

脂肪性肝病的实验室诊断

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摘要

关键词: 脂肪性肝病; 实验室诊断

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0 引言

脂肪性肝病是以肝脏内脂肪蓄积为特征的一类疾病, 肝活检虽为其诊断金标准, 并可帮助疾病分类及了解病变程度, 但具有一定的创伤性, 不适合动态随访, 而且存在很大程度的取样误差^[1], 所以发展无创性影像学和实验室诊断学检查就显得尤为重要. 近年来, 通过动物实验和临床研究, 脂肪性肝病的病因、形成及临床转归得到进一步了解, 同时也建立了一些判断肝脏内有无脂肪蓄积以及肝内脂肪浸润程度、疾病严重程度、是否合并肝内炎症和纤维化的实验室监测指标, 为动态随访、反映药物疗效和疾病的预后提供了很大的帮助. 实验室指标可分成两类, 一类是影响脂肪肝形成的指标, 另一类为脂肪肝形成后所表现出的血液学指标的变化, 现从这二个方面对可能用于脂肪肝的实验室诊断

指标进行总结, 希望能给临床脂肪性肝病的诊断和治疗带来帮助.

1 影响脂肪肝形成的指标

脂肪性肝病的病理进程大致可分为2步, 脂肪在肝脏的蓄积是该病的起因. 脂肪在肝脏内沉积受多种因素的诱导, 形成了不同的实验室检测策略.

1.1 脂肪在肝脏的蓄积是脂肪性肝病形成的先决条件, 肝脏是脂肪代谢重要靶器官, 游离的脂肪酸进入肝脏, 重新酯化变成三酰甘油(TG)贮存于脂肪组织或用作肌肉能量, 游离脂肪酸也可在肝脏中以乳糜微粒残体形式存在, 然后经TG脂酶水解. 当脂肪酸代谢有利于脂质合成时, 肝内TG就会堆积. 对非乙醇性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)患者断面研究发现脂肪肝患者血清总胆固醇、TG、低密度脂蛋白胆固醇、载脂蛋白B、脂蛋白(a)及游离脂肪酸显著高于对照组, 高密度脂蛋白胆固醇及载脂蛋白A1水平低于对照组^[2-4], 餐后血脂水平高于对照^[5]. TG和高密度脂蛋白胆固醇与肝细胞内脂肪含量之间的相关系数分别为0.3和-0.35^[6], 游离脂肪酸通过激活JNK信号通路诱导肝细胞发生脂凋亡^[7].

1.2 肝脏被认为胰岛素抵抗或代谢综合征损伤的主要靶器官, 胰岛素抵抗与肝脏脂肪堆积有关^[8]. NAFLD个体空腹C肽、胰岛素、血糖、TG和尿酸增高^[3], 基础游离脂肪酸增加, 胰岛素介导-脂解抑制的有效性降低^[4,9]. 空腹血糖和空腹胰岛素与肝细胞内脂肪含量之间的相关系数分别为0.47和0.56, 多因素判别分析和多重线性回归分析发现空腹胰岛素是与其他人体测量和代谢物测量无关的预示肝细胞内脂肪含量和ALT浓度独立的预示因子^[6]. HOMA胰岛素抵抗是NAFLD的预示因子, 比数比为2.38, 95%可信限为1.52-5.74^[10]. 实验室检测胰岛素抵抗指标较多, 包括葡萄糖耐量试验、C肽/胰岛素比值、HOMA模型胰岛素抵抗评估法、定量胰岛素敏感性检测指数、葡萄糖钳夹技术等.

临床上最常用的是HOMA模型, 而最可靠的为葡萄糖钳夹技术. 对日本人群血清铁蛋白浓度与内脏脂肪(visceral fat area, VFA)和皮下脂肪(subcutaneous fat area, SFA)及肝脂肪含量的研究发现, 血清铁蛋白与肝脏脂肪含量呈负相关($r: 0.28, P < 0.0001$), 与VFA和SFA呈正相关, $r: 0.254$ 和 0.231 , 与HOMA胰岛素抵抗呈正相关($r: 0.286, P = 0.0008$), 提示血清铁蛋白浓度可作为评估系统性脂肪含量和胰岛素抵抗程度指标^[11].

