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文献综述 REVIEW

幽门螺杆菌感染与糖化血红蛋白表达相关性的研究进展

李 伟, 杨 桢, 黄德强, 吕农华

李伟, 杨桢, 黄德强, 吕农华, 南昌大学第一附属医院消化内科 江西省消化系疾病研究所 江西省消化病研究重点实验室 江西省南昌市 330006
李伟, 在读硕士, 主要从事幽门螺杆菌与胃癌及癌前病变的关系研究.
作者贡献分布: 本文综述由李伟完成; 杨桢与黄德强修改; 吕农华审校.
通讯作者: 吕农华, 教授, 主任医师, 博士生导师, 330006, 江西省南昌市永外正街17号, 南昌大学第一附属医院消化内科, 江西省消化系疾病研究所, 江西省消化病研究重点实验室.
lunonghua@163.com
电话: 0791-8692705 传真: 0791-8623153
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Correlation between *Helicobacter pylori* infection and hemoglobin A1c expression

Wei Li, Zhen Yang, De-Qiang Huang, Nong-Hua Lv

Wei Li, Zhen Yang, De-Qiang Huang, Nong-Hua Lv, Department of Gastroenterology, the First Affiliated Hospital of Nanchang University; Gastroenterology Institute of Jiangxi Province; Jiangxi Provincial Key Laboratory for Digestive Diseases, Nanchang 330006, Jiangxi Province, China
Correspondence to: Nong-Hua Lv, Professor, Chief Physician, Department of Gastroenterology, the First Affiliated Hospital of Nanchang University; Gastroenterology Institute of Jiangxi Province; Key Laboratory of Digestive Diseases of Jiangxi Province, 17 Yongwaizheng Avenue, Nanchang 330006, Jiangxi Province, China. lunonghua@163.com
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Abstract

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that is closely related with the pathogenesis of chronic gastritis, peptic ulcer, gastric carcinoma as well as many extra-gastrointestinal tract diseases such as coronary heart disease, iron deficiency anemia, idiopathic thrombocytopenic purpura, and diabetes mellitus (DM). Hemoglobin A1c (HbA1c) level is useful in diagnosing and monitoring DM. Recent studies showed that *H. pylori* is involved in the up-regulation of HbA1c level in DM patients through modulating the expression of leptin and ghrelin, whose interactions affect obesity, insulin sensitivity, glucose homeostasis and DM. Further studies on the association between *H. pylori* infection and HbA1c will certainly provide new prospects for early diagnosis and treatment of *H. pylori*-related DM and its complications.

Key Words: *Helicobacter pylori*; Diabetes mellitus; Hemoglobin A1c; Insulin resistance

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摘要

幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是一种与胃黏膜疾病关系密切的革兰阴性菌, 研究发现其与糖尿病、冠心病、缺铁性贫血、特发性血小板减少性紫癜等胃肠外疾病亦紧密相关, 然而个中机制却仍不明确. 糖化血红蛋白(hemoglobin A1c, HbA1c)是糖尿病(diabetes mellitus, DM)患者血糖水平长期监控的重要指标, 研究发现, *H. pylori*感染阳性的DM患者外周血HbA1c水平较*H. pylori*阴性DM患者显著升高, 这很有可能是*H. pylori*通过下调胃黏膜瘦素和脑肠肽的表达, 造成宿主代谢紊乱和胰岛素抵抗而导致的. 关于*H. pylori*和HbA1c关系的早期研究具有一定的局限性, 更为全面、深入的研究势必为*H. pylori*感染相关性糖尿病的早期防治提供新的方向.

关键词: 幽门螺杆菌; 糖尿病; 糖化血红蛋白; 胰岛素抵抗

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0 引言

糖尿病(diabetes mellitus, DM)是一种病因不明的、遗传易感的代谢紊乱疾病, 在全球发病率逐年上升, 主要表现为胰岛素抵抗(insulin resistance, IR)和胰岛B细胞功能减退, 导致高血糖症(glucose homeostasis, GH), 引发一系列代谢紊乱综合征[1]. 长期高血糖会使血红蛋白发生非酶促

■背景资料
幽门螺杆菌(*H. pylori*)是一种与慢性胃炎、消化性溃疡、胃癌等胃黏膜疾病关系密切的革兰阴性菌, 其与糖尿病(DM)、冠心病、缺铁性贫血、特发性血小板减少性紫癜等胃肠外疾病亦紧密关联, 然而其中机制却仍不明确.

