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在线全文

牙周炎与代谢相关脂肪性肝病：从口腔菌群失调到肝脏代谢紊乱*

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【摘要】 牙周炎与代谢相关脂肪性肝病（metabolic dysfunction-associated fatty liver disease, MAFLD）均为高发性慢性病，给全球带来沉重的疾病负担，近年来的研究揭示两者之间存在密切关联。本文系统阐述了牙周炎与MAFLD的流行病学关联及其潜在的作用机制。在机制研究方面，本文重点探讨了两种主要途径：一是传统的血液循环途径，牙周致病菌及其介导的炎症反应通过体循环作用于肝脏；二是近年来提出的“口-肠-肝轴”途径，牙周炎通过改变口腔菌群，进而影响肠道微生态和肠屏障功能，最终导致肝脏代谢紊乱。这些研究为理解两种疾病之间的复杂关联提供了新的视角，也为MAFLD的防治提供了潜在的新策略。

【关键词】 牙周炎 代谢相关脂肪性肝病 口-肠-肝轴 综述

Periodontitis and Metabolic Dysfunction-Associated Fatty Liver Disease: From Oral Dysbiosis to Hepatic Metabolic Dysregulation

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[Abstract] Periodontitis and metabolic dysfunction-associated fatty liver disease (MAFLD) are both highly prevalent chronic diseases that impose a significant global burden. Recent studies have revealed a close association between them. This article systematically reviews the epidemiological link between periodontitis and MAFLD, as well as their potential underlying mechanisms. Regarding the investigation of underlying mechanisms, the article focuses on two primary pathways. Firstly, the classical hematogenous transmission pathway, in which periodontal pathogens and their mediated inflammatory responses affect the liver through the systemic circulation; secondly, the recently proposed “oral-gut-liver axis” pathway, in which periodontitis alters the oral microbiota, subsequently disrupting gut microbiota and intestinal barrier function, ultimately leading to hepatic metabolic dysregulation. These studies offer new perspectives for understanding the complex relationship between these diseases and provide potential novel strategies for the prevention and treatment of MAFLD.

[Key words] Periodontitis Metabolic dysfunction-associated fatty liver disease Oral-gut-liver axis Review

牙周炎是在菌斑生物膜作用下，多种因素参与的慢性炎症性疾病，其特征是牙周支持组织（包括牙龈、牙周膜和牙槽骨）的破坏。2021年全球疾病负担研究结果显示，重度牙周炎影响全球逾10亿人[1]。作为成年人牙齿丧失的主要原因，重度牙周炎不仅严重损害口腔健康与功能，亦与多种系统性疾病密切相关，对患者的整体健康状况及生活质量构成显著威胁[2]。

肝脏作为机体的代谢中枢，其与口腔健康的关系日益受到关注。代谢相关脂肪性肝病（metabolic dysfunction-associated fatty liver disease, MAFLD）曾被称为非酒精性脂肪肝病（non-alcoholic fatty liver disease, NAFLD），新命名旨在强调代谢紊乱在其发病机制中的核心地位[3]。MAFLD是遗传易感个体因营养过剩和胰岛素抵抗引起的慢性代谢应激性肝病，其疾病进程涵盖单纯性脂肪肝到非酒精性脂肪肝，并可能进一步发展为肝硬化和肝细胞癌[4]。随着全球肥胖和代谢综合征的流行，

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MAFLD已成为世界范围内日益严峻的公共卫生挑战[5]，早期识别并有效控制其危险因素具有重要临床意义。

口腔微生物群落处于一个动态且复杂的生态系统中，当宿主-微生物共生关系失衡，局部生态失调可触发跨器官的炎症级联反应[6]。鉴于肝脏与肠道间独特的解剖毗邻与功能协同性，肝脏成为最易受到微生物紊乱影响的靶器官之一[7]。研究表明，牙周炎引发的口腔菌群失调，可能通过血液循环或肠道途径影响MAFLD的病理生理过程[8]。本文将系统阐述牙周炎与MAFLD关联的研究进展，重点解析“口-肠-肝轴”在其中可能的作用机制，以期为MAFLD的早期干预和综合防治提供新的理论视角和潜在策略。

