综 述

BMI正常人群代谢相关性脂肪性肝病患者的特点

雷小维 综述 张利莉 审校
重庆医科大学附属第二医院 内分泌科(重庆 400010)

【摘 要】近年研究显示代谢相关性脂肪性肝病(metabolic associated fatty liver disease,MAFLD)在体质指数(body mass index,BMI)正常的人群中发病率并不低,但尚未受到应有重视。而BMI正常的MAFLD并非既往认为的良性疾病,它不仅具有与肥胖MAFLD患者相似的代谢紊乱、临床表现、并发症,同时在这些方面还有自己的特点,因此应当给予更多关注。本文将围绕BMI正常的MAFLD的发病机制、临床表现、预后和治疗等方面的特点做一综述,以期为个体化MAFLD治疗提供新的思路。

【关键词】代谢相关性脂肪性肝病;BMI正常人群;特点
【中图分类号】 R575.5 文献标志码 A DOI:10.3969/j.issn.2096-3351.2022.02.017

Features of patients with metabolic associated fatty liver disease in normal body mass index adults

LEI Xiaowei reviewing *ZHANG Lili* checking
Department of Endocrinology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

【**Abstract**】Recent studies have shown a high incidence rate of metabolic associated fatty liver disease (MAFLD) in people with normal body mass index (BMI), which has not been taken seriously in clinical practice. MAFLD with normal BMI is not the benign disease it was thought to be in the past; it not only has similar metabolic disorders, clinical manifestations, and complications to obese MAFLD patients, but also has its own features in these aspects, and therefore, it should be taken seriously in clinical practice. This article summarizes the features of MAFLD with normal BMI from the perspectives of pathogenesis, clinical manifestations, prognosis, and treatment, in order to provide a new idea for individualized treatment of MAFLD.

【**Key words**】Metabolic associated fatty liver disease; Patient with normal body mass index; Features

代谢相关性脂肪性肝病(metabolic associated fatty liver disease,MAFLD)的患病率逐年上升,引起了广泛关注。根据目前世界卫生组织的体质指数(body mass index,BMI)划分标准,可以将患者分为肥胖、超重、正常三类,非亚洲人的标准为:BMI < 25kg/m^{2}为正常,25kg/m^2 ≤ BMI < 30kg/m^{2}为超重,BMI ≥ 30kg/m^{2}为肥胖;亚洲人的标准为:BMI < 23kg/m^{2}为正常,23kg/m^2 ≤ BMI < 27.5kg/m^{2}为超重,BMI≥27.5kg/m^{2}为肥胖[1]。本文将MAFLD的非亚洲人群正常BMI定义为BMI < 25kg/m^2,MAFLD的亚洲人正常BMI为BMI < 23kg/m^2。目前,BMI正常的MAFLD患者约占总MAFLD人口的19.2%,一般人群中BMI正常的MAFLD患病率约为5.1%,BMI正常人群中的MAFLD患病率约为10.6%[2]。可见BMI正常MAFLD的发病率并不低,但却未受到相应的重视。同时BMI正常的MAFLD在心血管等并发症甚至死亡等方面的风险均不低,因此应当对BMI正常人群MAFLD的发生发展给予更多关注。本文就BMI正常的MAFLD患者的发病机制、临床表现和预后等方面的特点进行综述,以期为个体化MAFLD治疗提供新的思路。

1 风险因素和病理生理机制特点

BMI正常或肥胖的MAFLD患者在胰岛素抵抗、脂肪因子方面未发现明显差别。BMI正常的MAFLD患者常表现为体重正常,但有研究发现在MAFLD进展过程中,BMI正常的患者体重增加幅度甚至大于肥胖患者[3]。

基金项目:国家自然科学基金项目(81300702);重庆市科委自然科学基金项目(cstc2018jcyjAX0210)
第一作者简介:雷小维,硕士研究生。
通信作者:张利莉,主任医师,副教授,硕导。E-mail:zhanglili.jl@foxmail.com
引用本文:雷小维,张利莉.BMI正常人群代谢相关性脂肪性肝病患者的特点[J].西南医科大学学报,2022,45(2):172-175;DOI:10.3969/j.issn.2096-3351.2022.02.017

