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高尿酸血症与非酒精性脂肪肝病相关性研究进展

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[摘要] 非酒精性脂肪肝病与代谢综合征密切相关, 越来越多的证据表明高尿酸血症(hyperuricemia, HUA)参与非酒精性脂肪肝病的发生、发展。本文将重点阐述HUA与非酒精性脂肪肝病的相关性及可能的发病机制, 提出控制HUA可能成为NAFLD治疗的手段之一。

[关键词] 高尿酸血症; 非酒精性脂肪肝病; 发病机制

Research progress in correlation between hyperuricemia and non-alcoholic fatty liver disease

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Abstract Non-alcoholic fatty liver disease (NAFLD) tightly linked to metabolic syndrome (MS), a large number of evidence suggests that hyperuricemia involved in the occurrence and development of NAFLD. This article will focus on the correlation of hyperuricemia and NAFLD, and possible pathogenesis. Control of hyperuricemia is expected to become one of the therapies for treatment of NAFLD.

Keywords hyperuricemia; non-alcoholic fatty liver disease; pathogenesis mechanism

非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)是指除过量饮酒和其他明确的损肝因素外所致的肝细胞内脂肪沉积。目前NAFLD已经成为慢性肝疾病的主要原因, 我国NAFLD患病率已达26%^[1]。NAFLD与肥胖、血脂异常、糖尿病、胰岛素抵抗等代谢综合征各组分密切相关^[2]。

尿酸作为嘌呤代谢的终产物主要由细胞代谢分解的核酸和其他嘌呤类化合物以及食物中的嘌呤经酶的作用分解而来。人体中尿酸80%来源于内源性嘌呤代谢, 20%来源于富含嘌呤或核酸蛋白食物。尿酸排泄和分泌的失衡可导致高尿酸血症

(hyperuricemia, HUA)^[3-4]。近年来HUA的发病率逐渐升高, 在中国的患病率为13%~25%^[5]。HUA不仅是痛风的病理基础, 而且与高血压、肥胖、胰岛素抵抗、动脉粥样硬化密切相关^[6]。有研究^[7]表明: 尿酸参与NAFLD的发生发展, 两者相互影响。本文就HUA与NAFLD相关性的研究进展进行阐述, 提出管理尿酸水平可能延缓NAFLD的进展。

1 HUA 与 NAFLD 相关性

近年来大量研究表明HUA与NAFLD相关。一

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项来自中国对27 615名成人体检者的横断面研究^[8]表明：超声诊断的NAFLD患病率为27.1%，其中男性患病率37%，女性患病率16.8%，HUA患病率为19.6%，男性高于女性。HUA组NAFLD患病率高于正常血尿酸组(52.8% vs 20.9%，P<0.001)。血尿酸水平与男性、年龄、BMI、收缩压、舒张压、空腹血糖、三酰甘油、TC、LDL-C、ALT、AST及Scr呈正相关，与HDL-C呈负相关^[8]。一项来自美国的第三次全国健康和营养调查^[9]也得出相似结论。

为进一步研究HUA如何影响NAFLD的发生，一项来自中国社区的1 365名肥胖人群研究^[10]提示：血尿酸水平与NAFLD发病率呈独立线性关系，并且血尿酸水平在正常范围内该关系也成立。血尿酸水平可能是通过直接增加空腹血糖、血压、TG及减少HDL-C增加NAFLD发病率。最近一项来自上海某社区的中老年的横断面研究^[11]显示：肝脂肪含量与血尿酸水平呈正相关，并且是血尿酸水平升高的独立危险因素，LFC超过10%与血尿酸水平的升高及HUA发病率相关。

NAFLD主要发生在肥胖患者，但是最近的研究^[12]发现：正常体重者NAFLD发病率并不少见。那么非肥胖者血尿酸水平与NAFLD是否有关联呢？一项来自中国4 098名成年人的横断面研究^[13]显示：超声诊断肥胖者NAFLD患病率39.51%，非肥胖者NAFLD患病率14.88%，随着血尿酸水平升高，比起肥胖患者(BMI ≥ 25 kg/m²)，非肥胖者(18.5 kg/m² ≤ BMI < 25 kg/m²)有着更高的NAFLD发病率。