1　牙周炎影响MAFLD的发生发展

近年来流行病学证据逐步证实牙周炎与MAFLD存在显著关联。早期一项对172名日本女性的健康调查研究显示，牙周炎患者的血清天冬氨酸氨基转移酶（aspartate aminotransferase, AST）、丙氨酸氨基转移酶（alanine aminotransferase, ALT）、乳酸脱氢酶等肝功能指标水平显著高于牙周健康者[9]。我国一项纳入24 470名成年人的大规模横断面研究进一步发现，男性牙齿缺失数量与MAFLD存在显著相关性[10]。调整年龄性别等混杂因素后，存在深牙周袋人群患MAFLD的风险显著增高[11]。此外，与轻中度牙周炎患者相比，重度牙周炎患者发生MAFLD的风险更高，口内余留牙数< 20颗的也比≥20颗的男性成年人更容易患MAFLD [12]。这些横断面研究共同提示，牙周炎严重程度与MAFLD患病风险存在密切关联。

目前关于牙周炎和MAFLD相关性的前瞻性队列研究还相对有限。一项基于德国人群、平均随访超过5年的前瞻性队列研究发现，在调整了广泛的代谢性混杂因素后，重度牙周炎是成年人未来发生MAFLD的独立危险因素[13]。HELENIUS-HIETALA等[14]对6 165名芬兰成年人进行了长达13年的随访研究，结果发现：与牙周健康者相比，基线无肝病的重度牙周炎患者发生严重肝病的风险是其3.69倍，基线时患有MAFLD的重度牙周炎患者，这一风险则升高至6.94倍。此外，一项为期5年的队列研究指出，牙周附着丧失程度与肥胖伴单纯性脂肪肝患者的肝纤维化程度显著相关[15]。以上研究表明牙周炎不仅与MAFLD的发生相关，还会加速其向肝纤维化等晚期病理阶段的进展。

值得关注的是，初步的干预研究也为二者之间的关联提供了证据。YONEDA等[16]对10例患有牙周炎的MAFLD患者进行了牙周基础治疗，血清AST和ALT在治疗3个月后显著降低。另有一项对肝硬化患者的研究表明，患有牙龈炎和/或轻中度牙周炎的肝硬化患者，尤其是肝性脑病患者，接受牙周基础治疗30 d后，患者粪便和唾液样本中的微生物失调有所改善，血清炎症介质水平也有所下调；未接受牙周治疗的肝硬化患者，血清内毒素（lipopolysaccharide, LPS）和脂多糖结合蛋白水平在同时期有所增加[17]。这些发现提示，牙周干预可能通过改善口腔菌群失调和降低全身炎症水平，对MAFLD的病理进程产生积极影响。然而，现有证据仍基于小样本研究，这正是当前研究的瓶颈与未来突破的关键方向。目前已有数项旨在进一步验证该关联的临床试验注册并开展（表1）。未来需要通过多中心、大样本、长时间的随机对照试验进一步验证牙周治疗对MAFLD的确切疗效，其成果将有望为MAFLD的防治提供新的跨学科策略。

2　牙周炎影响MAFLD的作用机制

牙周炎对MAFLD的影响是一个涉及局部与全身、直接与间接的复杂过程，其核心机制可概括为两大相互关联的病理通路（图1）。一是血液播散途径，即牙周微生物组分或促炎因子进入体循环，直接作用于肝脏；二是“口-肠-肝轴”调控途径，即口腔菌群失调通过扰动肠道稳态，导致肠道屏障损伤与代谢产物紊乱，进而引发肝脏代谢紊乱。

