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非酒精性脂肪性肝病与肌肉减少症共同发病机制研究进展

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摘　要

随着人口老龄化的增加、生活水平的提高，肥胖、代谢综合征等问题日趋严峻，相关疾病如非酒精性脂肪性肝病、肌肉减少症等成为当下热点研究项目。目前广泛认为非酒精性脂肪性肝病与肌肉减少症之间存在共同发病机制，两病互相影响。对于非酒精性脂肪性肝病、肌肉减少症的早期发现、干预等十分重要。目前我国对于非酒精性脂肪性肝病和肌肉减少症共同机制的研究处于早期阶段，这篇综述主要讨论非酒精性脂肪性肝病和肌肉减少症的共同的发病机制。

关键词

非酒精性脂肪性肝病，肌肉减少症，线粒体功能障碍，胰岛素抵抗，肠道菌群，维生素D

Research Progress on Co-Pathogenesis of Non-Alcoholic Fatty Liver Disease and Sarcopenia

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Abstract

With the increase of population aging and the improvement of living standards, obesity, metabolic syndrome and other problems are becoming increasingly serious, and related diseases such as

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non-alcoholic fatty liver disease and sarcopenia have become hot research projects now. At present, it is widely believed that there is a common pathogenesis between non-alcoholic fatty liver disease and sarcopenia, the two diseases affect each other. It is very important for the early detection and intervention of non-alcoholic fatty liver disease and sarcopenia. Now, the research on the common mechanism of non-alcoholic fatty liver disease and sarcopenia is in the early stage in China. This review mainly discusses the common pathogenesis of non-alcoholic fatty liver disease and sarcopenia.

Keywords

Non-Alcoholic Fatty Liver Disease, Sarcopenia, Mitochondrial Dysfunction, Insulin Resistance, Gut Microbiota, Vitamin D

1. 引言

非酒精性脂肪性肝病(Non-Alcoholic Fatty Liver Disease, NAFLD)是一种与胰岛素抵抗(Insulin Resistance, IR)、代谢综合征(Metabolic Syndrome, MS)、肥胖等因素密切相关的肝脏疾病[1]。NAFLD 包括单纯性非酒精性肝脂肪变、非酒精性脂肪性肝炎(Non-Alcoholic Steatohepatitis, NASH)、非酒精性脂肪性肝炎相关性肝硬化和肝细胞癌(Hepatocellular Carcinoma, HCC) [2]。随着人民生活水平的提高，代谢综合征和肥胖等因素的全球化流行，NAFLD 的发病率也呈逐年增长的趋势，目前已经取代病毒性肝炎成为世界范围内最常见的慢性肝脏疾病，其全球总体患病率约为 32.4% (95% CI: 29.9~34.9)，男性(39.7%)显著高于女性(25.6%) [3]，在我国的整体患病率约为 29.6%，其中男性(34.75%)亦显著高于女性(27.50%) [4]，当 NAFLD 逐渐进展至重度肝硬化、肝癌阶段时，通常预后不佳死亡率较高，且由于该阶段疾病的不可逆性，相关研究预测在 2030 年以内 NAFLD 将成为肝移植的主要病因[5]。肌肉减少症(Sarcopenia)是指全身性肌肉力量减退、肌肉数量或质量降低以及出现机体相应临床表现，导致生活质量下降，甚至死亡的综合征，简称肌少症[6]。根据有无原发病因可将其分为原发性肌少症和继发性肌少症，原发性肌少症通常指年龄相关性肌少症，继发性肌少症则是各种疾病导致的肌少症[7]。肌少症常见于老年人、营养不良、慢性消耗性疾病、恶性肿瘤患者[8]。相关研究表明，与非肌少症患者相比，肌少症患者跌倒的风险和骨折风险显着增加[9]。随着我国人口老龄化的加剧、人民生活水平的提高，衰老、肥胖、代谢综合征等亦成为了导致疾病的重要因素[10]，与衰老、胰岛素抵抗等密切相关的肌少症同时也成为了威胁我国公共卫生安全的一大挑战。NAFLD 和肌少症的发病率逐年增加，目前广泛认为两病之间的关系复杂且互为因果，本文旨在讨论 NAFLD 和肌少症的共同发病机制。

2. 非酒精性脂肪性肝病与肌肉减少症的共同发病机制

2.1. 线粒体功能障碍(Mitochondrial Dysfunction, MD)

