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文献综述 REVIEW

铁超载与非酒精性脂肪性肝病的关系及其作用机制的研究进展

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背景资料
随着肥胖在全球范围内的流行, 非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)已经成为最常见的慢性肝脏疾病, 并可以进展为肝纤维化和肝硬化等晚期肝病. 铁代谢作为机体代谢的一部分, 能够调节机体的糖脂代谢和炎症反应, 越来越多的证据显示铁超载可能参与了NAFLD的发生与发展.

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Relationship between iron overload and nonalcoholic fatty liver disease: An update

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Abstract

As a component of the multiple hits, iron overload plays an important role in the development of nonalcoholic fatty liver disease (NAFLD). Iron overload could affect glucose, lipid, energy metabolism and inflammatory reaction. This paper reviews the relationship between iron overload and nonalcoholic fatty liver disease, in order to clarify how and why iron overload influences the progression of NAFLD.

Key Words: Iron overload; Non-alcoholic fatty liver disease; Oxidative stress; Glucose and lipid metabolism

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摘要

作为多重打击的一部分, 铁超载在非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)的发生发展过程中起到重要作用. 铁超载影响机体的糖、脂、能量代谢以及炎症反应. 因此本文就铁超载与NAFLD的关系加以综述, 以期能阐明铁超载对NAFLD的代谢调节机制.

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关键词: 铁超载; 非酒精性脂肪性肝病; 氧化应激; 糖脂代谢

核心提示: 对于非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)的治疗, 目前还缺少既安全又有效的手段, NAFLD患者常伴有全身的糖、脂和铁代谢紊乱. 铁清除疗法与其他药物的联合应用可能是一种行之有效的方法.

舒祥兵, 张莉, 黄杰, 季光. 铁超载与非酒精性脂肪性肝病的关系及其作用机制的研究进展. 世界华人消化杂志 2016; 24(22): 3398-3403 URL: http://www.wjgnet.com/1009-3079/full/v24/i22/3398.htm DOI: http://dx.doi.org/10.11569/wcjd.v24.i22.3398

0 引言

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是除外酒精和其他明确的损肝因素所致的以超过5%的肝细胞大泡性脂肪变为主要病理表现的临床综合征, 包括单纯性脂肪肝和脂肪性肝炎(nonalcoholic steatohepatitis, NASH), 以及相关的肝纤维化/肝硬化甚至是肝细胞肝癌[1,2]. 普遍认可的NAFLD形成的 “二次打击”学说认为胰岛素抵抗和氧化应激是NAFLD的主要发病机制[3]. 最近比较流行的多重打击学说提示铁代谢紊乱与糖脂代谢紊乱、氧化应激、内质网应激、线粒体功能失调以及肠源性内毒素等一同参与了NAFLD的发生和发展. 铁对人体至关重要, 而肝脏不仅可以通过产生相关铁蛋白来维持全身系统的铁平衡, 还可以储存多余的铁以减轻其他脏器的负担, 然而铁超载可以加重氧应激、炎症反应和影响机体糖脂代谢, 加重肝脏负担, 所以铁超载会对肝脏产生消极影响[4]. 本文通过整理相关文献报导, 以期能够阐明铁超载在NAFLD发生与发展中的作用.

