代谢正常肥胖个体发生非酒精性脂肪性肝病的相关性研究*

赵乃蕊 张 弛△ 李华珠 杨晓春 周桂莲 王 敏 熊 璞 刘 瑛

(湖南师范大学第一附属医院 湖南省人民医院内分泌科 湖南 长沙 410005)

摘要 目的:探讨代谢正常肥胖(Metabolically healthy obese,MHO)个体与非酒精性脂肪性肝病(Nonalcoholic fatty liver disease,NAFLD)发生的相关性。**方法**:选择2006年4月~2010年1月来湖南省人民医院体检中心体检人群共4076例,排除过量饮酒者、乙肝标志物阳性者及相关资料不全者共2830例纳入本研究。其中1367例在1~3年后再次体检。记录受检者身高、体重、血压、血脂、空腹血糖、腹部B超结果。NAFLD采用2010年中华医学会肝病学分会诊断标准中影像学诊断定义,行腹部B超检查进行诊断。**结果**:1.我院体检人群中MHO合并NAFLD者占51.34%,明显高于正常对照组(P=0.000),MHO组发生NAFLD的OR值为19.967(95%CI,12.646-31.533;P=0.000)。2.随访1~3年后,MHO中NAFLD发病率高于正常对照组(44.44% vs 7.02%,OR=10.600,95%CI,4.873-23.058;P=0.000)。**结论**:MHO个体合并NAFLD比例较正常对照者升高,MHO个体增加NAFLD患病风险。

关键词:肥胖;代谢正常肥胖;非酒精性脂肪性肝病;代谢综合征

中图分类号:R589.2 **文献标识码**:A **文章编号**:1673-6273(2012)14-2691-04

Study on the Relation between Metabolically Healthy Obese and Nonalcoholic Fatty Liver Disease*

ZHAO Nai-rui, ZHANG Chi△, LI Hua-zhu, YANG Xiao-chun, ZHOU Gui-lian, WANG Min, XIONG Pu, LIU Ying

(Department of Endocrinology, First Affiliated Hospital of Hunan Normal University, the People's Hospital of Hunan Province, Changsha, Hunan 410005)

ABSTRACT Objective: To investigate the relation between metabolically healthy obese and nonalcoholic fatty liver disease. Methods: 4076 subjects were examined for routine health in People's Hospital of Hunan Province from April 2006 to January 2010, 2830 individual were enrolled excluding those with hepatitis B viruses, excessive alcohol consumption and missing data. 1367 individual were followed up in 3 years. Data were collected of those individuals on body height, body weight, blood pressure, lipid profile and fast blood glucose. Diagnosis of NAFLD was made by B-ultrasound based on the criteria of Chinese Society of Hepatology of imaging diagnosis of NAFLD in 2010. Results: 1. The percentage of NAFLD in individuals with MHO was 51.34% in subjects with healthy examination in People's Hospital of Hunan Province, which was significantly higher than that in normal controls (P=0.000). The presence of MHO was associated with an increased risk of NAFLD (OR=19.967; 95%CI, 12.646-31.533, P=0.000). 2. Following up for 1 to 3 years, we found that the incidence of NAFLD in patients with MHO was significantly higher than that in normal controls (44.44% vs 7.02%, OR=10.600, 95% CI, 4.873-23.058, P=0.000). Conclusions: The percentage of NAFLD in individuals with MHO was significantly higher than that in normal controls, MHO may increase the risk of NAFLD.

Key words: Obese; Metabolically healthy obese (MHO); Nonalcoholic fatty liver disease(NAFLD); Metabolic syndrome(MS)

Chinese Library Classification(CLC): R589.2 Document code: A

Article ID:1673-6273(2012)14-2691-04

前言

随着对肥胖的深入研究,代谢正常肥胖(Metabolically healthy obese,MHO)作为肥胖的一个特殊亚型逐渐成为关注的热点。MHO尽管体内有大量的脂肪堆积,但仍具有正常的代谢表现,包括高胰岛素敏感性、正常的血脂、炎症状态,无高血压等[1]。非酒精性脂肪性肝病(Nonalcoholic fatty liver disease,NAFLD)是一种与胰岛素抵抗(insulin resistance,IR)和遗传易感密切相关的代谢应激性肝脏损伤,其疾病谱包括非酒精性单纯性脂肪肝(NAFL)、非酒精性脂肪性肝炎(NASH)及其相关肝硬化和肝细胞癌[2]。肥胖和NAFLD密切相关,而MHO该肥胖亚型人群中NAFLD的发病情况及MHO个体与NAFLD发生之间的相互关系目前国内外尚未见报道。本研究对我院体检人群MHO及NAFLD进行筛查,并通过1~3的随访观察,探讨MHO个体合并NAFLD的比例及新发NAFLD的危险性。