■同行评议者
李瑜元, 教授, 广州市第一人民医院内科

■研发前沿
DM患者的*H. pylori*感染率普遍高于非DM人群, 且根除后再感染更为常见, 此外, 实验还发现*H. pylori*感染状况与HbA1c表达水平之间关系密切, 这很有可能是由*H. pylori*过度激活机体炎症反应, 并抑制瘦素和脑肠肽在胃黏膜的表达而导致的.

的糖基化反应, 形成糖化血红蛋白(hemoglobin A1c, HbA1c), 后者进一步结合交联未糖化分子, 引起慢性并发症[2]. HbA1c的个体差异很小, 他反映机体近3-4 mo的血浆葡萄糖水平, 可为较长时间段的血糖浓度提供回顾性评估, 是更有效的血糖长期监控指标[3-5]. 大量前瞻性研究证明, 加强控制HbA1c水平能够显著降低DM患者心肌梗死等慢性并发症的发生[6,7]. 幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)作为一种与胃黏膜疾病关系密切的革兰阴性菌, 其亦与代谢紊乱、IR和DM有所关联, 然而其中具体机制仍不明确[8]. 大量研究显示, DM患者的*H. pylori*感染率显著高于非DM组, *H. pylori*感染状况与HbA1c表达水平之间密切相关, 揭示出*H. pylori*很有可能通过抑制瘦素和脑肠肽在胃黏膜的表达, 从而导致宿主各种代谢相关性疾病的发生[9,10].

1 幽门螺杆菌与糖化血红蛋白、糖尿病

*H. pylori*是一种定植在人胃黏膜的革兰阴性菌, 在发展中国家感染率很高, 与慢性胃炎、消化道溃疡、肠上皮化生、非典型增生、MALT淋巴瘤及胃癌的关系密切[11]. 近年来, *H. pylori*与胃肠外疾病之间的关系日益得到关注, 而关于*H. pylori*与DM的研究为数不多[12], 大致分以下几个方面.

1.1 DM患者的*H. pylori*感染率高于非DM人群 Hamed等[13]在实验中发现, DM患者更易感染*H. pylori*, 导致血管相关并发症的发病率也有所增加. Devrajani等[14]也发现DM患者较非DM人群更易感染*H. pylori*, 建议临床上加强对DM患者的血糖监测和*H. pylori*感染筛查. 此外, EL-Eshmawy等[15]检测了162名DM患者和80名健康志愿者的血清抗*H. pylori* IgG、IgA水平, 发现*H. pylori*感染与DM发生率呈正相关, 建议对DM患者进行*H. pylori*筛查. Jeon等[16]通过前瞻性队列研究发现, *H. pylori*感染与DM发病率的增高有关, 提出胃肠道抗生素治疗在DM防治中具有极大的潜能. 近期, Chen等[17]在美国进行的全国性大规模普查发现, *H. pylori*感染程度与HbA1c表达水平呈正相关, 这一现象在≥18周岁的调查对象中尤为显著.

■相关报道
近期美国一项全国性大规模调研发现, *H. pylori*感染程度与HbA1c表达水平呈正相关, 这一现象在≥18周岁的调查对象中尤为显著.

1.2 *H. pylori*感染者罹患DM及其并发症的几率增高 Rahman等[18]在亚裔印度人群中发现, *H. pylori* cagA阳性菌株感染者的血清高密度脂蛋白(high density lipoprotein, HDL)水平显著高于对照组, 提出*H. pylori*感染与宿主糖耐受和胰岛素分泌障碍密切相关. Zbrahim等[19]通过前瞻性实验证实, cagA+*H. pylori*菌株感染增加了DM患者发生尿微蛋白症和血糖控制不佳的概率. Polyzos等[20]进行的系统性回顾分析显示, *H. pylori*感染与IR密切相关, 认为*H. pylori*感染可能是DM和非酒精性脂肪肝的重要危险因素.