BMI正常的MAFLD患者身体脂肪比例常高于正常的人，一项研究显示脂肪质量与无脂肪质量比（Fat mass to fat-free mass ratio，FM/FFM）比率每增加1个标准差，非肥胖男性发生MAFLD风险约增加0.55倍，非肥胖女性约增加0.42倍[4]。一方面，BMI正常的MAFLD患者表现为中心性肥胖，内脏脂肪比例增加。相同的BMI，亚洲人的内脏脂肪比例高于其他人群[5]。所以虽然亚洲人体重指数较低，但代谢综合征和MAFLD的患病率仍较高[6-7]。另一方面，其还可以表现为肌少症和骨骼肌质量减少，但脂肪比例上升[8]。一项来自韩国的10年回顾性队列研究显示，肌肉质量减少与非肥胖受试者的MAFLD发生显著相关，与肥胖受试者无明显相关[9]。

在饮食与生活方式方面，BMI正常的MAFLD患者除了具有与肥胖MAFLD患者相似的高热量、高糖（BMI正常的患者中高果糖饮料和食物尤其突出）、高脂肪（主要为饱和脂肪和反式脂肪）、高动物蛋白等饮食特点和久坐生活方式外[10-11]，BMI正常的MAFLD患者视黄醇摄入量比正常人少，胆固醇摄入量比肥胖患者高，多不饱和脂肪酸摄入量比肥胖患者低[12]。高动物脂肪摄入量是肥胖人群患MAFLD的独立预测因素，碳水化合物摄入能量百分比是非肥胖人群MAFLD的独立预测因素，每周低于2 h中等强度的体力活动水平在2种人群中均为独立预测因素[13]。

肠道微生物对MAFLD的发生发展也具有重要作用[14]。一项纳入了171名经活检证实MAFLD的亚洲患者及31名非MAFLD对照者的研究发现，BMI正常的患者和超重/肥胖患者肠道中的优势菌群不同，肠道微生物群变化可以影响MAFLD严重程度，而这种关联在BMI正常的MAFLD中更为显著。同时，仅在非肥胖MAFLD患者中观察到：随着MAFLD的进展，韦氏菌科和肠杆菌科逐渐富集，而乳球菌科逐渐减少，韦氏菌科和肠杆菌科与乳酸菌科呈负相关，总胆汁酸水平以及粪便样本中的丙酸盐水平随着纤维化严重程度的增加而升高，这意味着优势菌群的差异以及这种细菌之间的相互作用可能通过影响胆汁酸代谢对非肥胖患者发病和进展起特定作用[15]。

遗传因素在MAFLD的发生发展中有重要地位，跨膜6超家族成员2（TM6SF2）、含Patatin样磷脂酶结构域的蛋白质3（PNPLA3）、胆固醇酯转移蛋白（CETP）、膜结合O-酰基转移酶结构域7（MBOAT7）、PEMT都可能与BMI正常的MAFLD有关[16-18]。PNPLA3的rs738409G等位基因可独立于胰岛素抵抗和肥胖、血脂异常等代谢共病作用于脂肪肝，一项来自香港的纳入了911名社区受试者的研究发现PNPLA3的rs738409G等位基因在BMI正常的患者中比例高于肥胖MAFLD患者（78.4%vs.59.8%）[19]。但BMI正常患者的代谢情况不比肥胖患者差，可能与该基因可通过与环境因素和其他基因变异的相互作用来调节自身对MAFLD的影响有关。但近期一项包括来自意大利、英国、西班牙和澳大利亚的共1 339名经活检证实MAFLD的受试者的研究显示该基因在BMI正常MAFLD和超重/肥胖MAFLD中无明显差异，考虑可能与环境因素、生活方式、不同种族的实际脂肪比例差异等均有关。

2 临床特征及预后

BMI正常的MAFLD患者多数无特殊表现，常通过影像学检查偶然发现，部分患者可能有疲劳、腹部胀满不适等非特异性不适。大多数研究中BMI正常的MAFLD人群中男性发病略占优势[20]，BMI正常的患者发病年龄比肥胖患者低[21]。一项纳入669名活检证实的MAFLD患者的意大利研究发现，BMI正常的患者平均年龄为46岁，而超重或肥胖患者的平均年龄约为49岁[22]。MAFLD患者的体重、腰围、血脂、血压、血糖、糖化血红蛋白、血尿酸、肝酶、IR指数通常高于BMI健康对照者，随着肝脏损害加深，还常出现铁蛋白升高[23-24]。一项大型荟萃分析显示，BMI正常的MAFLD患者发生高血压、高甘油三酯、2型糖尿病、代谢综合症的风险（odds ratio，OR）约为未患病BMI正常人群的2.64、5.89、5.29、5.43倍[25]。BMI正常的MAFLD患者空腹血糖、糖化血红蛋白、IR指数、血压、血脂比肥胖患者低，荟萃分析发现BMI正常的MAFLD患者约有12.0%的人患2型糖尿病（超重或肥胖的患者约为43.0%）[6]。Zou等[25]分析发现BMI正常患者发生高血压、高甘油三酯、代谢综合症的OR约为肥胖患者的0.60、0.64、0.32倍。但BMI正常的患者血红蛋白高于肥胖患者，并且血红蛋白水平是BMI正常MAFLD患者的NASH严重程度的独立预测因子[26]。巴西一项研究也发现血红蛋白是BMI正常的MAFLD纤维化≥2级的唯一独立预测因子，意味着或许血红蛋白可能成为BMI正常的患者预测组织学严重程度的一项指标[27]。