1 资料与方法

1.1 研究对象

* 基金项目:湖南省科技计划项目(2011SK3160)

作者简介:赵乃蕊(1985-),女,硕士研究生,研究方向:代谢综合征,电话:13787076558,E-mail: 104107zmr@163.com

△通讯作者:张弛,E-mail: zhang_ch1@yahoo.com.cn

(收稿日期:2012-01-06 接受日期:2012-01-30)

选择 2006 年 4 月 -2010 年 1 月来湖南省人民医院体检中心体检人群共 4076 例，排除过量饮酒者、乙肝标志物阳性及相关资料不全者，共 2830 例纳入研究。

1.2 方法

临床指标检测：身高、体重、血压分别由湖南省人民医院体检中心固定的 3 位医务人员进行检测。体重指数 (BMI) = 体重 (kg) / 身高 ^{2} (m)。生化指标检测：血脂、空腹血糖均空腹测定，由湖南省人民医院检验科检验人员完成。腹部肝脏 B 超：利用东芝 TOSHIBA 彩超仪 (探头频率 3.5MHz) 作肝脏检查，由湖南省人民医院 B 超室人员完成。

1.3 入组标准

代谢正常肥胖 (MHO)：即肥胖但代谢正常者，需同时符合下列 4 项标准[3-5]。

①BMI≥25kg/m^2；②既往无糖尿病病史，未使用降糖药物，且空腹血糖≤6.1mmol/L；③既往无高血压病病史，未使用降压药物，且血压 <140/90mmHg；④既往无高脂血症病史，未使用调脂药物，且空腹血甘油三酯 <1.7mmol/L，及空腹血高密度脂蛋白≥0.9mmoL/L (男) 或≥1.0mmol/L (女)。

NAFLD 诊断标准：根据 2010 年中华医学会肝病学分会诊断标准[6]中的影像学诊断定义，并排除过量饮酒、病毒性肝炎、自身免疫性肝病等可导致脂肪肝的其他肝病。

具备以下 3 项腹部 B 超声表现中的两项者：①肝区近场回声弥漫性增强 ("明亮肝")，回声强于肾脏；②肝内管道结构显示不清；③肝脏远场回声逐渐衰减。

肥胖伴 MS：即肥胖 (BMI≥25kg/m^2) 且合并 MS 者。

正常对照：即体重正常 (18.5kg/m^2≤BMI<23kg/m^2) 且未合并 MS 者。

1.4 统计 统计分析采用 SPSS l3.0 软件完成。计数资料以率 (%) 表示，组间比较采用 X^2 检验，如某一格的期望值＜5，则采用 Fishers 精确概率计算法。危险度的大小用 OR 值表示。P＜0.05 认为差异具有统计学意义。

2 结果

2.1 体检人群中 MHO 合并 NAFLD 的比例

在 261 例 MHO 中，NAFLD 患者 134 例，占 51.34%；在 213 例肥胖伴 MS 中，NAFLD 患者 167 例，占 78.40%；在 538 例正常对照组中，NAFLD 患者 27 例，占 5.02%。MHO 与正常对照组相比，MHO 合并 NAFLD 的比例高 (P=0.000)；MHO 与肥胖伴 MS 相比，MHO 合并 NAFLD 的比例低 (P=0.000) (图 1)。

