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Hans汉斯

Pathogenesis of Nonalcoholic Fatty Liver Disease in Children and Adolescents

Chao'an Zheng[1], Junfen Fu[2*]

[1]School of Medicine, Zhejiang University, Hangzhou Zhejiang
[2]Department of Endocrinology, The Children's Hospital Zhejiang University School of Medicine, Hangzhou Zhejiang
Email: *fjf68@zju.edu.cn

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Abstract

Nonalcoholic fatty liver disease (NAFLD) has become the main manifestation of chronic liver disease in children and adolescents with the increasing incidence of obesity worldwide. NAFLD represents a broad spectrum of diseases, including nonalcoholic fatty liver, non-alcoholic steatohepatitis (NASH), cirrhosis and liver carcinoma. Although it is generally believed that NAFLD is closely related to obesity and insulin resistance, the specific pathogenesis of NAFLD remains unclear. In this article, we will review the pathogenesis of nonalcoholic fatty liver disease in children and adolescents.

Keywords

Children, Adolescents, Non-Alcoholic Steatohepatitis, Nonalcoholic Fatty Liver Disease, Pathogenesis

儿童青少年非酒精性脂肪肝病的发病机制

郑朝安[1]，傅君芬[2*]

[1]浙江大学医学院，浙江 杭州
[2]浙江大学医学院附属儿童医院内分泌科，浙江 杭州
Email: *fjf68@zju.edu.cn

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摘　要

随着全球肥胖发病率的上升，非酒精性脂肪性肝病(Nonalcoholic fatty liver disease, NAFLD)已经成为儿童

*通讯作者。

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及青少年慢性肝病的主要表现。NAFLD代表一个广泛的疾病谱，包括非酒精性单纯性脂肪肝(nonalcoholic fatty liver, NAFL)、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)、肝硬化及肝癌。虽然目前普遍认为NAFLD与肥胖以及胰岛素抵抗密切相关，但其具体的发病机制尚未明确。在本文中，我们将对儿童青少年非酒精性脂肪性肝病的发病机制进行综述。

关键词

儿童，青少年，非酒精性脂肪性肝炎，非酒精性脂肪性肝病，发病机制

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1. 引言

儿童青少年非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)定义为 18 周岁以下，无过量饮酒的情况下并且除外明确可导致肝脏病变的病因外，出现以肝细胞脂肪变性和慢性脂质堆积为特征的临床病理综合征[1]。NAFLD 代表一个广泛的疾病谱，包括非酒精性单纯性脂肪肝(nonalcoholic fatty liver, NAFL)、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)、肝硬化及肝癌。因研究对象的人口特征、研究与诊断方法存在差异等因素，NAFLD 的全球患病率尚未达成一致。Younosis 等学者的研究发现 NAFLD 的患病率存在地域差异，中东(32%)和南美(31%)的患病率较高，而亚洲(27%)、美国(24%)、欧洲(23%)及非洲(14%)的患病率相对较低[2] [3]。2014 年中国学者的研究发现，既往乙型肝炎为导致肝脏病变的最常见疾病，但目前已被 NAFLD 超越，在各种肝脏疾病中，NAFLD 的比例高达 49.3% [4]。预计到 2030 年，全球的 NAFLD 患病率为 28.4%。

NAFLD 的患病人数逐年增加，并且呈现低龄化趋势。肥胖症为儿童青少年 NAFLD 的独立危险因素。在美国，儿童肥胖患病率逐年升高，NAFLD 的儿童患病率已达到 3%~11% [5]，也呈逐年上升趋势。在亚洲地区，儿童的 NAFLD 患病率为 6.3%，其中中国的儿童 NAFLD 患病率目前还比较低，仅为 3.4% [6]，但也较前有所升高。

但目前儿童青少年 NAFLD 的发病机制尚未完全清楚，20 世界末提出的“二次打击”学说得到学术界的广泛认可[7]，目前普遍认为与饮食、胰岛素抵抗、基因、氧化应激及肠道菌群等多种因素相关，即多种因素造成细胞和信号通路之间复杂的相互作用，促成疾病的发生发展。第一阶段，胰岛素抵抗、肝细胞内脂肪酸及甘油三酯堆积导致肝脏脂肪变性伴或不伴脂肪性肝炎，此为“一次打击”[8]；第二阶段，肝脏脂肪过量蓄积导致肝细胞炎症、氧化应激、线粒体功能障碍、免疫应答等多重二次打击，最终进展为 NASH、肝纤维化，甚至肝硬化[9] [10] [11]。因此，关于儿童青少年 NAFLD 的发病机制研究至关重要，有助于对 NAFLD 进行早期防治并且减少终末期肝病的发生，本文将对儿童青少年 NAFLD 的发病机制进行综述。

