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长期应用质子泵抑制剂对非酒精性脂肪肝影响的研究进展

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摘　要

质子泵抑制剂(PPI)是目前最常用的抑酸药物，广泛应用于酸相关胃肠道疾病。同时，PPI的合理使用以及长期使用的安全性问题受到广泛关注。近年来，有研究发现PPI的使用可能会导致肠道微生物群紊乱，增加非酒精性脂肪肝(NAFLD)的患病风险。因此，了解肠道微生物在两者之间的关系至关重要。本文总结了肠道菌群在PPI的使用及NAFLD患病中的影响，以及PPI的长期使用与NAFLD发病的关系，以引起临床医生对长期使用PPI的不良反应关注，旨在为未来基于肠道菌群调节的PPI相关的NAFLD并发症的预防提供参考。

关键词

质子泵抑制剂，非酒精性脂肪肝，肠道菌群

Research Progress of the Effects of Long-Term Use of Proton Pump Inhibitors on Non-Alcoholic Fatty Liver Disease

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Abstract

Proton pump inhibitors (PPIs) are the most commonly used acid-suppressing drugs and are wide-

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ly used in acid-related gastrointestinal diseases. Meanwhile, the rational use of PPIs and the safety of long-term use have been extensively concerned. In recent years, some studies have found that PPI use may lead to gut microbiota disruption and increase the risk of non-alcoholic fatty liver disease (NAFLD). Therefore, it is crucial to find out the relationship between the gut microbiota in the two. This article summarizes the influence of gut microbiota in the use of PPIs and the prevalence of NAFLD, as well as the relationship between the long-term use of PPIs and the development of NAFLD, in order to draw the attention of clinicians to the adverse effects of long-term use of PPIs, with the aim of providing a reference for the future prevention of PPI-associated NAFLD complications based on the regulation of the intestinal microbiota.

Keywords

Proton Pump Inhibitors, Non-Alcoholic Fatty Liver Disease, Gut Microbiota

1. 简介

非酒精性肝病(non-alcoholic fatty liver disease, NAFLD)是代谢功能障碍在肝脏中的表现，其与肥胖、2 型糖尿病、代谢综合征有显著关系[1]。NAFLD 定义为除外过量饮酒(男性 > 30 g/d，女性 > 20 g/d)及其他继发性肝病的情况下，超过 5%的肝细胞存在脂肪变性[2]，当伴有炎症及肝细胞损伤时称为非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)，进一步可发展为肝纤维化、肝硬化、肝细胞癌[3]。NAFLD 发病趋势逐年上升，其全球发病率约为 25% [4]，是目前全球最常见的慢性肝脏疾病。NAFLD 发病机制尚不明，有研究表明 NAFLD 的发病与肠道菌群失调关系密切。

质子泵抑制剂是全球最常用的处方药之一，通过抑制 H+/K+-ATP 酶提高胃内 PH，广泛用于酸相关疾病，如胃食管反流病、消化性溃疡、糜烂性食管炎、幽门螺旋杆菌感染等。PPI 的常用药物包括奥美拉唑、泮托拉唑、雷贝拉唑、兰索拉唑等，其总体用药安全性高，耐受性良好。然而过去的几十年，PPI 处方的不合理使用情况明显增加，与其长期使用相关的风险也被广泛关注。长期使用 PPI 会增加患者发生胃肠道肿瘤、胃肠道感染、炎症性肠病、心肌梗死、肺炎、骨折、痴呆等疾病发病风险[5] [6] [7]。近期，有研究发现 PPI 的使用可能会增加 NAFLD 及 NASH 的患病风险，其机制尚不明确，可能与 PPI 导致的肠道菌群紊乱有关。肠道微生物在人体的代谢、营养、生理、防御和免疫过程中起着关键作用，其组成与丰度的变化与个体的健康密切相关[8]。

本文就长期使用 PPI 对 NAFLD 患病的影响作出综述，重点关注肠道菌群失调在其中的作用。

2. 长期使用 PPI 对肠道菌群的影响

PPI 的使用会使胃酸分泌减少，改变胃内 PH 值[9]，导致胃排空延迟，引起肠道菌群组成发生变化[10] [11]，表现为肠道微生物种类的丰度及多样性变化。一般情况下，口咽部细菌因无法适应低 PH 胃酸而较少在胃肠道存活，PPI 的使用使得胃酸屏障减弱，会影响下消化道微生物群的生态平衡。在 PPI 使用者的粪便微生物组中发现多种口腔细菌的过度表达，例如胃口链球菌，血管链球菌，细小单胞菌等[10] [12] [13] [14]。在观察性研究中，发现 PPI 使用者肠道微生物群 α 多样性降低，增加了艰难梭菌、沙门氏菌属、志贺氏菌属和弯曲杆菌属引起的肠道感染风险[15] [16] [17]。一项包含 1815 名成年人的三个队列研究发现，