1.3 大多数NAFLD患者有中心脂肪堆积^[4], 体脂增加. 增加的脂肪组织除具有储存能量的功能外, 还具有自/旁分泌功能. 瘦素、脂联素和TNF- α 是脂肪细胞分泌的对NAFLD的形成起重要作用的细胞因子. 瘦素主要是通过抑制食欲、促进外周的脂肪分解及抑制脂肪的合成来调节体脂肪的稳定^[12-13]. 同时还参与肝脏对脂质代谢的调节作用, 减少TG合成, 促进脂肪氧化. 动物实验发现, NAFLD大鼠血清瘦素水平升高、肝脏瘦素受体表达下降^[14]. NAFLD患者血清瘦素水平明显高于对照组, 脂肪肝患者瘦素水平的升高可能是瘦素产生抵抗, 致高瘦素血症^[15]. NAFLD患者的血清瘦素水平是升高的, 且与脂肪肝的发生、发展有关. 脂联素通过激活AMP激酶和PPAR γ 途经, 使得肝细胞脂肪酸氧化增加, 合成减少, 并抑制葡萄糖的生成, 从而降低肝细胞内TG和糖元含量, 改善胰岛素抵抗^[16-19]. 非肥胖NASH患者血清脂联素水平降低, 与胰岛素、TNF- α 等相比, 血清脂联素是区分坏死性炎症等级和纤维化分值高低的唯一指标^[5,9,20-21]. 血清脂联素与高密度脂蛋白胆固醇呈正相关^[10], 与TG呈负相关($r = -0.22, P = 0.04$), 空腹胰岛素负相关($r = -0.37, P < 0.01$), HOMA胰岛素抵抗负相关($r = -0.39, P < 0.01$)^[10,20]. 多重回归分析发现, 脂联素与肝脂肪变性和坏死性炎症及纤维化呈负相关, NASH患者的餐后血脂水平高于对照, 而且与空腹脂联素有关. 对照组脂肪餐后血清脂联素水平升高, 而NASH患者则表现为轻微下降, 是NASH患者肝脏脂肪变性程度的独立预示因子. 两组实验对象血清游离脂肪酸对脂肪餐后的反应与脂联素相反, 餐后脂肪代谢损伤可能是低脂联素血症、NASH及高心血管危险相联系的又一机制^[5], 低脂联素水平可能是NAFLD的预示因子^[20,22]. 多重回归分析发现, 脂联素对NAFLD有保护作用, 比数比为 0.22 , 95% 可信限为 $0.09-0.55$. 提示低脂联素血症和胰岛素抵抗与NAFLD有关^[10], 低脂联素血症是与

胰岛素抵抗无关的NASH特征, 脂联素水平降低与NAFLD肝细胞更广泛围坏死性炎症有关^[21]. 超质量儿童及NAFLD患儿的血清脂联素水平低于正常体质量儿童, 血清脂联素水平与体质量指数、胰岛素、血糖和ALT呈负相关, 提示脂联素在儿童NAFLD发病中同样起较为直接的作用^[23]. 与脂联素的生理作用相反, TNF- α 有降低胰岛素敏感性和趋炎作用. NASH患者血清TNF- α 水平高于对照^[21,24], 可溶性肿瘤坏死因子受体(soluble tumor necrosis factor receptor, sTNFR)被认为是较好的TNF- α 生成和炎症疾病严重程度的指示剂, 对NASH患者的研究发现, NASH伴明显纤维化或中等程度炎症患者的血清sTNFR水平较纤维化不明显或炎症较轻或对照高, 但sTNFR与脂肪沉积等级无关. sTNFR与NASH患者肝纤维化之间有显著相关^[25].