1 铁超载与氧化应激、炎症反应及糖脂代谢

1.1 铁超载和氧化应激、炎症反应 在人体中铁的吸收与转运是一个复杂的过程, 铁通过消化道完成摄取与排出, 通过呼吸道完成氧化代谢[5]. 作为主要的代谢器官, 肝脏可以通过很多途径调节铁平衡, 铁转运蛋白(Ferroportin)可以把细胞中的铁转运到循环中. 铁调素(Hepcidin)是肝脏分泌的一种肽类激素, Nemeth等[6]发现铁能够调节Hepcidin的分泌, 分泌的Hepcidin通过降解Ferroportin抑制细胞铁转出. Hepcidin控制着十二指肠铁的吸收和单核巨噬细胞系统铁的释放. 在肝脏中, 铁主要储存在库普弗细胞(Kupffer cells)中, 铁堆积能够使其活化从而产生促炎性因子, Hepcidin表达水平增高, 引起氧化应激和炎症反应, 导致细胞凋亡和坏死[7]. 同样的, 在体外培养的HepG2细胞中, 铁超载能够诱导氧化应激, 同时能够增加细胞的脂质沉积[8]. Finberg等[9]发现白介素-1(interleukine 1, IL-1)和IL-6等促炎症因子能够激活Hepcidin 的转录. Verga Falzacappa等[10]进一步研究发现IL-6可以通过IL-6/STAT3信号通路调节Hepcidin的表达, 表明炎症反应同样也可以加重肝脏的铁沉积. 当肝脏铁超载时,可以通过Fenton反应产生氧自由基(reactive oxygen species, ROS), 打破细胞的氧化还原平衡, 产生慢性氧化应激和脂质过氧化, 损伤肝细胞的DNA、脂质、蛋白和一些微小的抗氧化分子, 导致肝细胞炎性坏死和凋亡[11,12]. 同时Vecchi等[13]发现氧化应激还能够通过诱导Hepcidin的表达从而调节铁代谢, 因此铁超载、氧化应激和炎症反应是一个恶性循环, 而铁超载在NAFLD进展中起着中介作用.

1.2 铁超载和糖脂代谢紊乱 NAFLD被认为是代谢综合症在肝脏中的表现, 许多体内外研究表明铁超载能够直接影响脂代谢[14]. Graham等[15]在铁超载的小鼠中发现, 肝脏铁超载通过影响3-羟基-3-甲基戊二酰辅酶A(HMG-CoA)还原酶的转录活性, 从而增加胆固醇的合成. 与此相反的是, Brunet等[16]发现在铁超载的大鼠模型中, 虽然增加了酰基辅酶A胆固醇酰基转移酶的表达和降低了HMG-CoA还原酶的表达, 但是肝脏的胆固醇堆积并没有明显改变. 上述不同的研究结果表明许多因素可能会影响铁超载和脂代谢的关系. 由于糖异生信号通路可以通过Hepcidin调节铁代谢, 提示铁超载和糖代谢具有相关性[17], 同时Choi等[18]也发现铁超载通过影响糖异生相关基因的表达, 从而增加血糖、胰岛素抵抗和脂质堆积, 影响糖异生相关基因的表达. 也有研究发现血清铁蛋白(ferritin)和胰岛素的敏感性、胰岛素的分泌、总胆固醇以及血清甘油三酯具有相关性[19,20]. 在糖尿病患者中, 血清脂联素水平与体质量指数、血清甘油三酯和ferritin水平相关, 而血清ferritin和脂联素的关系最为密切[21]. 在脂肪细胞中, 铁能够诱

研发前沿

近年来, 随着对NAFLD发病机制的进一步了解, 铁清除(放血和螯合剂)疗法治疗NAFLD的临床研究正在逐步展开, 鉴于目前NAFLD发病机制的多样化, 铁清除疗法可能是NAFLD药物治疗的的一个有益补充.

相关报道

不同的动物和临床试验研究发现, NAFLD常伴有铁超载的发生, 不同的NAFLD动物模型, 其铁超载的表现不一样. 铁剂能够促进NAFLD向脂肪性肝炎(nonalcoholic steatohepatitis, NASH)和肝纤维化发展, 虽然NAFLD患者的日常铁摄入量明显高于正常人, 不过铁清除疗法治疗NALFD的临床研究却出现相互矛盾的结果, 铁清除疗法是否有益于NAFLD患者还存在争议.

创新盘点

本文总结了铁超载和NAFLD的关系, 以及铁清除疗法治疗NAFLD患者的临床研究报导, 阐述了铁超载调节NAFLD的作用机制, 为铁清除疗法治疗NAFLD提供理论和临床依据.

导胰岛素抵抗和抑制脂肪分解[22,23]. 在HepG2细胞中, 游离脂肪酸(free fatty acid, FFA)和铁剂刺激可以增加细胞的脂质堆积和影响脂肪酸β氧化相关基因的表达, 当铁超载改善时, 能够通过AKT/PKB(protein kinase B)信号通路增加胰岛素受体的活性, 改善糖代谢紊乱[24]. 对5位不伴有糖尿病的遗传性血色病患者的临床研究也发现, 改善铁超载, 可以增加胰岛素的分泌[25].

