发风险低的个体化治疗策略是未来研究的任务。

对于重度 MASLD 患者, 应考虑采取针对性的术前干预措施: 包括围术期干预, 联合术前药物治疗(二甲双胍、GLP-1 受体激动剂等); 术后加强随访和动态检测计划, 重点关注肝功能、血糖控制和体重减轻。整合基于 MRI 的质子密度脂肪分数(PDFF)或超声衍生的脂肪分数(UDFF)等影像学工具, 可以提供肝脏脂肪消退的精确纵向监测。

6. 临床指导建议

6.1. 术前干预措施

轻度 MASLD 患者, 主要依赖生活方式干预, 包括: 低热量、低碳水化合物、高蛋白的饮食控制, 以减少肝脏脂肪积累; 增加体力活动, 如中等强度的有氧运动, 每周至少 150 分钟, 以改善胰岛素敏感性和肝脂肪代谢; 以减少肝脂肪变性、降低手术风险, 并改善术后代谢恢复能力。而中重度 MASLD 患者, 在生活方式干预的基础上, 可能需要考虑药物治疗以改善肝功能, 并在术前进行详细的肝功能评估, 以确保手术的安全性和有效性。可考虑 GLP-1 受体激动剂(如司美格鲁肽)、SGLT2 抑制剂或维生素 E 以改善肝功能; 术前利用影像学检查(如超声、MRI-PDFF)评估肝脂肪变性程度; 血清生物标志物(如 NFS、FIB-4、ELF)评估纤维化进展。确保术前控制肝功能异常, 以降低围手术期风险, 提供手术获益。

6.2. 术后管理策略

轻度 MASLD 患者继续健康生活方式, 防止肝病进展, 保持低碳水、高蛋白饮食习惯, 避免术后体重反弹; 维持规律运动, 提高胰岛素敏感性; 定期监测肝功能(ALT、AST)、肝脂肪含量及代谢指标(HbA1c, HOMA-IR)。对于中重度 MASLD 患者需要术后密切随访肝功能, 在术后 3、6、12 个月进行影像学 and 血清学监测, 以评估 MASLD 逆转情况; 必要时药物干预; 若术后仍存在肝纤维化或代谢异常, 可考虑 GLP-1 受体激动剂或派莫特罗等抗炎治疗。

6.3. 个体化营养管理

补充足够的蛋白质、维生素(如维生素 D、B 族维生素), 减少术后营养不良的风险。

7. 结论

本研究回顾了代谢性脂肪性肝病(MASLD)严重程度对袖状胃切除术(SG)术后体重减轻效果的影响, 结合近十年的最新研究数据, 探讨了 MASLD 在减重手术后的临床意义和机制。通过系统分析, 得出结论: MASLD 的严重程度能够影响 SG 术后体重减轻的效果, 尤其是重度患者术后%EWL 较低, 取得满

意减重效果时间较轻度或无 MASLD 患者延迟, 该过程与糖脂代谢紊乱及全身多系统验证密切相关。

此外, 术前 MASLD 的精准评估可优化术后管理, 未来需要更多深入研究来进一步明确 MASLD 在减重手术后的作用机制, 并制定针对 MASLD 患者的最佳治疗方案选择和术后管理方案, 以提高长期代谢获益。

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