1.3 DM患者的*H. pylori*根除率 Ataseven等[21]发现接受*H. pylori*序贯治疗的DM患者, 其*H. pylori*根除率显著低于非DM组. 此外, 他们进一步对比了成人和儿童DM患者之间*H. pylori*根除率的差异, 认为这是由于儿童没有*H. pylori*反复感染病史和抗生素使用史、抗生素耐药菌株更少所造成的. Ojetti等[22,23]均在对接受*H. pylori*根除治疗的DM患者的随访中发现, DM患者的*H. pylori*根除治疗后复发率显著高于非DM患者.

1.4 DM合并*H. pylori*感染加大了DM并发症和胃癌的风险 Ikeda等[24]按照HbA1c水平将2 603名受试者进行分组, 发现*H. pylori*感染合并高血糖症增加了罹患胃癌的危险度. Toporowska-Kowalska等[25]发现, *H. pylori*感染显著恶化了DM患者代谢调控, 建议在DM患者中合理筛查*H. pylori*感染状况以控制并发症. Baradaran等[26]发现DM肾病患者血清镁水平与*H. pylori*特异性IgG抗体水平呈正相关. Tanriverdi等[27]在93名DM患者中发现*H. pylori*感染过度激活了机体免疫应答, 间接导致尿微蛋白发生, 但由于实验样本量太小, 结果不具统计学意义. Ibrahim等[19]称感染cagA阳性*H. pylori*菌株的DM患者发生尿微蛋白症的概率显著高于对照组, 提出cagA基因型或可作为DM尿微蛋白的早期标志.

1.5 其他 Schimke等[28]进行的样本量为1 179的统计研究发现, *H. pylori* cagA抗体与T2DM及其并发症之间并无联系. Khalil等[29]对100名T1DM患者进行为期1年的随访, 发现*H. pylori*感染患者与非感染者的HbA1c水平无统计学差异. Gunji等[30]称, 尽管*H. pylori* IgG血清阳性和DM之间无统计学关联, 但*H. pylori*感染显著增加了IR的发生率, 且DM患者中*H. pylori*相关性胃炎的发病率却远高于对照组. Akanuma等[31]指出, 根除*H. pylori*能够改善DM患者BMI指数, 但对于控制HbA1c却无显著效果. 这些研究结果使得*H. pylori*感染在DM血糖水平中所扮演的角色更加扑朔迷离.

2 幽门螺杆菌上调糖化血红蛋白表达的可能机制

瘦素和脑肠肽是哺乳动物体内参与能量代谢的

激素, 二者协同调节脂代谢、胰岛素平衡和糖自稳. 脑肠肽是一种由胃底腺细胞、十二指肠内皮细胞等分泌的缩氨酸多肽类激素, 他能抑制胰岛素的分泌, 降低能量消耗并促进体质量增加[32]. 瘦素是由白色脂肪组织产生, 能够减少食物摄入、增强机体能量消耗[33]. 目前普遍认为, *H. pylori*慢性感染不断刺激辅助性T细胞1(T helper cells 1, Th1)极化, 抑制Th2细胞介导的过敏反应, 并刺激大量炎症因子的释放, 在保护机体的同时也可以造成炎症损伤[34], 进一步参与调节瘦素和脑肠肽这两种与代谢相关的激素水平, 从而影响宿主HbA1c表达水平, 最终导致代谢紊乱疾病. *H. pylori*感染与低水平的脑肠肽循环密切相关, 这可能是通过降低胃黏膜脑肠肽生成细胞的功能、增强胃部瘦素水平来实现的[35].

2.1 *H. pylori*感染过度的效应 研究报道, *H. pylori* cagA能够诱导大量促炎因子的释放, 介导胃黏膜上皮细胞信号转导, 导致了免疫炎症瀑布, 进一步引起代谢相关的炎症紊乱[36,37]. Arslan等[38]发现, 肥胖症患者的*H. pylori*特异性IgG水平显著高于对照组(57.2% *vs* 27.0%).