1.4 NASH与脂类、糖和能量代谢有关, β -肾上腺素能受体在调节能量消耗中起重要作用. 通过对251例日本男性的研究发现, β -肾上腺素能受体基因的16和27位的多态性在肥胖人群与正常人群之间无差异, 但Gly16纯合子的高密度脂蛋白胆固醇低于Arg16纯合子, Gln27Glu27杂合子的血清TG浓度高于Gln27Gln27纯合子. Gln27Glu突变杂合子脂肪肝发病率较高, 其比数比为 1.92 , 95% 可信限为 $1.01-3.68$ ^[26]. 肝脂肪病变在 β -脂蛋白缺乏血症和纯合子低 β -脂蛋白血症个体中均有报道, 肝细胞脂蛋白分泌不足, 尤其是选择性载脂蛋白B100缺乏与肝脏脂肪病变有关. 载脂蛋白B合成不足导致前 β -脂蛋白(极低密度脂蛋白)合成减少, 从而不能有效地将肝脏脂类运出^[27-31]. 对微粒体TG转运蛋白启动子区-493 G/T和锰-SOD基因1183 T/C多态性研究发现, NASH患者TG转运蛋白G等位基因和锰-SOD T等位基因携带频率较高. 转运蛋白基因启动子区G等位基因导致转运蛋白合成降低, 肝细胞的脂质输出减少, G等位基因的携带者有更大范围的肝小叶区脂肪浸润; 由T等位基因翻译的锰-SOD进入线粒体较少, 使线粒体的抗氧化损伤能力下降^[32]. 胱硫醚合成酶缺乏可导致严重的高同型半胱氨酸血症, 患者中肝脏脂肪变性较为常见. 在NAFLD患者中, 同型半胱氨酸与TG、极低密度脂蛋白胆固醇、胰岛素及胰岛素抵抗指数呈正相关, 与叶酸、维生素B12负相关. NAFLD患者血清同型半胱氨酸显著高于其他组, NASH患者血清同型半胱氨酸显著高于NAFLD患者, 血清同型半胱氨酸能显著预示NASH中坏死性炎症

相关报道

FibroTest.

的严重程度. 血清同型半胱氨酸是区分NASH和NAFLD的指标之一^[33]. 血色素沉着病是一种慢性铁超负荷状态, 多余的铁在组织内沉积, HFE基因C282Y突变与血色素沉着病有关, H63D突变本身虽然不会引起血色素沉着病, 但与C282Y突变相关联则与血色素沉着病有关. NASH患者中HFE C282Y和H63D突变的比率显著高于对照人群. 突变者的血清铁蛋白, 铁, 转铁蛋白饱和度及肝可染铁均高于无突变者. 突变者的ALT水平亦高于无突变者, 有C282Y突变者的肝纤维化程度较无突变者重^[4,34-35]. 抗胰蛋白酶是肝脏产生的蛋白酶抑制剂, 抗胰蛋白酶缺乏可引起肝脏和肺部疾病, 较常见的两个突变是S (Glu264Val)和Z (Glu342Lys)等位基因, 突变蛋白以Schiff阳性、淀粉酶抵抗包含体形式沉积在肝细胞粗面内质网, 引起肝细胞损伤. NAFLD患者携带有抗胰蛋白酶PiS等位基因的频率显著高于正常对照, 血清 α 1-抗胰蛋白酶的水平显著低于对照, 携带有抗胰蛋白酶PiS等位基因NAFLD患者血清铁蛋白水平高于其他患者, 高血压的发病率高于其他患者^[34,36-37]. TNF- α 基因启动子的多态性与其合成增加有关. 对TNF- α 基因启动子区238位和308位基因多态性分析发现, NAFLD患者238位的突变频率较对照高, TNF- α 基因启动子有突变的NAFLD患者具有较高的胰岛素抵抗指数和较严重的葡萄糖耐量受损. TNF- α 基因启动子区的多态性可能是胰岛素抵抗、NAFLD和NASH的易感基因^[38].