PPI 的使用者肠道 20%的菌群相对丰度发生变化，其中与艰难梭菌感染相关的链球菌科增加、瘤胃球菌科减少，与胃肠道细菌过度生长相关的微球菌科、葡萄球菌丰度升高，这与既往两项研究结果一致[12] [18] [19]。在一项大规模的健康双胞胎队列研究对 1827 名成年人的粪便样本的进行 16SrRNA 分析，发现 PPI 使用者粪便样本中的丹毒菌科、毛螺球菌科及瘤胃球菌科显著减少，放线菌门、拟杆菌门、厚壁菌门(特别是乳酸杆菌科和梭状芽胞杆菌门)和变形菌门与 PPI 使用成正相关，在细菌科水平上，链球菌科及微球菌科增加最为显著。值得注意的是，横断面研究存在许多混杂因素，可能导致结果不准确。为了尽量去除混杂因素对结果的影响，有学者进行了一项包括了 49 名健康参与者的纵向研究[20]，随机分配受试者接受连续 7 天的 PPI 或者 H2RA，在干预前后对参与者口腔及粪便样本进行基因测序。结果发现与使用 H2RA 的参与者相比，PPI 的使用对肠道微生物的变化有更显著的影响，也更容易引起口腔细菌到肠道的传播，如与结直肠癌密切相关的有核梭杆菌在服用 PPI 后约 9%的参与者中发现，但在 H2RA 组中未观察到该现象。同时，研究者检索了 GMrepo V.2 数据库，发现由 PPI 及 H2RA 诱导的肠道微生物群改变与心血管疾病、肝硬化、炎症性肠病、结直肠癌等相关，揭示了与 PPI 相关的某些疾病风险较高的潜在机制。

3. NAFLD 与肠道菌群的关系

肠道菌群的丰度及多样性的变化与 NAFLD 的发生有潜在关系[21] [22] [23] [24]。与健康个体相比，NAFLD 患者的肠道微生物群 α 多样性较低[25]，其肠道菌群在门、类、科和属水平上均表现出显著变化，在细菌门水平上，发拟杆菌门减少，厚壁菌门和变形菌门的水平增加[23]。在细菌科水平上，肠杆菌科增加，而疣微菌科及理研菌科有所减少[23]。细菌属水平的变化表现在埃希氏菌属、嗜肽菌属增加，厌氧孢子杆菌属、孢子菌属、真杆菌属、粪杆菌属和普雷沃氏菌属的减少[23]。NAFLD 病变的严重程度同样受到肠道菌群失调及肠道微生物群代谢功能转变的影响[26]，NASH 患者的拟杆菌属丰度显著增加，而普雷沃氏菌丰度降低。肝纤维化患者表现出更高丰度的瘤胃球菌[27]。肠道微生物群中细菌的成分及其产生的代谢物，可以通过门静脉携带至肝脏[28]，从而导致肝细胞损伤、炎性改变甚至纤维化改变。近期一项研究将 NASH 患者肠道微生物群接种到无菌小鼠中，同时进行高脂饮食喂养，发现该组小鼠附睾脂肪量、肝脂肪变性、多灶性坏死和炎性细胞浸润显著增加，且存在更高丰度的肠杆菌科及链球菌科[29]。肠道菌群失调增加了内源性酒精、短链脂肪酸、禁食诱导的脂肪因子的水平[30]，影响胆汁酸代谢，促进了脂质累积及慢性炎症[21]。研究观察到 NAFLD 患者中丁酸盐水平降低，作为有效的抗炎介质，丁酸盐的降低会导致肠道通透性的增加，大大提高了脂多糖易位到循环血清中的风险[21]。口服补充丁酸盐可以预防单纯脂肪变性进展为脂肪性肝炎[31]。

肠道微生物群丰度及多样性的变化与 NAFLD 密切相关，目前对利用益生菌、益生元和合生元等纠正肠道菌群失调而改善 NAFLD 进行了广泛研究，提补充一些细菌代谢物可能具有治疗益处[21]。