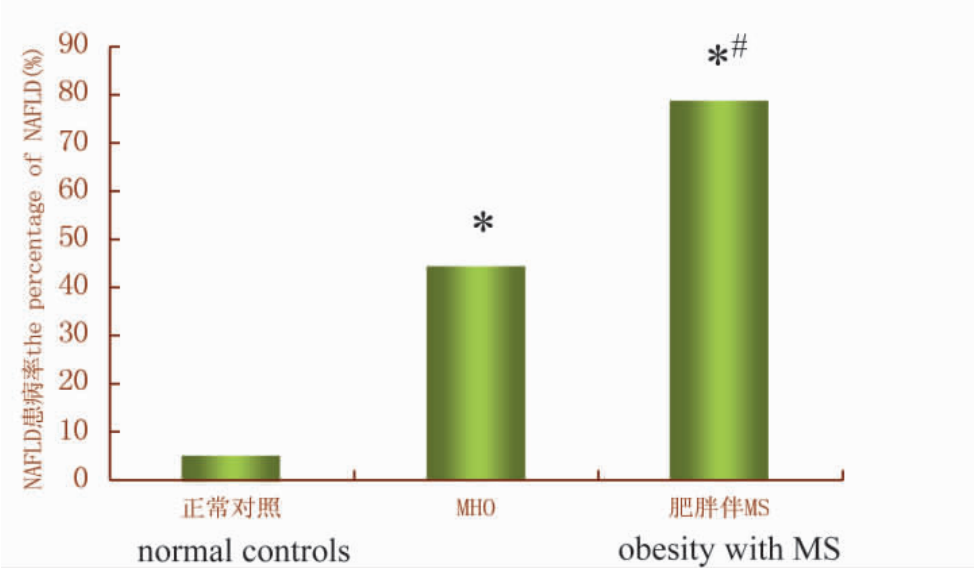

图 1 体检人群中 MHO 及肥胖伴 MS 合并 NAFLD 的比例

Fig.1 The percentage of NAFLD in MHO and obesity with MS in subjects for routine health examination

注：与正常对照组比较，*P<0.05，与 MHO 比较，#P<0.05

Note: compared with normal controls , *P<0.05, compared with MHO, #P<0.05

MHO 发生 NAFLD 的 OR 值为 19.967 (95% CI，12.646-31.533；P=0.000)；肥胖伴 MS 发生 NAFLD 的 OR 值为 68.709 (95%CI，41.414-113.995；P=0.000) (表 1)。

2.2 各组体检个体随访后发生 NAFLD 的风险

三组体检人群共 1012 例，其中 526 例在 1~3 年间再次来我院体检。随访 (13.43± 3.08 月) 后，MHO 中 45 例非 NAFLD 体检个体中，20 例新发 NAFLD，发病率为 44.44%，明显高于正常对照组，差异有统计学意义 (P<0.05)；随访 (15.69± 6.62 月) 后，肥胖伴 MS 中 20 例非 NAFLD 体检个体中，9 例新发 NAFLD，发病率为 45.00%，明显高于正常对照组，差异有统计学意义 (P<0.05)；随访 (14.47± 4.58 月) 后，正常对照组 228 例非 NAFLD 体检个体中，16 例新发 NAFLD，发病率为 7.02%；各组随访时间差异无统计学意义 (P>0.05)。MHO 新发 NAFLD 的 OR 值为 10.600，(95%CI，4.873-23.058；P=0.000)；肥胖伴 MS 中新发 NAFLD 的 OR 值为 10.841，(95%CI，3.921-29.974；P=0.000) (表 2)。

表 1 MHO 及肥胖伴 MS 发生 NAFLD 的 OR 值

Table 1 The odds ratio of the percentage of NAFLD in MHO and obesity with MS

	NAFLD(n=328)		非 NAFLD(n=684) Non-NAFLD		OR	95%可信区间 95% Confidence interval(CI)	P
	n	%	n	%			
正常对照 Normal controls	27	9.12	511	48.40	-	-	-
MHO MHO	134	20.39	127	27.32	19.967	12.646-31.533	0.000
肥胖伴 MS obesity with MS	167	70.49	46	24.28	68.709	41.414-113.995	0.000

表 2 随访 1~3 年后，MHO 及肥胖伴 MS 中发生 NAFLD 的 OR 值

Table 2 Following up for 1 to 3 years, the odds ratio of the incidence of NAFLD in MHO and obesity with MS

	随访发生 NAFLD Follow-up on the incidence of NAFLD (n=45)		随访未发生 NAFLD Follow-up on the incidence of non-NAFLD(n=248)		OR	95%可信区间 95% confidence interval (CI)	P
	n	%	n	%			
正常对照 Normal controls	16	35.56	212	85.48	-	85.48	-
MHO MHO	20	44.44	25	10.08	10.600	10.08	0.000
肥胖伴 MS Obesity with MS	9	20.00	11	4.44	10.841	4.44	0.000

3 讨论

肥胖可以导致 2 型糖尿病、动脉粥样硬化、高血压、非酒精性脂肪性肝病的发病率增加[7]，引起冠心病、脑卒中等严重后果。MHO 作为肥胖中的一种特殊亚型，被认为具有抵抗肥胖相关代谢紊乱的作用，其在肥胖人群中约占 10-30%[8-11]。目前 NAFLD 在肥胖人群中的发病率逐渐增高，NAFLD 和心血管疾病、恶性肿瘤的发生风险相关[12,13]，且被认为是代谢综合征的肝脏表现[14]。肥胖是发生 NAFLD 的最主要的危险因素，研究发现 70%的超重或肥胖患有 NAFLD[15]。MHO 作为肥胖人群中的特殊亚型，其与 NAFLD 的相关性研究报道较罕见，且尚未见 MHO 有无发生 NAFLD 风险的报道。