非肥胖MAFLD与肥胖MAFLD的组织学谱都包括单纯脂肪变性、肝细胞气球样变、小叶炎症等[28]。在初始状态，BMI正常的MAFLD患者的组织学特征往往比肥胖患者轻，MAFLD活性评分更低[29]。一项荟萃分析发现BMI正常的MAFLD中约25.1%存在显著小叶炎症，而肥胖患者约为35.5%，另一项意大利的研究中BMI正常的MAFLD患者发生纤维化≥2级、脂肪性肝炎者均约为17.5%，而在超重或肥胖患者分别约为40.0%、42.0%[22]。但这并不意味着BMI正常的MAFLD患者有更好的临床结局，有纵向研究显示其晚期纤维化、严重

肝损伤、肝硬化的患病率更高[30-31]，一项纳入了24个国家或地区的93项研究的荟萃分析发现，BMI正常的MAFLD患者中3.0%发生了肝硬化，而肥胖MAFLD患者有2.0%发生了肝硬化。既往认为BMI正常的患者远期预后可能更好，但近期研究发现BMI正常的患者可能比BMI不正常的患者肝外并发症发生率和死亡率更高[30,32-33]。BMI正常的或非肥胖非酒精性脂肪性肝病人群中，心血管疾病发病率为1.87%（肥胖患者为0.24%），全因死亡率为1.21%（肥胖患者为0.75%），心血管相关死亡率为0.4%（肥胖患者为0.24%），肝脏相关死亡率为0.41%（肥胖患者为0.24%）[2]。可见BMI正常的MAFLD患者有可能比超重或者肥胖的MAFLD患者预后更差，BMI正常的MAFLD患者应当得到更多重视，尽早开始治疗。

3 治疗

有研究显示，改善MAFLD过程中，非肥胖患者的体重减轻幅度小于肥胖患者[3]。通过改善生活方式，超重/肥胖MAFLD患者体重降低7%～10%即可达到组织学改善及全身获益[34]，而BMI正常的MAFLD患者减重小于7%就可能达到组织学及全身获益。减重可通过饮食调整及增加体力活动来实现。改善饮食可以从降低胆固醇、碳水化合物比例，将饱和脂肪酸改为不饱和脂肪酸，增加纤维素摄入，补充微量营养素等方面着手[35-36]。调整饮食的同时应增加体力活动。一项纳入209名患者的横断面研究显示，体力活动可增加骨骼肌质量，从而改善肌肉减少症和肌肉/脂肪组织质量比，通过降低胰岛素抵抗来促进BMI正常的个体的代谢健康[37-38]。有研究发现，饮食控制和增加体力活动甚至可以在部分患者总体体重未发生变化的情况下改善肝脂肪变性。在生活方式改善的基础上，可根据疾病活动程度适当应用药物治疗，BMI正常的患者药物治疗与超重/肥胖患者无明显差别[39-40]。

4 小结

BMI正常人群的MAFLD患者虽然代谢综合症发病率似乎比肥胖患者低，但其长期预后可能更差。对BMI正常人群的MAFLD患者，应积极改善生活方式和减重，提高骨骼肌质量。具有合并症或已发生脂肪性肝炎的患者，应改善代谢紊乱以及进行相应的保肝抗炎治疗，以期达到组织学及全身获益，进而改善患者的长期预后。

（利益冲突：无）

参 考 文 献

[1] WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies[J]. Lancet, 2004, 363(9403): 157-163.

[2] YE Q, ZOU BY, YEO YH, *et al*. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis[J]. Lancet Gastroenterol Hepatol, 2020, 5(8): 739-752.