2. 饮食因素与胰岛素抵抗

2.1. 营养过剩与饮食结构的改变

随着社会经济的发展和物质条件的改善，儿童肥胖及 NAFLD 的发病率呈现全球增多趋势，这与过度摄食及饮食结构改变密切相关。过度摄食破坏了肝脏及脂肪组织调节能量代谢的生理机制，使肝脏脂

肪负荷增加，并干扰胰岛素受体磷酸化从而加剧胰岛素抵抗。胰岛素信号通路失调是脂肪代谢失衡的一种体现，最终可导致甘油三酯失衡、脂肪酸线粒体氧化及脂蛋白排泄及转运[12]。富含甘油三酯的乳糜微粒约 80%被转运到外周脂肪组织，释放游离脂肪酸，最后被脂蛋白脂肪酶摄取利用。载脂蛋白 C-III (ApoC-III)是脂蛋白脂肪酶抑制剂，胰岛素抵抗患者不能有效抑制肝脏中 ApoC-III，从而抑制外周脂肪组织脂蛋白脂肪酶、增加肝脏摄取富含甘油三酯的乳糜微粒[13]。此外脂肪组织可产生炎症因子和脂肪因子如肿瘤坏死因子-alpha (Tumor Necrosis Factor, TNF-α)、白介素-6 (Interleukin-6, IL-6)、瘦素(leptin)和脂联素等加剧肝脏损伤，其中 leptin 可活化肝脏星状细胞并抑制其凋亡，从而参与 NAFLD 的发生发展及进展为 NASH 和肝硬化的过程[14] [15]。

果糖、蔗糖等近年来被广泛作为食物甜味添加剂，由此带来的健康问题值得关注。高热卡饮食(富含脂肪、果糖/蔗糖)可加剧肝脏脂肪变性和肝损害，高血糖通过激活碳水化合物反应元件结合蛋白(ChREBP)，在肝脏脂肪变性过程中起着重要作用[13]。果糖代谢不同于葡萄糖，它通过葡萄糖转运蛋白 5 (GLUT5)几乎完全在肝脏代谢，一旦进入肝脏细胞，主要被果糖激酶转换成果糖-6-磷酸，再经二磷酸果糖酶水解为果糖-1,6-二磷酸，从而进入糖酵解及糖异生途径，果糖代谢将增加尿酸含量。尽管摄入的果糖将转化为葡萄糖而非甘油三酯，但果糖可诱导肝脂肪合成酶的生成、增加极低密度脂蛋白和肝脏脂肪细胞沉积[16]。虽然果糖不会使胰岛素急剧增加，但最终增加了胰岛素抵抗、空腹血糖和胰岛素水平，高果糖饮食与肝细胞凋亡、肝纤维化及血脂异常密切相关[17]。

2.2. 母亲、胎儿宫内生长与新生儿期营养

近年来越来越多研究显示母亲在围产期、孕早期甚至受孕前期的生理和代谢状态与儿童 NAFLD 发病、甚至进展为 NASH 密切相关[18]。怀孕前控制性的减肥可降低子代发生 NAFLD 的风险，这可能与一些关键基因的表观遗传修饰有关，并且对后代也有长远影响[19]。多项研究显示宫内发育迟缓与儿童肥胖、脂代谢紊乱、肝脂肪变性和脂肪性肝炎关系密切[20]，具体机制可能与表观遗传修饰相关[19]。此外，早期体重增长过快(尤其是出生前 3 月)，可增加儿童及成年期 NAFLD 的发病风险[21]。