2 脂肪肝形成后引起的血液学改变

肝脏发生脂肪性病变时肝细胞内蓄积的脂质可直接和/或通过氧应激和脂质过氧化导致肝细胞坏死或凋亡以及炎症反应. 肝细胞膜的通透性发生改变, 细胞内成分渗出或漏出, 血液中相关成分的浓度发生变化.

2.1 1999-2002年开展的美国国家健康与营养评估调查(national health and nutrition examination survey, NHANES)发现, 排除丙型肝炎患者和酗酒者, 人群中血清ALT>716.8 nkat/L和/或AST>716.8 nkat/L者占9.8%, 较1988-1994年的调查异常率高, 但引起转氨酶升高因素与1988-1994年的NHANES相似, 主要与BMI、腰围、TG及血糖增高有关, 与非乙醇性脂肪性肝病危险因素之间存在较强的相关性^[39]. 经年龄、性别、人种和饮酒量校正后, ALT、ALP和CRP浓度处于上1/4分布者发生代谢综合征的危

险性较处于下1/4分布者显著增加相比, 高ALT发生代谢综合征的比数比为2.5 (95%可信限为1.38-4.51)、ALP的比数比为2.28 (95%可信限1.24-4.2)、CRP的比数比为1.33 (95%可信限为1.09-1.63). AST/ALT比值处于上1/4者发生代谢综合征的危险性较下1/4者显著降低, 其比数比为0.40 (95%可信限为0.22-0.74). 进一步, 经腰围、胰岛素敏感指数、急性胰岛素反应和受损糖耐量校正后, ALT和AST/ALT比值与代谢综合征发生之间的相关性仍然存在^[40]. 多元回归分析显示, 内脏性肥胖、高瘦素血症和高胰岛素血症与血清ALT增高密切相关. 与其他肝病所致转氨酶升高不同, NASH患者转氨酶升高常有如下特点: (1)通常为轻度升高, 多在正常值上限的2-3倍以内, 甚至仅为正常值范围偏高, 而5-10倍以上增高者较少见^[41-43]; (2)持续时间长, 短期内一般无明显波动, 除非能够有效控制体质量^[41-42]; (3)通常无临床症状, 鲜见肝炎相关表现; (4)与乙醇性肝病相比, NASH患者的脂肪变性程度要严重, 以ALT升高为主, AST/ALT比值小于1, 即使发生脂肪性肝硬化, 其比值亦小于1.3, 故与乙醇性肝炎两者比值通常大于2.0相鉴别^[44-45]; (5)通常合并ALP和GGT轻度至中度增高, GGT增高幅度通常大于ALP^[44-45].

2.2 脂肪变性可增加氧化应激反应, NASH患者的总抗氧化应激能力较对照低, 平均总过氧化水平和氧化应激指数要高于对照^[46-47]. 肝脏抗氧化酶活性在NAFLD患者中升高, 红细胞和血浆铜/锌SOD、谷胱甘肽过氧化物酶和促酶活性显著高于对照, 然而, 红细胞和血浆抗氧化防护并不能反映肝细胞内的过氧化反应^[48]. 胰岛素抵抗、氧化应激反应和较低程度的系统性炎症状况与儿童肥胖相关肝病有关. NASH肥胖儿童的血铁蛋白、C反应蛋白和红细胞谷胱甘肽过氧化物酶活性高于转氨酶、肝脏正常的肥胖儿童, 且NASH肥胖儿童空腹葡萄糖/胰岛素比值、铁蛋白和C反应蛋白同时异常人数占41%^[49]. 与对照相比NASH患者血浆超敏C反应蛋白、纤维蛋白原、IL-8、IL-18和TNF- α 水平和血浆纤溶酶原激活抑制因子-1活性等趋炎生化标志显著升高, 趋炎生化标志与年龄、BMI、血压、HOMA胰岛素抵抗积分、血浆TG和肝脏酶活性无关, 与内脏脂肪有关^[11,24,50]. 非肥胖NASH患者血清脂联素水平降低, 与胰岛素、TNF- α 等相比, 血清脂联素是区分坏死性炎症等级和纤维化分值高低的唯一指标^[9]. 氧应激诱导