2.1　血液循环途径

菌斑微生物是牙周病的始动因子，其与宿主免疫应答之间的失衡是导致牙周组织破坏的核心机制[18]。在牙周炎进展过程中，牙周致病菌及其代谢产物可突破局部上皮屏障进入血液循环，同时浸润的免疫细胞释放大量肿瘤坏死因子α（tumor necrosis factor alpha, TNF-α）、白细胞介素（interleukin, IL）-6、IL-1β等促炎因子，导致机体呈现慢性低度炎症状态[19]。这些循环中的生物活性物质通过门静脉系统抵达肝脏，激活肝内固有免疫细胞，启动一系列炎症级联反应，从而参与MAFLD的病理进程。

研究表明，牙龈卟啉单胞菌（*Porphyromonas gingivalis, P.gingivalis*）表面的多种毒力因子（如胶原酶、氨基肽酶、胰蛋白酶）及细菌结构（包括脂多糖和菌毛）可通过血液循环作用于肝脏[20]。动物实验证实，牙髓腔感染*P. gingivalis*导致高脂饮食小鼠肝脏脂肪酸代谢紊乱加重，出现明显的肝纤维化[21]。FUJITA等[22]在大鼠牙龈注射放射性标记的*P.gingivalis*-LPS，药代动力学结果显示大部分LPS通过血液循环扩散，并在肝脏中的蓄积量显著高于肾脏、大脑和脾脏等其他器官。值得注意的是，与健康肝脏

表 1 牙周炎与MAFLD相关临床研究及注册试验总结

Table 1 Summary of clinical research and registry trials on periodontitis and MAFLD

Study design	Author/Registration number, Country	Year/Status	Participants	Conclusion/Study aims
Cross-sectional	SAITO, *et al.* Japan	2006	n = 172 (Women)	The serum liver function index of patients with periodontitis was significantly higher than that of healthy individuals.
Cross-sectional	QIAO, *et al.* China	2018	n = 24 470	Tooth loss in men is significantly associated with MAFLD.
Cross-sectional	IWASAKI, *et al.* Japan	2018	n = 1 226	PPD ⩾ 4 mm may be a risk factor for ultrasound-diagnosed MAFLD.
Cross-sectional	WEINTRAUB, *et al.* USA	2019	n = 5 421	MAFLD was associated with tooth loss and periodontitis.
Cohort study	AKINKUGBE, *et al.* Pomerania	2017	n = 2 623	A history of periodontitis may be a risk factor for MAFLD.
Cohort study	HELENIUS-HIETALA, *et al.* Finland	2020	n = 6 165	As a preventable disease, periodontal disease might present a modifiable risk factor for chronic liver disease.
Cohort study	KUROE, *et al.* Japan	2021	n = 4 812	A higher clinical attachment level was associated with an increased probability of liver fibrosis in obese adults with MAFLD.
Case-control study	YONEDA, *et al.* Japan	2012	n = 10 (Patients with MAFLD and periodontitis)	Non-surgical periodontal treatments in MAFLD patients carried out for 3 months ameliorated the liver function parameters, such as serum levels of AST and ALT.
Case-control study	BAJAJ, *et al.* USA	2018	n = 80 (Cirrhosis patients with or without periodontitis)	Cirrhotics patients, especially those with hepatic encephalopathy, demonstrated improved dysbiosis in stool and saliva, as well as improved endotoxin, LBP, and salivary and serum inflammatory mediators following periodontal therapy.
Cohort study	NCT06052150, USA	Research in progress	n = 100 (Patients with cirrhosis)	To learn about dental evaluation and periodontal cleaning along with scheduled follow -up on the dental and overall health of patients with cirrhosis, and also to determine what barrier(s), if any, exist to improve oral health in this population.
Case-control Study, Cohort study	ChiCTR2300073979, China	Research in progress	n = 116 (MAFLD) n = 70 (MAFLD with moderate to severe periodontitis)	A case-control study was conducted to investigate the correlation between periodontitis and MAFLD. A cohort study was further employed to explore whether basic periodontal treatment could slow the progression of MAFLD while controlling periodontitis.
Case-control study	ChiCTR2200055902, China	Research in progress	n = 40 (MAFLD with moderate to severe periodontitis)	To study the effect of subgingival scaling and root planing combined with water laser on clinical indicators of patients with MAFLD.