4. 长期使用 PPI 对 NAFLD 患病风险的影响

韩国一项包含了 1,463,556 人的回顾性研究发现 PPI 使用者与非 PPI 使用者相比，患脂肪肝的风险更高(HR = 1.68, 95% CI: 1.61~1.75)，在调整了年龄、性别、吸烟、饮酒等多种混杂因素后，两者关联依然显著(HR = 1.50, 95% CI: 1.44~1.57)。将 PPI 的数量按照累计的每日限定剂量分层后，观察到在使用 PPI 的 180 天内，随着服用 PPI 的时间延长，脂肪肝的发病风险随之增加[32]。一项纳入了 301 例人群的病例对照研究表明[33]，在无麸质饮食的乳糜泻患者中，接受 PPI 暴露 1 年后，有 72 发生 MS 是代谢综合征，112 例发生肝脂肪变性，进一步行多变量分析提示 PPI 暴露与代谢综合征(OR = 22.9, P < 0.001)及肝脂肪变性(OR = 9.2, P < 0.001)相关。亚组分析提示，在未使用 PPI、PPI 使用时间小于 6 个月(PPI 停药)和 PPI 使用时间大于 6 个月之间，只有 PPI 暴露时间大于 6 个月是代谢综合征和肝脂肪变性的危险因素。近期

一项横断面研究也发现与未使用 PPI 的参与者对比，PPI 的使用与 NAFLD 患病呈正相关，发生严重的脂肪变性的风险更高[34]。该研究还探讨了 PPI 的使用时间与 NAFLD 的相关关系，结果表明服用 PPI 超过 5 年的受试者发生 NAFLD 的风险增加(OR = 2.016, 95% CI: 1.366~2.975, P = 0.031)。在一项动物实验中[35]，利用高脂饮食喂养编码胃 H+/K+-ATP 酶 α 亚基的基因 Atp4a 中具有点突变并发生胃酸缺乏的小鼠及野生型 Atp4a 小鼠 9 周，发现两者在体重或白色脂肪组织含量上无明显差异，但缺乏胃酸的小鼠胰岛素敏感性降低、肝脂肪变性更严重，粪便标本中肠球菌的比例显著增高。同时该实验观察到缺乏胃酸会加重 NASH，Atp4aSL/SL 型小鼠有更高的 ALT 水平，更严重的肝细胞炎症及纤维化。该研究还收集了接受 PPI 治疗的健康人群前后的粪便样本，发现肠球菌的数量显着增加，与动物实验结果一致。提示 PPI 的使用可以通过影响肠道菌群的改变而促进 NAFLD 及 NASH 的发生。值得注意的是，该实验的动物模型使用了高脂饮食喂养，高脂饮食本身可以导致肠道微生物群改变，因此难以评估其结果中菌群的改变是否为胃酸缺乏引起。既往已有研究表明，使用 PPI 诱导的肠道微生物群的变化与肥胖人群及其相似[36] [37] [38] [39]。为了消除高脂饮食的影响，近期一项研究[40]仅予以泮托拉唑处理小鼠，观察了其对肠道微生物群及肝脏组织学的影响。考虑到短时间的 PPI 干预可能不足以引起肠道微生物群的变化，该研究予以泮托拉唑处理小鼠 60 天，观察到粪便样本中厚壁菌门和变形菌门的丰度增加，其中嗜胆菌属的增加既往已观察到其会促进炎症的发生，导致肠道屏障功能及胆汁酸代谢紊乱，加重肝脂肪变性[41]。与对照组相比，泮托拉唑处理组小鼠肝脏可观察到微泡脂肪变性，肝脏内脂质含量更高，这可能与肠道屏障的改变有关。肠道屏障功能的改变会增加循环中脂多糖水平[42] [43]，加重肝纤维化的发生。脂多糖是革兰氏阴性菌的主要外膜成分，与肝脏中 Toll 样受体 4 结合，并诱导以 IKKβ/NF-κB 增加和 JNK 激活为特征的信号通路[44]。Toll 样受体 4 可以激活纤维化表型，产生趋化因子和粘附分子，从而募集 Kupffer 细胞，Kupffer 细胞增加 TGFβ 的产生，而激活肝纤维化[45] [46]。PPI 处理的小鼠中观察到脂多糖信号转导的通路被激活，TGFβ 组织水平增加，这提示 PPI 的使用不仅可以促进肝脂肪变性导致 NAFLD 的发生，同时也与肝纤维化有着潜在联系。

5. 讨论

近年来，大量文献报道了 PPI 长期应用的风险，而其中对 NAFLD 的影响尚不明确。多项横断面研究表明，与未使用 PPI 参与者相比，使用 PPI 者 NAFLD 的患病风险更高，且观察到与使用时间和剂量有关。动物实验中也观察到相似的结果。目前关于 PPI 长期使用导致 NAFLD 的机制尚不清楚，推测其导致的肠道微生物群的紊乱可能起主要作用。PPI 的使用导致肠道微生物群本身及其代谢物发生改变，影响肠道通透性，促进炎症反应，增加 NAFLD 的患病风险，加重肝纤维化。但目前仍缺乏多中心、大样本的前瞻性实验来研究两者之间的关系。总而言之，对于不合理使用 PPI 所带来的不良反应提示临床医师在临床开具 PPI 处方时应考虑到其长期使用带来的风险，更严格地评估用药指征，避免增加并发症发生的风险。

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