硫氧还蛋白(thioredoxin, TRX)生成,与健康人群或单纯性脂肪性肝病患者相比,NASH患者血清TRX水平显著升高,与血清铁蛋白正相关,与肝组织铁负荷及组织学严重程度密切相关。如降低肝细胞铁负荷,血清TRX和ALT水平显著下降。铁相关的氧应激参与了NASH的病理进程,血清TRX是区分NASH与单纯性脂肪性肝病的指标之一^[51-52]。Haukeland *et al*^[53]对NAFLD患者的研究发现,NAFLD患者的血清IL-6、CC-化学因子配体2/单核细胞趋化蛋白-1(CC-chemokine ligand2/monocyte chemoattractant protein-1,CCL2/MCP-1)和CCL19水平升高,NASH患者的血清CCL2/MCP-1较单纯性脂肪性肝病患者高。NASH患者的高血清CCL2/MCP-1可能在从单纯性脂肪性肝病到NASH的转变过程中起重要作用。NASH患者的总抗氧化应激能力较对照低,平均总过氧化水平(total peroxide level)和氧化应激指数要高于对照,总过氧化水平与总抗氧化反应的比值作为氧化应激指数。在NASH患者中,纤维化分值与总过氧化水平正相关、与总抗氧化反应负相关、与氧化应激指数正相关(r : 0.607, -0.506和0.728),没有观察到坏死性炎症等级与氧化状况参数之间有相关性。结果提示NASH与氧化能力增加有关,特别是与伴肝纤维化相关^[46]。由于缺少准确的诊断NASH的临床或生化指标,排除乙醇性肝炎的诊断就很有必要。但较难获得患者的精确饮酒量,特别是女性患者。慢性酗酒的生化标志:血清AST、ALT、GGT、透明质酸、平均红细胞体积(MCV)和糖链缺乏转铁蛋白(CDT)。乙醇性肝炎患者血清AST、AST/ALT比值、GGT、CDT和MCV水平较NASH患者高,除CDT外,这些生化指标在许多NASH与乙醇性肝炎之间有交叉。NASH患者的血清CDT水平低于阈值,2.66%,乙醇性肝炎患者的血清CDT水平高于阈值。提示血清CDT水平可用于NASH和乙醇性肝炎之间的区分^[54]。

2.3 纤维化是NASH患者中常见的组织学发现,但诱导因素不清楚。NASH患者的血清透明质酸水平显著高于对照,肝硬化患者的血清透明质酸水平显著高于NASH和对照组。NASH患者和肝硬化患者血清TNF- α 和IL-8水平高于对照组,血清透明质酸与IL-8, TNF- α , ALT和AST水平缺乏相关性^[18]。血清透明质酸在不同等级的纤维化中有显著差异,且与纤维化程度显著正相关,诊断性能分析发现:血清透明质酸诊断不同程度肝纤维化的ROC曲线下的面积

为0.67,诊断中等程度肝纤维化ROC曲线下的面积为0.87,诊断严重程度肝纤维化ROC曲线下的面积为0.89,诊断肝硬化的ROC曲线下的面积为0.92。若NAFLD患者中严重程度肝纤维化的发病率20%,血清透明质酸的阈值取值46.1 ng/L,其诊断严重程度肝纤维化ROC曲线下的面积最大,灵敏度为85%,特异性为80%,阳性预示值51%,阴性预示值96%,测定NAFLD患者血清透明质酸有助于诊断严重程度肝纤维化和监测从纤维化到肝硬化转变^[55]。