[3] KIM NH, KIM JH, KIM YJ, *et al*. Clinical and metabolic factors associated with development and regression of nonalcoholic fatty liver disease in nonobese subjects[J]. Liver Int, 2014, 34(4): 604-611.

[4] DAI HJ, XIANG JL, HOU YN, *et al*. Fat mass to fat-free mass ratio and the risk of non-alcoholic fatty liver disease and fibrosis in non-obese and obese individuals[J]. Nutr Metab (Lond), 2021, 18(1): 1-21.

[5] LIM U, MONROE KR, BUCHTHAL S, *et al*. Propensity for intra-abdominal and hepatic adiposity varies among ethnic groups[J]. Gastroenterology, 2019, 156(4): 966-975.e10.

[6] LU FB, ZHENG KI, RIOS RS, *et al*. Global epidemiology of lean non-alcoholic fatty liver disease: a systematic review and meta-analysis[J]. J Gastroenterol Hepatol, 2020, 35(12): 2041-2050.

[7] YOUNOSSI Z, TACKE F, ARRESE M, *et al*. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis[J]. Hepatology, 2019, 69(6): 2672-2682.

[8] ALFERINK LJM, TRAJANOSKA K, ERLER NS, *et al*. Nonalcoholic fatty liver disease in the Rotterdam study: about muscle mass, sarcopenia, fat mass, and fat distribution[J]. J Bone Miner Res, 2019, 34(7): 1254-1263.

[9] LEE MJ, KIM EH, BAE SJ, *et al*. Age-related decrease in skeletal muscle mass is an independent risk factor for incident nonalcoholic fatty liver disease: a 10-year retrospective cohort study[J]. Gut Liver, 2019, 13(1): 67-76.

[10] JENNISON E, BYRNE CD. The role of the gut microbiome and diet in the pathogenesis of non-alcoholic fatty liver disease[J]. Clin Mol Hepatol, 2021, 27(1): 22-43.

[11] HOUTTU V, BOULUND U, GREFHORST A, *et al*. The role of the gut microbiome and exercise in non-alcoholic fatty liver disease[J]. Therap Adv Gastroenterol, 2020, 13: 1756284820941745.

[12] FEDERICO A, ROSATO V, MASARONE M, *et al*. The role of fructose in non-alcoholic steatohepatitis: old relationship and new insights[J]. Nutrients, 2021, 13(4): 1314.

[13] KWAK JH, JUN DW, LEE SM, *et al*. Lifestyle predictors of obese and non-obese patients with nonalcoholic fatty liver disease: a cross-sectional study[J]. Clin Nutr, 2018, 37(5): 1550-1557.

[14] RUUSKANEN MO, ÅBERG F, MÄNNISTÖ V, *et al*. Links between gut microbiome composition and fatty liver disease in a large population sample[J]. Gut Microbes, 2021, 13(1): 1-22.

[15] LEE G, YOU HJ, BAJAJ JS, *et al*. Distinct signatures of gut microbiome and metabolites associated with significant fibrosis in non-obese NAFLD[J]. Nat Commun, 2020, 11(1): 4982.

[16] ADAMS LA, MARSH JA, AYONRINDE OT, *et al*. Cholesteryl ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity[J]. J Gastroenterol Hepatol, 2012, 27(9): 1520-1527.

[17] MARTIN K, HATAB A, ATHWAL VS, *et al*. Genetic contribution to non-alcoholic fatty liver disease and prognostic implications[J]. Curr Diab Rep, 2021, 21(3): 1-8.

[18] THANGAPANDI VR, KNITTELFELDER O, BROSCH M, *et al*. Loss of hepatic Mboat7 leads to liver fibrosis[J]. Gut, 2021, 70(5): 940-950.

[19] WEI JL, LEUNG JCF, LOONG TCW, *et al*. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy [J]. Am J Gastroenterol, 2015, 110(9): 1306-1314; quiz 1315.

[20] LI YF, CHEN YZ, TIAN X, *et al*. Comparison of clinical characteristics between obese and non-obese patients with nonalcoholic fatty liver disease (NAFLD) [J]. Diabetes Metab Syndr Obes, 2021, 14: 2029-2039.

[21] LI J, ZOU BY, YEO YH, *et al*. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis[J]. Lancet Gastroenterol Hepatol, 2019, 4(5): 389-398.

[22] FRACANZANI AL, PETTA S, LOMBARDI R, *et al*. Liver and cardiovascular damage in patients with lean nonalcoholic fatty liver disease, and associationwith visceral obesity[J]. Clin Gastroenterol Hepatol, 2017, 15(10): 1604-1611.e1.