3. 基因

随着二代测序技术的发展，基因多态性与儿童 NAFLD 发病的相关性得到越来越多的关注，其发生率因种族而异，西班牙最高约 36%、非洲裔加勒比海人 14%、亚洲人 10.2%、非西班牙白种人 8.6% [22]。与 NAFLD 相关基因多态性包括 PNPLA3 rs738409 [23]、NCAN rs2228603 [24]、LYPLAL1 rs12137855 [24]、GCKR rs780094 [24]、PPP1R3B rs4240624 [24]、APOC3 rs2854117/rs2854116 [25]、FDFT1 rs2645424 [26]、FTO rs9939609 [27]、MC4R rs12970134 [27]、GC rs222054 [28]、LCP1 rs7324845 [28]、SLC38A8 rs11864146 [28]、LPPR4 rs12743824 [28]、SAMM50 rs2143571 [29]、PARVB rs6006473/rs5764455/rs6006611 [29]、IL-6 [30]、TM6SF2 [31]等。其他与氧化应激相关并参与 NAFLD 进展为 NASH 的基因包括 SOD2 rs4880、IRS-1 rs1801278、KLF-6 rs3750861 [32]。

3.1. PNPLA3 基因

PNPLA3 (Patatin like phospholipase containing domain 3)基因位于 22 号染色体，编码脂肪营养蛋白，该蛋白表达于肝脏和脂肪组织，具有脂肪生成和分解的作用。PNPLA3 基因 rs738409 单核苷酸多态性(I148M)，其变异率因种族而异，西班牙人 0.46，高加索人 0.305，非洲裔美国人 0.186 [33]，在不同种族成人[33]及儿童[23]中均证实与 NAFLD 发病相关。研究显示该基因多态性可使脂肪营养蛋白酶活性增强，从而促进肝脏脂肪合成[34]；同时该变异也可降低肝脏细胞水解甘油三酯的能力从而导致肝脏脂肪变性

[35]。

3.2. GCKR 基因

GCKR (Glucokinase regulator protein)基因编码葡萄糖激酶调节蛋白，可抑制肝脏和胰岛细胞中葡萄糖激酶的活性，与 PNPLA3 基因一起共同参与肝脏脂肪变性[36]。GCKR 基因 rs738409 多态性(P446L)，其变异率在高加索人为 0.466，西班牙人 0.355，非洲裔美国人 0.129 [36]。GCKR 基因 P446L 多态性可增加肝脏葡萄糖激酶活性，从而增加糖酵解速率、增加肝脏葡萄糖代谢及脂肪合成的底物丙二酰辅酶 A 的浓度，从而促进肝脏脂肪沉积[37]。

3.3. APOC3 基因

APOC3 (Apolipoprotein C-III)基因单核苷酸多态性 rs2854117 和 rs2854116 (C482T 和 T455C)与 NAFLD 和胰岛素抵抗相关[25]。APOC3 基因多态性可增加血浆载脂蛋白 C3 浓度，而载脂蛋白 C3 可抑制脂蛋白脂肪酶进而减少甘油三酯的清除，这些不能清除的乳糜微粒增加了空腹及餐后高甘油三酯血症的可能性，循环中增加的乳糜微粒最后在肝脏经受体介导途径清除，最终导致 NAFLD 和胰岛素抵抗[38]。

3.4. FDFT1 基因

研究显示，FDFT1 (Human farnesyl-diphosphate farnesyltransferase 1)基因 rs2645424 多态性与 NAFLD 发病相关[26]，它编码的角鲨烯合成酶可将两分子法尼焦磷酸转换为鲨烯作为胆固醇合成的前体，对胆固醇合成具有重要调节作用，FDFT1 基因 rs2645424 多态性可促进角鲨烯合成酶基因的表达，最终增加肝脏胆固醇沉积[39]。

4. 氧化应激

过多的游离脂肪酸进入肝脏，超过线粒体的数量导致不完全氧化底物(如脂肪酸、神经酰胺等)的蓄积，增加了 β-氧化、减少了可用的氧化辅酶因子(烟酰胺腺嘌呤二核苷酸 NAD 和黄素腺嘌呤二核苷酸 FAD)，从而降低了呼吸链的流出，最终导致电子蓄积、活性氧自由基(Reactive oxygen species, ROS)的产生和细胞损伤。呼吸链复合酶氧化反应的变化损害了线粒体的催化功能、使线粒体 DNA 发生突变，进一步加剧了氧化应激损伤，最终导致肝细胞死亡、加快 NASH 进程[40]。肝细胞过量脂肪酸氧化应激损伤主要来源于线粒体、过氧化物酶体和微粒体，细胞色素 P450 4A 是过氧化物酶体氧化反应的一种关键酶，胰岛素抵抗、高胰岛素血症抑制了细胞色素 P450 4A 的活性，可显著增加过氧化物酶体的氧化应激反应，这种抑制作用增加了细胞毒性 ROS 的产生和脂质过氧化。这些产物可弥散进入细胞外间隙，影响肝脏 Kupffer 细胞和星状细胞，诱导 NFkB 信号通路，导致 TNF-a 及其他促炎、促纤维化的细胞因子的产生[13]。