Messier 等[16]将 104 例久坐绝经后肥胖妇女分为 MHO 组及代谢异常肥胖组，通过比较后发现 MHO 与代谢异常肥胖者相比发生 NAFLD 的风险低。Stefan 等[17]在其研究中发现 MHO 个体与代谢异常肥胖者相比，MHO 肝脏脂肪堆积程度减少 54%。Pajunen 等[18]研究显示 MHO 与体重正常合并 MS 者相比，MHO 者肝脏脂肪百分含量低，但以上研究均未对 MHO 进行追踪随访观察。本研究发现 MHO 个体中合并 NAFLD 者比例高，占 51.34%，明显高于正常对照组（5.02%）；MHO 组合并 NAFLD 的风险较正常对照组明显增加（OR 值为 19.967），而在肥胖伴 MS 组中合并 NAFLD 的风险更高（OR 值为 68.709）。在 1~3 年的随访研究中发现 MHO 可明显增加 NAFLD 患病风险，提示 MHO 可预测 NAFLD 的发生。本研究还发现 MHO 组和肥胖伴 MS 组增加 NAFLD 的患病风险类似，提示 MHO 发生 NAFLD 的潜在危险性与伴有 MS 者一样高。肝脏是糖、脂代谢的主要场所，其承担着多种物质的合成、分解、转化等代谢过程。肥胖者常出现血清 FFA 水平升高，过量的 FFA 从脂肪组织转送到肝脏细胞，导致肝内甘油三酯增加，引起肝脏 IR[19]，促使了 NAFLD 的形成。这可能是 MHO 个体 NAFLD 高合并率及高患病风险的主要原因。此外还可能包括瘦素抵抗、肝细胞及免疫细胞的功能变化等原因，具体机制有待进一步研究。NAFLD 是否是 MHO 个体由代谢正常向代谢异常进展过程中的疾病表现？Adams 等[20]研究指出 NAFLD 是发生 2 型糖尿病、血脂异常（高甘油三酯和/或低高密度脂蛋白）、高血压的高危因素。Fabbrini 等[21]认为肝内甘油三酯含量正常的肥胖者可抵抗肥胖相关代谢合并症的出现，研究发现过多的肝内甘油三酯含量是肥胖人群代谢异常的明显标志。总体看来 MHO 与 NAFLD 之间可互相影响，但目谁因谁果尚未明确，亟待进一步研究。本研究所发现的 MHO 个体增加 NAFLD 的患病风险亦需大样本前瞻性研究加以证实并对其机制进行深入探讨。

参考文献 (References)

[1] Karelis AD, Faraj M, Bastard JP,et al. The metabolically healthy but obese individual presents a favorable infi ammation profi le [J]. J Clin Endocrinol Metab, 2005, 90:4145-4150

[2] de Alwis NM, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears[J]. J Hepatol, 2008, 48 Suppl l:S104-S112

[3] Kayoung Lee. Metabolically obese but normal weight (MONW) and metabolically healthy but obese (MHO) phenotypes in Koreans: characteristics and health behaviors [J]. Asia Pac J Clin Nutr, 2009, 18 (2): 280-284

[4] 范晶，周波，李启富，等. 肥胖特殊亚型分布及影响因素的横断面社区调查[J]. 上海医学, 2011, 34(5):345-350
Fan Jing, Zhou Po, Li Qi-fu, et al. Cross-sectional study on distribution and risk factors of special subgroups of obesity in community based-s-

ubjects[J]. Shanghai Med, 2011, 34(5):345-350(In Chinese)

[5] 中华医学会糖尿病学分会代谢综合征研究协作组. 中华医学会糖尿病学分会关于代谢综合征的建议 [J]. 中华糖尿病杂志, 2004, 12(3):156-161
Metabolic syndrome study group of Chinese Diabetes Society. Suggestions of Chinese Diabetes Society on metabolic syndrome [J]. Chin J Diabetes, 2004, 12(3):156-161(In Chinese)

[6] 中华医学会肝脏病学分会脂肪肝和酒精性肝病学组. 非酒精性脂肪性肝病诊疗指南[J]. 中华肝脏病杂志, 2010, 18(3):163-166
Fatty liver and alcoholic liver disease study group of Chinese Society of Hepatology. Guidelines for diagnosis and treatment of nonalcoholic fatty liver diseases[J]. Chin J Hepatol, 2010, 18(3):163-166(In Chinese)