[23] CHRYSAVGIS L, ZTRIVA E, PROTOPAPAS A, *et al*. Nonalcoholic fatty liver disease in lean subjects: prognosis, outcomes and management[J]. World J Gastroenterol, 2020, 26(42): 6514-6528.

[24] ZENG J, YANG RX, SUN C, *et al*. Prevalence, clinical characteristics, risk factors, and indicators for lean Chinese adults with nonalcoholic fatty liver disease[J]. World J Gastroenterol, 2020, 26(15): 1792-1804.

[25] ZOU ZY, WONG VWS, FAN JG. Epidemiology of nonalcoholic fatty liver disease in non-obese populations: meta-analytic assessment of its prevalence, genetic, metabolic, and histological profiles[J]. J Dig Dis, 2020, 21(7): 372-384.

[26] BERNHARDT P, KRATZER W, SCHMIDBERGER J, *et al*. Laboratory parameters in lean NAFLD: comparison of subjects with lean NAFLD with obese subjects without hepatic steatosis [J]. BMC Res Notes, 2018, 11(1): 1-101.

[27] AKYUZ U, YESIL A, YILMAZ Y. Characterization of lean patients with nonalcoholic fatty liver disease: potential role of high hemoglobin levels[J]. Scand J Gastroenterol, 2015, 50(3): 341-346.

[28] DENKMAYR L, FELDMAN A, STECHEMESSER L, *et al*. Lean patients with non-alcoholic fatty liver disease have a severe histological phenotype similar to obese patients[J]. J Clin Med, 2018, 7(12): 562.

[29] SOOKOIAN S, PIROLA CJ. Systematic review with meta-analysis: the significance of histological disease severity in lean patients with nonalcoholic fatty liver disease[J]. Aliment Pharmacol Ther, 2018, 47(1): 16-25.

[30] WANG QY, YOU H, OU XJ, *et al*. Non-obese histologically confirmed NASH patients with abnormal liver biochemistry have more advanced fibrosis[J]. Hepatol Int, 2019, 13(6): 766-776.

[31] HAGSTRÖM H, NASR P, EKSTEDT M, *et al*. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: a long-term follow-up study[J]. Hepatol Commun, 2018, 2(1): 48-57.

[32] ZOU B, YEO YH, NGUYEN VH, *et al*. Prevalence, characteristics and mortality outcomes of obese, nonobese and lean NAFLD in the United States, 1999-2016[J]. J Intern Med, 2020, 288(1): 139-151.

[33] HUANG JF, TSAI PC, YEH ML, *et al*. Risk stratification of non-alcoholic fatty liver disease across body mass index in a community basis[J]. J Formos Med Assoc, 2020, 119(1 Pt 1): 89-96.

[34] FAN JG, CAO HX. Role of diet and nutritional management in non-alcoholic fatty liver disease[J]. J Gastroenterol Hepatol, 2013, 28 Suppl 4: 81-87.

[35] ULLAH R, RAUF N, NABI G, *et al*. Role of nutrition in the pathogenesis and prevention of non-alcoholic fatty liver disease: recent updates[J]. Int J Biol Sci, 2019, 15(2): 265-276.

[36] HAN RT, MA JL, LI HK. Mechanistic and therapeutic advances in non-alcoholic fatty liver disease by targeting the gut microbiota [J]. Front Med, 2018, 12(6): 645-657.

[37] JIN YJ, KIM KM, HWANG S, *et al*. Exercise and diet modification in non-obese non-alcoholic fatty liver disease: analysis of biopsies of living liver donors[J]. J Gastroenterol Hepatol, 2012, 27(8): 1341-1347.

[38] KIM G, LEE SE, LEE YB, *et al*. Relationship between relative skeletal muscle mass and nonalcoholic fatty liver disease: a 7-year longitudinal study[J]. Hepatology, 2018, 68(5): 1755-1768.

[39] TACKE F, WEISKIRCHEN R. Non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)-related liver fibrosis: mechanisms, treatment and prevention[J]. Ann Transl Med, 2021, 9(8): 729.

[40] JALILI R, SOMI MH, HOSSEINIFARD H, *et al*. The evaluation of effective drugs for the treatment of non-alcoholic fatty liver disease: a systematic review and network meta-analysis[J]. Adv Pharm Bull, 2020, 10(4): 542-555.

(2021-07-21收稿, 2021-11-05修回)