NAFLD肝纤维化患者血清层黏蛋白、透明质酸、IV型胶原和谷草转氨酶水平较对照组高,层黏蛋白单项诊断性能最佳,层黏蛋白与IV型胶原组合的诊断总有效率虽然与层黏蛋白单项相同,特异性也得到提高(从89%升到100%),但诊断灵敏度从82%下降到64%,测定血清中细胞外基质成分,特别是层黏蛋白对确定NAFLD患者的肝纤维化有帮助^[56]。NAFLD患者循环抗脂质过氧化抗体IgG水平高于对照组,相同的抗体在进行性肝纤维化或肝硬化中升高。Logistic回归分析发现,抗丙二醛抗体滴度高于参考阈值的NAFLD患者较抗体滴度在参考范围的NAFLD患者有较高的进行性肝纤维化/肝硬化危险性,相对危险度比为2.82,95%的可信限为1.35-5.90, $P = 0.007$ 。提示氧化应激启动的免疫反应是NAFLD进展到明显纤维化的独立预示因子^[57]。利用肝纤维化对AST和血小板的不同作用,AST与血小板的比值即APRI积分预示严重肝纤维化和肝硬化的ROC曲线下的面积分别为0.80和0.89。APRI积分是一种简单的又相对准确的慢性肝脏疾病患者肝脏纤维化标志物^[58]。Ratziu *et al*^[59]将纤维化程度分为5级,从无纤维化到肝硬化,分别用F0到F4表示,对包含 α 2微球蛋白、载脂蛋白A1、触珠蛋白、总胆红素、 γ -GT和坏死性炎症及ALT在内的纤维化指数FibroTest在NAFLD患者肝纤维化诊断性能进行了评价,发现NAFLD患者的FT值高于对照组,其诊断NAFLD患者F3F4 ROC曲线下的面积分别为0.81-0.92,如阈值取0.3,其阴性预示值为90%,敏感性77%,如阈值取0.7,其阳性预示值为73%,特异性为98%,FibroTest是一种简单的、非侵入的、可靠地预示NAFLD患者肝纤维化的定量估价方法^[60-61]。

以上对目前常用的一些脂肪性肝病的实验室诊断指标进行了总结,随着对脂肪性肝病病理进程的进一步认识和生物技术的发展,新的

应用要点

检测手段和指标会越来越多, 如何选择诊断性能较佳的早期指标是临床和实验室所面临的新问题.

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• 消息 •

2006上海中日早期胃肠肿瘤国际研讨会通告

本刊讯 由上海市胃肠肿瘤重点学科、日本早期胃癌检诊协会、上海交通大学瑞金医院消化肿瘤学科群共同主办“2006上海中日早期胃肠肿瘤国际研讨会”将于2006-11-09/11在上海召开。

1 会议内容

由日本及香港专家主讲: 功能性消化不良和早期胃癌的临床识别; 根除*H pylori*预防胃癌研究; 内镜诊断早期胃癌的深度及组织学类型; 早期胃癌EMR、ESD及外科手术治疗; 早期胃癌和大肠癌标本处理及病理检查规范及国际共识意见; 大肠锯齿状腺瘤、大肠癌及新生癌的诊断, 外科手术及综合治疗。

由中国专家主讲: 放大内镜诊断早期胃癌; 中国早期胃癌临床现状及前景; 胃肠肿瘤腹腔镜治疗; 大肠侧向生长型肿瘤诊治; 大肠癌早期诊断及筛查; 胶囊内镜、双气囊小肠镜及小肠超声内镜诊断小肠肿瘤及临床评估。

2 征文

征文内容包括胃癌、大肠癌、小肠肿瘤基础研究、流行病学调查, 早期胃肠癌诊断及治疗。论文(电子版)按中华消化杂志格式书写附500字以内中文摘要, 欢迎网上投稿。截止日期: 2006-08-10。来稿寄至: 上海市瑞金二路197号上海瑞金医院消化科 汤美萍 (请写明2006胃肠肿瘤大会稿件), 邮政编码: 200025。联系电话: 021-64370045-665246, E-mail: wuyunlin1951@163.com。

会议将授予国家继续教育 I 类学分8分。