2 铁超载和NAFLD的关系

2.1 铁超载与NAFLD动物模型 在methionine-and choline-deficient(MCD)加铁剂诱导的铁超载NAFLD大鼠模型中, 与正常饮食大鼠相比, 虽然其肝脏脂肪堆积和脂质过氧化产物降低, 但是其肝脏坏死性炎症和中央静脉周围纤维化水平明显增加[26]. 在db/db小鼠中, 给予铁剂可以诱导肝脏氧化应激、免疫细胞的活化以及肝脏气球样变性, 从而导致NASH的发生[27]. Meli等[28]随后在高脂饮食诱导的铁超载NAFLD大鼠中发现, 与正常饮食大鼠相比, 其血清转铁蛋白饱和度、ferritin及Ferroportin水平明显降低, 并伴随着血清Hepcidin、肝脏铁堆积、肝脏炎症及氧化应激水平的升高. 在高脂高能量饮食模型中, 同样伴随着铁代谢的紊乱, 进一步分析发现, 肝脏铁超载和胰岛素抵抗相关[29]. 同样的, 在胆碱缺乏饮食小鼠中, 其血清Hepcidin和Ferroportin水平呈负相关, 且铁堆积和肝脏脂肪变性相关[30]. Shpyleva等[31]进一步发现在MCD诱导的NASH模型中, 不同的动物品系会导致铁超载动物模型的相关特性有差别.

2.2 铁超载与NAFLD患者 肝脏铁是产生氧化应激的原料并能导致肝细胞功能的损伤, 尽管铁超载和NAFLD的关系还存在争议[32-34], 但是很多研究发现铁超载和NAFLD的发生发展密切相关[35,36], 一项大样本的临床研究发现, 与正常人相比, NAFLD患者的日常铁、血红素铁和非血红素铁的摄入量明显升高, 进一步分析发现, 日常过多的铁和血红素铁的摄入是NAFLD的危险因素[37]. 血清铁反应了人体铁的储存, 其升高预示着铁超载的发生[38]. 有研究发现, 在NAFLD患者中, 有30%患者的血清ferritin水平升高, 且与血清ferritin正常的NAFLD患者比, 血清ferritin升高的NAFLD患者的血清谷丙转氨酶(almandine aminotransferase, ALT), 谷草转氨酶(aspartate aminotransferase, AST)以及谷氨酰转肽酶(galactosyl glucosyl transferase, GGT)水平明显升高, 肝脏脂肪变性、玻璃样变等更加严重, 同时血清ferritin可以作为NAFLD患者向NASH和纤维化进展的独立预测指标[39,40]. 对299例伴有和不伴有代谢综合征的NAFLD患者的研究虽然发现血清铁和ferritin在这两组患者之间没有明显差异, 但是在NAFLD患者中, 血清ferritin和ALT及AST水平呈正相关[34]. Radmard等[35]发现与肝酶水平低的男性NAFLD患者比, 肝酶水平高的的男性患者铁堆积更加明显, 然而在女性患者中, 并没有发现这种相关性. 此外, 肝脏铁超载能够加重肝脏损伤, 增加NAFLD进展为肝纤维化的风险[41,42]. Sorrentino等[43]进一步发现在NAFLD相关的纤维化患者中, 肝脏铁超载还与肝细胞肝癌的进展有关. 除了血清ferritin, 高Hepcidin水平同样能够导致铁超载的发生. 与正常人相比, NAFLD患者的尿液和肝脏Hepcidin的基因表达水平明显升高, 且两者的水平与肝脏铁堆积的程度相关[44]. 同时Aigner等[45]发现NAFLD患者的肝脏铁转出相关蛋白的表达明显降低, Hepcidin的基因水平明显升高, 高Hepcidin水平与肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)及肝脏铁堆积相关. 表明增加Hepcidin的生成可以导致肝脏铁转出障碍, 从而诱导肝脏铁堆积. 冯烨等[46]对60例NAFLD患者的相关性分析发现铁超载并不与NAFLD发生直接联系, 铁超载可能通过炎症为中介引起脂质过氧化异常和脂代谢紊乱来影响NAFLD的发生与发展. 上述研究提示铁超载介导的氧化应激和炎症反应等与其他因素共同作用于肝脏, 导致NAFLD的发生和发展[47].