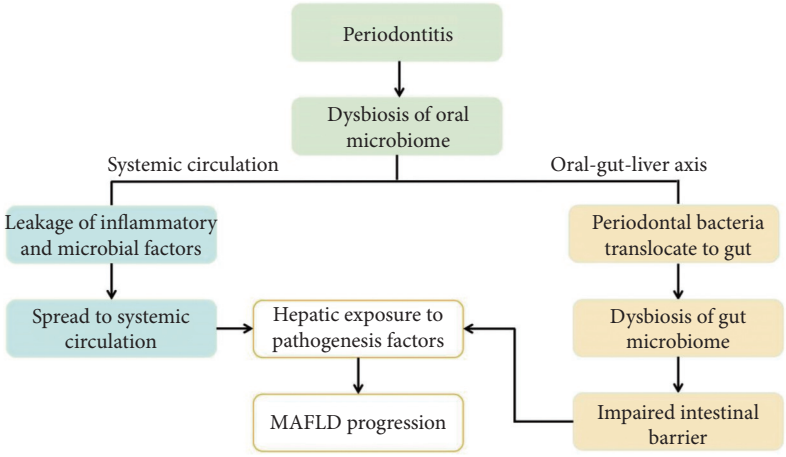

图 1 牙周炎影响MAFLD的潜在途径

Fig 1 Potential pathways through which periodontitis may influence MAFLD

相比，*P.gingivalis*-LPS在脂肪肝中的蓄积量更多，清除时间也更长。肝脏免疫细胞，特别是库普弗细胞(Kupffer cells, KCs)，是血源性途径的关键效应细胞。KCs通过其表面的受体(包括TLR和NOD)识别循环中的病原相关分子模式(pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(damage-associated molecular patterns, DAMPs)[23]，包括经血液循环迁移至肝脏的牙周致病菌LPS，这种识别触发核因子κB信号通路的活化，导致促炎细胞因子大量产生，进而促进肝细胞胰岛素抵抗和脂肪变性[24-25]。此外，有研究指出，细菌感染与炎症微环境通过扰乱肝脏代谢，进而升高油酸与棕榈油酸的水平，这种现象进一步加剧了非酒精性脂肪性肝炎中与肝脂肪变性相关的脂毒性[26-27]。

综上，牙周炎通过血源性传播途径影响MAFLD的双

重机制已得到初步阐明: 一方面是通过口腔微生物组分直接作用于肝脏细胞; 另一方面是微生物介导的炎症反应调控肝脏代谢。这些发现为理解口腔感染与肝脏疾病之间的病理联系提供了重要的分子基础。

2.2　口-肠-肝轴

口-肠-肝轴(oral-gut-liver axis)是近年来提出的一个重要概念, 指口腔与肝脏之间通过肠道微生物组及其代谢产物建立的间接通讯通路。这一通路的提出, 突破了传统上仅关注血行传播的局限, 为理解牙周炎等口腔疾病如何系统性影响远端器官(如肝脏)的生理病理状态提供了全新的理论视角。

2.2.1　口-肠轴: 口腔菌群影响肠道菌群稳态

人类口腔中定植着超过700种微生物, 构成了人体内仅次于肠道的第二复杂的微生物生态系统。在健康的生理状态下, 口腔菌群与宿主维持着动态平衡。然而, 牙周炎症状态下, 微生态平衡遭到破坏, 致病菌过度增殖, 代谢产物及其引发的宿主免疫反应共同导致口腔微环境改变。由于口腔和消化道直接相通, 成年人每天约吞咽1000 ~ 1 500 mL唾液, 所含细菌浓度高达10^8 CFU/mL [28-30], 其中潜在病原菌可能借此进入肠道, 影响菌群稳态。