线粒体主要负责机体能量转换，是机体内三磷酸腺苷(Adenosine Triphosphate, ATP)合成场所[11]。目前大量研究表明，MD 在代谢性疾病的发生、发展中起到重大作用[12]。线粒体可以通过脂肪酸 β 氧化供能，在肝脏的脂质代谢功能中起到至关重要的作用。发生 MD 时，脂肪酸代谢异常，导致细胞中脂肪分

解小于合成、脂肪在细胞内进一步积聚，最终发生细胞脂肪变性。目前相关研究表明，在 NAFLD 患者中存在脂肪酸 β 氧化和 ATP 合成异常[13]。有研究表明 MD 或线粒体呼吸链受抑制产生的线粒体活性氧参与炎症小体的激活过程，从而促进炎症反应[14]，该机制会进一步损伤肝细胞从而促进 NAFLD 的进展。通常肝细胞能通过选择性自噬来调控线粒体和过氧化物酶体的质量和数量而直接调节肝脏代谢[15]。相关研究表明，在 NAFLD 患者以及肥胖和高脂饮食喂养小鼠的肝脏中，自噬过程受到干扰[16]。同时，线粒体作为体内能量转换的场所，其正常功能活动同样是肌肉功能正常的必备条件。随着衰老、运动减少、机体代谢下降、肌肉萎缩等因素影响，会出现肌细胞内线粒体数量减少以及功能受损。MD 时线粒体将增加活性氧的产生，损伤细胞 DNA、减少蛋白质合成，促进细胞凋亡，其在骨骼肌中影响尤为明显[17]。加之线粒体自噬系统异常导致功能受损的线粒体清除失败，其在肌细胞内蓄积导致肌细胞破坏增加[18]。

2.2. 胰岛素抵抗(Insulin Resistance, IR)

IR 会引起机体脂代谢紊乱，IR 时，胰岛素会抑制甘油三酯(TG)的水解，促进周围组织摄取游离脂肪酸，导致合成脂肪作用减弱[19]。此时肝脏的 TG 作用会受到抑制，长期作用下会发生肝脏脂肪沉积，形成脂肪肝[1]。同时功能受损的脂肪细胞会释放大量细胞因子、激素等进行细胞肥大、增生，导致发生炎症反应以及加重 IR [2]。同时相关研究表明，炎症发生时机体产生大量瘦素[20]、抵抗素[21]、白介素-6 [22]等炎症因子均在 NAFLD 和 IR 中发挥重要作用。在骨骼肌系统中，IR 可导致血糖控制不佳及高胰岛素血症，从而引起蛋白质降解增加及合成降低，造成肌肉力量和质量的损失[23]。同时肌少症也会导致骨骼肌代谢下降、葡萄糖利用下降，导致高血糖和高胰岛素血症以及最终的 IR [24]。在正常人群中，骨骼肌对葡萄糖的清除率可达 80%，而在肌少症人群中因骨骼肌质量下降、数量减低等导致对葡萄糖摄取减少，导致 IR 的发生[25]。同时肌少症通常有肌肉组织脂肪异位沉积，一项为期 5 年的关于腿部成分、力量和肌肉质量的动态变化的观察性研究显示，在所有受试者中肌肉质量均显著下降，与此形成鲜明对比的是，受试者的肌间脂肪面积均显著增加[26]。而目前有研究显示，肌束之间的脂肪细胞浸润增加与步态受损和 IR 相关[27]。同时发生肌少症时骨骼肌内巨噬细胞和脂肪酸之间的相互协同作用也可导致胰岛素作用受损，导致骨骼肌 IR 加重肌少症[28]。