[7] Lau DC, Douketis JD, Morrison KM, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children[J]. CMAJ, 2007, 176:1-13

[8] Bluher M. The distinction of metabolically 'healthy' from 'unhealthy' obese individuals[J]. Curr Opin Lipidol, 2010, 21:38-43

[9] Karelis AD, St-Pierre DH, Conus F, et al. Metabolic and body composition factors in subgroups of obesity: what do we know? [J]. J Clin Endocrinol Metab, 2004, 89:2569-2575

[10] Kuk JL, Ardern CI. Are metabolically normal but obese individuals at lower risk for all-cause mortality? [J]. Diabetes Care, 2009, 32:2297-2299

[11] Wildman RP. Healthy obesity [J]. Curr Opin Clin Nutr Metab Care, 2009, 12:438-443

[12] Sorderberg C, Stal P, Askling J, et al. Decreased survival of subjects with elevated liver function tests during a 28 year follow-up[J]. Hepatology, 2010, 51:595-602

[13] Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes [J]. Hepatology, 2006, 44:865-873

[14] Rector RS, Thyfault JP, Wei Y, et al. Non-alcoholic fatty liver disease and the metabolic syndrome: An update [J]. World J Gastroenterol, 2008, 14:185-192

[15] Caballería L, Auladell MA, Torán P, et al. Risk factors associated with non2alcoholic fatty liver disease in subjects from primary care units[J]. BMC Gastroenterology, 2008, 8: 442-491

[16] Messier V, Karelis AD, Robillard ME, et al. Metabolically Healthy but Obese Individuals:Relationship with Hepatic Enzymes[J]. Metabolism Clinical and Experimental, 2010, 59:20-24

[17] Stefan N, Kantartzis K, Machann J, et al. Identification and characterization of metabolically benign obesity in humans[J]. Arch Intern Med, 2008, 168:1609-1616

[18] Pajunen P, Kotronen A, Korpi-Hyövälti E, et al. Metabolically healthy and unhealthy obesity phenotypes in the general population: the FIN-D2D Survey[J]. BMC Public Health, 2011, 11:754

[19] Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction[J]. Eur J Clin Invest, 2002, 32(Suppl 3):14-23

[20] Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study[J]. Gastroenterology, 2005, 129:113-121

[21] Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications[J]. Hepatology, 2010, 51(2): 679-689

(上接第 2657 页)

[8] Liang XH, Jack son S, Seaman M, et al. Induction of autophagy and inhibition of tumo rigenesis by beclin 1 [J]. Nature, 1999, 402(6762): 672-676

[9] Aita VM, Liang XH, Murty VV, et a1. Cloning and genomic organization of beclin 1, a candidate tumor suppressor gene on chromosome 17 q21[J]. Genomic, 1999, 59(1): 59-65

[10] Tangir J, Muto MG, Bercowitze RS, et al. A 400 kb novel deletion unit centromeric to the BRCA1 gene in sporadic epithelial ovarian cancer[J]. Oncogene, 1996, 12(4):735-740

[11] Futreal PA, Marks JR, Marks JR, et al. Detection of frequent allelic loss on proximal chromosome 17q in sporadic breast carcinoma using microsatellite length polymorphisms [J]. Cancer Res, 1992,52(9): 2624-2627

[12] H Saito, J Inazawa, S Saito, et al. Detailed deletion mapping of chromosome 17q in ovarian and breast cancers: 2 cM region on 17q21.3 often and commonly deleted in tumors[J]. Cancer Res, 1993, 53(14): 3382-3385

[13] Gao X, Zacharek A, Salkowski A, et al. Loss of heterozygosity of the BRCA1 and other loci on chromosome 17q in human prostate cancer [J]. Cancer Res, 1995, 55(19):1002-1005

[14] Cuervo AM, Dice JF, Knecht E. et al. A receptor for the selective uptake and degradation of proteins by lysosomes [J]. Science, 1996, 273(26):501-503

[15] Ding ZB, Shi YH, Zhou J, et al. Association of Autophagy Defect with a Malignant Phenotype and Poor Prognosis of Hepatocellular Carcinoma[J]. Cancer Res, 2008 Nov 15, 68(22):9167-9175

[16] Tang H, Da L, Mao Y, et al. Hepatitis B virus X protein sensitizes cells to starvation-induced autophagy via up-regulation of beclin 1 expression[J]. Hepatology, 2009 Jan, 49(1):60-71