通过成人血尿酸水平与NAFLD病理组织学的关系研究发现：血尿酸水平与脂肪变性的严重程度密切相关，相比血尿酸水平正常者，HUA患者小叶炎症更加严重，NAS评分更高，而纤维化、气球样变及脂肪变性无明显区别，logistic回归分析^[14]显示：控制铁蛋白、ALT、AST后，HUA与进展的小叶炎症独立相关。一项来自意大利的研究^[15]也表示：随着血尿酸水平升高，小叶炎症更加严重。

尿酸水平每升高1 mg/dL，NAFLD的发病率大约升高1.03倍^[16]，前瞻性研究结果表明，高的血清尿酸基线水平是肝脂肪变性的独立危险因素^[17]。

2 HUA 影响 NAFLD 的可能机制

大量临床研究^[18-19]表明HUA与NAFLD、代谢综合征、胰岛素抵抗、氧化应激、NOD样受体蛋

白3(NOD-like receptor protein 3, NLRP3)密切相关。但目前HUA影响NAFLD发生的机制尚未明确，可能通过以下几个方面起作用。

2.1 氧化应激及内质网应激

Lanaspa等^[20]提出HUA可促进线粒体氧化应激导致肝脏脂质合成，将HepG2暴露在不同浓度的尿酸中72 h，随着尿酸浓度的升高，TG的含量逐渐升高，为进一步研究尿酸如何刺激脂肪合成，将HepG2在高浓度的尿酸中暴露24 h，发现尼克酰胺腺嘌呤二核苷酸磷酸氧化酶4异位到线粒体，导致超氧化物产生(ROS)及线粒体形态和功能改变，继而顺乌头酸酶失活，柠檬酸盐释放到细胞质，激活ACC及FAS等脂肪合成酶，导致脂质从头合成途径增加。

内质网应激被认为是NAFLD脂肪聚集的机制之一^[21]。有研究^[22-23]报道：在糖尿病小鼠中，调节内质网应激可改善肝脂肪变性，同时伴随着糖代谢紊乱的修复及胰岛素敏感性的提高。Choi等^[24]发现尿酸诱导内质网应激，激活PERK-eIF2- α ，信号通路，增加ATF6介导的XBP-1mRNA剪切，在HepG2和老鼠的肝原代细胞中，尿酸通过内质网应激激活SREBP-1导致脂质合成相关酶的表达，促进肝脂质沉积，而加入抑制尿酸进入细胞的药物丙磺舒后，可抑制激活内质网应激相关的标志物，此外，该研究发现氧化应激与内质网应激有相互交联作用，在肝细胞中，尿酸诱导的氧化应激先于内质网应激发生。

2.2 胰岛素抵抗

有文献^[25]报道：尿酸可能通过降低内皮细胞NO水平导致胰岛素抵抗。一项动物实验模型^[25]表明：相对正常饮食的老鼠，高尿酸饮食的老鼠胰岛素敏感性明显下降，糖代谢受损，同时血TG及肝内TG的水平升高。进一步研究发现：在肝细胞、骨骼肌细胞及脂肪细胞中，HUA通过增加胰岛素受体底物(insulin receptor substrate, IRS)1-丝氨酸磷酸化，减少AKT-丝氨酸磷酸化、来抑制AKT对胰岛素的反应，从而导致了胰岛素抵抗，同时上述现象在HepG2细胞中也成立，而加入丙磺舒或抗氧化剂(N-乙酰半胱氨酸)后，可减少细胞内脂肪的聚集，改善胰岛素信号通路^[26-27]。