2.3 铁清除与NAFLD的治疗 有研究发现在HepG2细胞和大鼠肝脏中, 螯合剂作为一种有效的铁清除剂能够增加糖的吸收和利用, 进而活化胰岛素信号通路, 增加胰岛素的敏感性[24]. 此外, 放血疗法也能够降低血清ferritin, 转铁蛋白饱和度, TNF-α水平和肝脏铁堆, 从而改善肝功能[45]. 在NAFLD合并糖耐量损伤的患者中, 1 mo的放血疗法诱导的铁清除能够改善患者的空腹血糖、肝功能和增加胰岛素的敏感性[48]. Valenti等[49]对198例没有合并糖尿病的NAFLD患者的研究同样发现6-8 mo的放血疗

法可以改善胰岛素抵抗和肝功能. 日本一项研究发现放血疗法在没有降低患者体重的情况下, 不仅可以明显改善NASH患者的肝功能, 同时并没有发现任何明显的不良反应[50]. 一项对38例NAFLD伴有高铁蛋白血症患者的随机对照研究也发现, 与生活方式调节相比, 放血疗法可以明显改善患者的肝功能和糖耐量[51]. 然而, 在另一项研究中, 4 mo的放血疗法虽然可以改善NAFLD患者的血清ferritin、转铁蛋白饱和度及胰岛素抵抗, 但对肝功能和体重则没有明显影响[52]. 最新一项随机对照研究也发现虽然6 mo放血疗法可以明显降低NAFLD患者的血清ferritin水平, 但是并不能改善患者的肝功能、肝脏脂质堆积和胰岛素抵抗[53]. 上述不同的研究结果表明, 铁清除疗法对NAFLD患者是否有疗效还存在争议, 但是针对合并铁超载的NAFLD患者, 铁清除疗法不失为一种行之有效的改善NAFLD的治疗手段, 由于不同种族和人群的NAFLD患者表现出不同的临床特性, 所以必须把握适量和个性化治疗的原则, 以免造成贫血、组织缺氧等其他问题. 特别需要注意的是, NAFLD合并心脏损伤的患者应更加注意放血疗法可能带来的不良反应.

3 结论

肝脏铁超载作为铁代谢紊乱在肝脏中的表现, 能够增加氧化应激、炎症反应和影响糖脂代谢, 提示铁超载可能与NAFLD的发生发展密切相关. 到目前为止, 虽然铁超载和NAFLD的关系还存在争议, 但是许多临床研究表明, 铁清除治疗能够改善NAFLD患者肝功能和糖代谢紊乱. 虽然NAFLD患者并不全部表现为铁超载, 但是糖、脂质等能量代谢过程中始终伴随着铁代谢的动态平衡. 因此在NAFLD的早期就注意改善铁超载可能是有效防范单纯性脂肪肝向NASH、肝纤维化、肝癌转变的切入点, 铁清除疗法对NAFLD的防治可能是一个有益的补充.

应用要点

铁清除疗法作为NAFLD治疗的方法之一, 可能更适用于伴有铁超载的的NAFLD患者. 由于不同的NAFLD患者表现出不同的临床的特点, 临床应用时须把握适量和个性化原则, 以免造成贫血等不良反应.

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名词解释

铁超载: 又称铁负荷过多, 是指由于铁的供给超过铁的需要, 而引起体内总铁量过多, 广泛沉积于人体一些器官(尤其是心脏、肝脏)和组织的实质细胞, 常伴有纤维组织显著增生, 导致多脏器功能损害. 按发病原因的不同, 铁超载分为原发性(遗传性血色病)、继发性和局限性三类.

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同行评价

本文对于铁超载与酒精性脂肪肝目前研究进展详述, 选题内容新颖, 反应了目前该领域的前沿热点和研究深度. 引用文献较全面, 资料较为详实, 结构层次合理.

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