2.2 *H. pylori*感染与糖尿病 Slomiany等[39]称脑肠肽能够调节一氧化氮合酶(NOS)水平, 在*H. pylori*感染引发的炎症应答中起着重要作用. 此外, 他们还发现*H. pylori*菌壁抗原能够刺激胃黏膜产生大量脑肠肽, 后者通过诱导Src活化而削弱*H. pylori*感染引起的胃黏膜炎症反应. Kawashima等[40]在*H. pylori*感染阳性的萎缩性胃炎患者的血浆中检测到低水平的脑肠肽, 这种下降与胃黏膜损伤程度有所关联. Celinsk等[41]发现在消化性溃疡修复过程中, 褪黑素和瘦素的水平显著升高. Jeffery等[42]发现, *H. pylori*感染能够下调脑肠肽和脑肠肽酰基转移酶(GOAT)的表达, 从而影响机体内分泌, 而*H. pylori*根除后脑肠肽的分泌则得以恢复. Ozen等[43]对经济滞后地区的473名儿童进行调研, 提出*H. pylori*感染很可能通过抑制瘦素、脑肠肽、胰岛素样生长因子的表达, 导致青少年生长发育迟缓. Francois等[44]人通过前瞻性实验发现, *H. pylori*根除治疗对于血清瘦素、脑肠肽水平以及体质量指数大有影响, 认为*H. pylori*感染与瘦素和脑肠肽的低表达直接相关.

2.3 代谢相关性疾病与*H. pylori*的胃黏膜定植 Wehrens等[45]发现瘦素受体缺陷组小鼠*H. pylori*感染水平远高于野生组, 表明瘦素受体缺乏小鼠抗*H. pylori*免疫应答能力显著降低. 有学者在链脲霉素构建的T1DM大鼠模型中发现, *H. pylori*感染导致胃黏膜损伤的严重程度和HbA1c水平呈正相关[46].

2.4 *H. pylori*根除治疗与脑肠肽的分泌和胰岛素抵抗的缓解 日本学者称, *H. pylori*能造成宿主免疫功能低下, 有助于DM发生; 当根除*H. pylori*后, IR症就有可能得到缓解[47]. Jang等[48]发现根除*H. pylori*有助于胃黏膜脑肠肽的释放. Thor等[49]发现*H. pylori*感染阳性的胃食管返流患者的血浆脑肠肽水平显著降低并且随着*H. pylori*根除治疗逐渐回升, 提出脑肠肽和迷走神经活动可能是*H. pylori*感染与反流性疾病研究中被忽视的重要环节.

3 结论

研究表明*H. pylori*感染与糖尿病性视网膜、神经系统及肾脏病变的关系密切[50], 通过积极开展*H. pylori*根除治疗以辅助达到降低DM并发症发生率这一控制方式具有良好的发展前景. 此外, 胃肠道抗生素治疗可能会对高BMI和糖耐受的DM患者大有裨益. *H. pylori*感染与HbA1c水平之间的关系研究需要综合考虑宿主基因型和不同环境影响因素, 因此我们迫切需要开展多人种、多地区、多层面的调研, 为*H. pylori*感染相关DM的防治寻找新的方向.

■**名词解释**
糖化血红蛋白(HbA1c): 血液中的葡萄糖与血红蛋白A的链缬氨酸残基发生不可逆的、非酶促的缩合反应而形成的一类次要血红蛋白, 他是DM诊断和长期监测更为有效的指标.

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■应用要点
研究表明*H. pylori*感染与糖尿病性视网膜、神经系统及肾脏病变的关系密切, 通过积极开展*H. pylori*根除治疗以辅助达到降低DM并发症发生率, 这一控制方式具有良好的发展前景.

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编辑 张姗姗 电编 鲁亚静

■同行评价
本文有较好的科学性和实用性, 对糖尿病的临床诊断和治疗提供了较好的参考价值.

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