2.3 NLRP3 炎性小体

NLRP3炎性小体是细胞内的大分子蛋白复合物，可以被病原和危险相关的分子模式识别

和激活，导致促炎症因子和促纤维化因子(IL-18和IL-18)的分泌。它在肥胖及胰岛素抵抗中起重要作用，并且与脂代谢紊乱、肝细胞脂质聚集有关^[28]。有研究^[29-30]表明：尿酸、升高的ROS可激活NLRP3炎性小体。黄嘌呤氧化酶(xanthine oxidase, XO)是调节尿酸生产的关键酶，同时XO的生成还伴随着ROS的产生^[31]。文献[32]报道：XO活性在NAFLD患者中显著升高；国内的一项研究^[33]显示：尿酸在体内外都可以诱导NLRP3炎性小体的激活，在HepG2细胞中敲除NLRP3炎性小体能明显的减少尿酸诱导的脂质沉积，同时敲除NLRP3炎性还能显著减轻游离脂肪酸(free fatty acid, FFA)诱导的HepG2细胞脂质沉积。敲除XO表达可显著降低FFA诱导的HepG2细胞中尿酸生产及ROS含量，并且可以抑制NLRP3炎性小体的激活。此外该研究发现：腺氨酸活化蛋白激酶/活性氧簇(AMPK/ROS)通路及NF-κB通路不参与尿酸对NAFLD的作用。由此得出，XO通过调控尿酸生产诱导肝细胞脂质沉积是通过NLRP3炎性小体信号通路。另外该研究^[33]发现：抑制NLRP3炎性小体的关键分子NLRP3后，HUA导致IRS丝氨酸磷酸化升高受到抑制，胰岛素信号通路分子AKT丝氨酸磷酸化下降有部分回升，提示NLRP3炎性小体激活参与尿酸诱导的胰岛素抵抗。

最近的一项研究^[34]表明：磷脂酶的干扰以及嘌呤核苷酸、肝X受体、维甲酸X受体的降解在HUA患者NAFLD的进展中起重要作用，同时该研究显示：磷脂酸、胆甾醇酯的上调以及次黄嘌呤核苷酸的下调导致了氧化应激及胰岛素抵抗。

总之，尿酸通过多种方式影响NAFLD的发生、发展，目前需要更多的证据来表明降低HUA对NAFLD的益处。

3 HUA与其他疾病的关系

近年来，HUA与其他疾病的关系也逐渐成为研究的焦点。有研究^[35]证明：尿酸是心血管事件的独立预测因素。并且用别嘌呤醇治疗HUA后可改善心血管疾病的预后^[36]。Liang等^[37]提出尿酸通过抑制NO合成以及激活RAS系统导致高血压，反过来，高血压可增加尿酸重吸收导致HUA。国内学者^[38]发现：在小鼠模型中，别嘌呤醇可减轻果糖诱导的HUA，足突细胞损伤以及尿蛋白含量。Prasad等^[39]发现绝经后妇女的血管内皮损害与血尿酸水平的升高独立相关，在血管内皮损害的绝经后妇女中，血尿酸水平越高，炎症标志物(CRP，

中性粒细胞)越高。最新一项研究^[40]表明：在调整了年龄、性别、肥胖、抗高血压药物治疗或使用利尿剂等混杂因素后，血尿酸水平与CRP、纤维蛋白原、铁蛋白、补体C3、红细胞沉降率等炎性指标呈正相关。体外研究^[40]发现：HUA可能通过激活IκB激酶/IκBα/NF-κB信号通路诱导炎症分子表达，这种作用可以被苯溴马隆减弱，并且在N-乙酰半胱氨酸干预下，尿酸的作用被完全阻断。

4 结语

HUA在NAFLD发生、发展中的作用为控制HUA治疗NAFLD提供了依据。在NAFLD动物模型中，予以别嘌呤醇和苯溴马隆降尿酸治疗后，血尿素水平降低，肝脂肪变性也得到改善^[41]。最近国内学者^[42]提出HUA与NAFLD异病同治的规律及分子机制，发现中药配伍(丹参、大黄、茯苓、泽泻、当归、白术)是治疗两病使用最多的药物，这些药物是通过调控5个重要分子(26S酶体，ERK1/2，NF-κB，AKT和UBC)和一个生物学通路(LXR/RXR通路)对两病发挥协同治疗效应。目前尚需进一步的研究阐明HUA参与NAFLD的发病机制，管理血尿酸水平有望成为NAFLD治疗措施之一。

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