5. 肠道菌群与肠屏障通透性

近年来，肠道生态系统可参与调节宿主的粘膜/全身免疫反应、代谢及营养状况，近年来越来越多的研究证实了肠道菌群与肥胖、胰岛素抵抗及 NAFLD 的相关性[41]。肠道微生物可产生高度保守的病原体相关分子模式(Pathogen-associated molecular patterns, PAMPs) (如脂多糖、木糖醇)，并被特定模式识别受体(Pattern recognition receptors, PRRS) (Toll 样受体、Nod 样受体)识别。研究显示 NAFLD 患者肠道菌群改变、肠道通透性增加，增加了肝脏暴露于 PAMPs 或其他肠道组织损伤相关分子的风险，因此饮食和/或肠道菌群相关的肠道产物可通过受损的肠道渗透性屏障、激活固有免疫反应参与 NAFLD 的发生[41] [42]。肠道菌群可将不可吸收的多糖分解为单糖和短链脂肪酸，从而产生更多卡路里；单糖还可激活碳水化合物反应元素结合蛋白，增加肝脏脂肪合成和蓄积[42]。另有研究发现肠道菌群可改变宿主胆汁酸构成，

从而拮抗肠道法尼醇 X 受体(arnesoid X receptor, FXR)，导致肥胖、胰岛素抵抗等代谢障碍，胆汁酸也可激活肝脏 FXR 和 G 蛋白结合受体 5 (TGR5)影响 NAFLD 的发生发展过程[43]。

6. 其他

6.1. 微量元素与 VitD 代谢

微量元素在调节免疫及抗氧化方面具有重要作用，肝脏金属解毒过程的破坏与 NAFLD 发病关系密切，这可能与氧化应激反应有关，研究显示铜和铁的代谢紊乱可参与 NAFLD 发病过程。近年来大量研究显示维生素 D 缺乏与肥胖、代谢综合征及 NAFLD 相关，这与维生素 D 可参与代谢、抗炎及抗纤维化作用密切相关，维生素 D 缺乏可通过 CD14/LBP 激活 TLR2、TLR4，并刺激下游炎症反应信号分子从而导致脂肪变性和炎症反应[44] [45]。

6.2. Hedgehog 信号通路

Hedgehog 信号通路与发育过程中组织器官形态新生密切相关，健康成人 Hedgehog 信号通路处于静息状态，当肝细胞受损产生 Hedgehog 受体后激活，从而使成熟肝脏细胞完成创伤修复及新生，但上调该信号通路可能导致肝脏慢性炎症、纤维化甚至肝细胞肝癌[46]。儿童 Hedgehog 信号通路数量及活性均大于成人，但随着青春期进展及肝脏发育成熟其特征接近成人，研究证实肝脏纤维化严重程度与 Hedgehog 信号通路活性呈正相关，青春期前男性汇管区 Hedgehog 信号高表达、肝脏纤维化更严重[47]。这意味着对于青春前期儿童更小的损伤即可导致肝脏明显的损害，这也解释了儿童单纯性脂肪肝较成人更容易进展为脂肪肝炎及肝硬化。

7. 总结

综上所述，儿童青少年 NAFLD 的发病机制及其进展是一个复杂的过程，其中许多问题仍未明确。最初的“二次打击”理论不能完全解释 NAFLD 的发病机制，其中涉及多种因素。近几十年来，许多实验表明肠道微生物群通过肝肠轴在 NAFLD 发病机制中起关键作用。最近，随着技术的发展(特别是全基因组关联分析)，越来越多的研究聚焦于遗传易感性，并发现了各种基因变异，这些变异可能会改变肝脏以及脂肪组织中的脂质和糖代谢。其中的一些信号通路和分子将成为未来临床治疗的潜在靶点。

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