本课题组围绕牙周炎唾液菌群在口-肠轴中的作用开展了一系列研究。结果证实, 即使在肠道本身健康的情况下, 移植牙周炎患者的唾液菌群即可破坏受体小鼠的肠道微生态和免疫稳态[31]。继而课题组利用多种疾病模型展开深入研究, 发现牙周炎患者唾液菌群所诱导的肠道菌群失调, 与阿尔茨海默病、焦虑、骨质疏松等多种全身性疾病存在显著关联[32-34]。综上, 本课题组前期研究结果提示: 牙周炎患者的唾液菌群可能通过吞咽途径影响肠道菌群稳态与免疫平衡, 成为促进多种全身性疾病进展的重要远端诱因。

2.2.2　肠道屏障损伤的机制及后果

肠道不仅是消化吸收器官, 更是机体最重要的免疫和屏障器官之一。完整的肠道屏障功能包括: 由肠上皮细胞及其间的紧密连接蛋白构成的机械屏障; 由黏液层和肠道共生菌产生的抑菌物质等构成的化学屏障; 由肠相关淋巴组织和弥散的免疫细胞构成的免疫屏障; 以及由肠道共生菌群与宿主微环境互作形成的生物屏障[35]。

研究表明, 口腔来源的微生物是导致肠道屏障损伤的重要原因之一。在小鼠模型中, 局部应用多种牙周致病菌(如牙龈卟啉单胞菌、齿垢密螺旋体、福赛斯坦纳菌和具核梭杆菌)可诱发口腔及肠道菌群失调, 破坏肠道屏障功能, 并加剧肝脏脂肪堆积与肝细胞线粒体氧化应激[36-37]。我们前期的研究也证实, 将牙周炎患者的唾液菌群灌胃给结肠炎小鼠, 可激活肠道免疫系统, 促进Th2细胞免疫应答和M2型巨噬细胞极化, 进而破坏肠道屏障, 加重结肠炎症状[38]; 此外, 牙周炎患者唾液菌群也被证实会加重肥胖小鼠的肠道菌群紊乱及肠屏障损伤[39]。在MAFLD患者中, 这种肠道通透性异常(即“肠漏”现象)已被广泛报道。与健康受试者相比, MAFLD患者肠道通透性显著增加, 十二指肠活检样本显示紧密连接蛋白表达下调, 且这一变化在中重度脂肪肝患者中更为明显[40]。

2.2.3　肠-肝轴信号传导通路

肠道屏障的破坏, 使得原本被限制在肠腔内的细菌组分和菌群代谢产物得以通过门静脉系统“易位”至肝脏, 从而开启肠-肝轴的致病环节。肠-肝轴是指肠道及其微生物区系与肝脏之间形成的双向调控通路。肠道和肝脏具有同一发育起源, 又因肠黏膜和血液循环系统发生解剖和功能上的紧密关联。门静脉作为肠肝物质交换的关键通道, 一方面将肠道吸收的物质输送至肝脏, 另一方面也是肝脏向肠道输送胆汁酸等成分的重要路径[41]。随着微生物组学的日益发展, 越来越多的研究证实肠-肝轴在MAFLD的发生发展过程中起着关键作用。

2.2.3.1　细菌组分易位: 以LPS为核心

肠道菌群紊乱和肠屏障通透性增加通常伴随血清PAMPs(尤其是LPS)高表达, 这是MASLD患者的重要病理特征[42]。正常情况下, LPS诱导的肝脏炎症是机体清除病原体的重要防御反应。而在MASLD中, 过量的肠源性LPS可结合KCs表面的TLR4并激活NF-κB介导的信号通路产生炎症级联反应[43]。类似地, 研究显示, 将牙周炎患者的唾液微生物灌胃给予肥胖小鼠, 可促进肠源性LPS易位至肝脏, 激活TLR4介导的肝脏炎症反应, 进而干扰肝脏糖脂代谢[39]。而抑制LPS则能显著改善MASLD病理进程[44]。因此, 肠源性LPS可能是牙周炎经肠-肝轴影响MASLD病理进程的关键介质。