2.3. 肠道菌群

在机体内，肠道菌群直接参与维持肠道屏障完整性、抵御外来病原体、调节宿主免疫炎症反应、协调机体消化功能、代谢等活动[29]。肠道菌群通过肠－肝轴与肝脏相互作用，肠道内的细菌及其代谢物可通过门静脉系统到达肝脏，又能将肝脏中的胆汁、肽类、蛋白质和抗体等物质运输至肠道，称为肠－肝轴途径，其是肠道菌群影响肝脏代谢的关键环节，肠道菌群的紊乱及代谢物的异常均可导致 NAFLD 的发生[30]。当肠道菌群各菌落之间的相对丰度组成发生改变，称为生态失调[31]，可导致 2 型糖尿病、代谢综合征和 NAFLD 等代谢性疾病。相关研究表明，NAFLD 患者肠道中拟杆菌的增加和厚壁菌的减少与 NAFLD 的疾病进展有关[32]，NAFLD 患者肠道内变形杆菌、肠杆菌、埃希氏菌等机会性致病菌的相对丰度增加，瘤胃球菌、粪球菌、普雷沃氏菌和乳酸杆菌等生理性菌群的丰度降低。此外有研究报道，肠道细菌的代谢产物如短链脂肪酸、胆汁酸、三甲胺和乙醇等可通过 G 蛋白偶联受体[33]、法尼醇 X 受体[34]、加重肝脏 IR、增加脂肪组织炎症[35]等途径导致或加重 NAFLD。在肌少症中，相关研究表明肠道菌群的差异性与衰老相关肌肉损失以及人体健康状况有关[36]。一项基于小鼠的动物实验显示移植健康老年人粪便菌群的小鼠肌肉质量高于移植体弱老年人粪便菌群的小鼠[37]。已有研究证实肠道菌群可通过影响蛋白质合成[38]、肠－肌轴[39]、线粒体代谢[40]等途径影响肌肉质量和功能，与老年性肌少症密切相关。

2.4. 维生素 D

维生素 D 是一种脂溶性维生素，参与维持人体内钙磷代谢平衡、骨骼系统的生长发育，同时在减轻 IR、调节免疫、抗纤维化和抗炎等方面均有重要作用[41]。维生素 D 作用于细胞核受体中的维生素 D 受体(Vitamin D Receptor, VDR)发挥生物作用，VDR 在回肠帕内特细胞中表达水平较高。动物实验研究表明，维生素 D 可通过调节回肠帕内特细胞特异性 α-防御素(α-Defensin, DEFA)影响肠道菌群平衡，继而达到调节代谢、影响 NAFLD 的发生与发展[42]。同时维生素 D 可通过 VDR 调节转录因子 FoxP3 的表达来维持调节性 T 细胞的活性并抑制 Th17 细胞炎症反应[43]，与单纯性脂肪肝及脂肪性肝炎的发生发展有重要关系。同时，维生素 D 能降低 IR 从而减少 NAFLD 的发生[44]，主要通过增加胰岛素靶组织中相应的受体、促进脂肪和肌肉组织中的脂肪酸分解代谢、下调炎症因子表达等途径影响胰岛素敏感性实现。维生素 D 同样对骨骼肌力量、肌肉状态等具有重要影响，维生素 D 缺乏会增加年龄相关疾病发生的风险，增加肌少症发病率[45]。研究表明，维生素 D 可以通过有丝分裂原激活的蛋白激酶信号传导通路调节 C2C12 骨骼肌肌管的增殖和分化，也可以调节肌肉中钙离子通道状态，抑制 FOXO1 基因表达，并影响泛素－蛋白酶体系统，而泛素－蛋白酶体系统在骨骼肌肌肉减少、萎缩中发挥重要作用[46]。同时，维生素 D 可通过 VDR 调节蛋白质合成、II 型肌纤维数量和体积进而影响骨骼肌质量、数量以及功能，在肌少症的发生和发展中起重要作用。

3. 结语与展望

目前相关研究表明，非酒精性脂肪性肝病与肌肉减少症有许多共同的病理生理机制。随着人口老龄化趋势日渐明显、人们生活水平逐渐提高，肥胖、代谢综合征等相关疾病发生率逐年增加，代谢相关性疾病如 NAFLD、肌少症已逐步成为威胁公共健康的重要因素。而目前关于 NAFLD 和肌少症之间的共同发病机制仍不完全明确，已有的研究表明如线粒体功能障碍、胰岛素抵抗、肠道菌群、维生素 D、炎症因子、营养与代谢状态等因素均在两者的发病过程中起重要作用。由于目前针对 NAFLD、肌少症的治疗药物有限，在临床治疗中仍以运动、饮食干预措施为主，但由于 NAFLD、肌少症等的发生与代谢状态、年龄等相关，特别是在老年、糖代谢、脂代谢异常患者中，运动、饮食干预措施实施难度较高。为此仍需进一步对两病相关发病机制进行深入研究，且目前相关研究仍以动物实验为主，深入学习 NAFLD、肌少症的病因、临床表现等或有助于进一步理解疾病临床机制、预后转归，为后续深入研究其病理生理机制创造条件，进一步为临床诊断、患者管理、药物干预等手段提供依据。

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