2.2.3.2　微生物代谢物紊乱: 多通路协同作用

除了细菌组分直接易位外, 肠道菌群代谢谱的紊乱也通过多种代谢产物共同作用于肝脏。在三甲胺/氧化三甲胺(trimethylamine-n-oxide, TMAO)通路中, 膳食胆碱与肉碱首先经肠道微生物代谢生成三甲胺, 继而该产物在肝脏中被黄素单加氧酶氧化, 最终形成TMAO, 高水平的TMAO可通过促进泡沫细胞形成和加剧胰岛素抵抗等多种机制, 驱动肝脏脂肪变性与炎症进展[45]。其次, 肠道多种共生菌如厌氧类杆菌、链球菌和乳酸杆菌等将不可消化的碳水化合物发酵产生短链脂肪酸(short-chain fatty acids, SCFAs), 生理状态下, SCFAs可通过激活AMPK信号通路, 进而抑制肝脏脂肪生成, 其代谢异常则

削弱了这一保护作用[46]。作为肠-肝循环的关键介质,胆汁酸代谢紊乱会削弱其在维持肝脏糖脂代谢平衡中的作用,并可能通过激活法尼醇X受体等途径促进MAFLD的进展[47]。此外,氨基酸代谢也扮演着重要角色,此外,氨基酸代谢失衡在疾病发展中也具有重要意义。本课题组最新研究发现,色氨酸代谢在牙周炎相关MASLD中具有干预潜力:向牙周炎肥胖小鼠补充色氨酸代谢产物吲哚-3-丙酸或益生菌罗伊氏乳杆菌,可有效激活肠道色氨酸-芳香烃受体信号通路,促进肠屏障功能修复,显著抑制LPS向肝脏易位,从而改善肝脏病理表型[48]。该结果与代谢组学研究相互印证——氨基酸代谢紊乱,尤其是支链氨酸水平的异常升高,与MAFLD的严重程度密切相关[49-50]。以上研究共同表明,靶向调控特定的微生物代谢通路,可能成为干预牙周炎相关肝代谢紊乱的潜在新策略。

3 结语

综上,牙周炎与MAFLD的关联是一个由多通路、多机制共同参与的复杂过程。鉴于牙周炎与MAFLD的密切关联,临床医生,尤其是肝病科、内分泌科及全科医生,在评估和管理MAFLD患者时,应将口腔健康状况(特别是牙周炎筛查)纳入常规问诊或简易评估体系。识别并管理重度牙周炎,可能是对MAFLD高危人群进行早期、多靶点干预的重要一环。

现有证据表明,牙周炎不仅通过血液循环途径直接向肝脏输送致病菌及其代谢产物,触发肝内免疫炎症反应,还通过“口-肠-肝轴”这一系统性通路参与MAFLD的发生与发展。随着微生物组学、代谢组学等高通量技术的发展,“口-肠-肝轴”在全身性疾病中的作用机制正被逐步揭示。然而,当前研究仍存在一定局限,包括缺乏大规模前瞻性队列以明确因果关联,对特定口腔菌群在肠-肝轴中的功能角色尚不清晰,以及牙周干预对MAFLD病程改善的确切效应仍需更多临床证据支持。未来的研究需通过跨学科合作,整合口腔医学、肝病学与微生物学研究,有望在机制解析与临床转化上实现突破,从而将牙周健康管理纳入MAFLD的一体化防治体系,为这一日益严峻的公共健康问题提供新的防控思路与综合解决方案。

* * *

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