非酒精性脂肪性肝病与维生素D关系研究进展

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[摘要] 随着我国经济快速发展,居民的饮食结构、生活方式的改变,非酒精性脂肪性肝病(nonalcoholic fatty liver disease,NAFLD)的发病率也呈明显上升趋势,且发病年龄呈年轻化趋势。因此,了解NAFLD的发病机制对于防治该病具有重大的现实意义。目前大量的研究表明,NAFLD的发病机制十分复杂,维生素D(vitamin D,VitD)参与NAFLD的发病机制受到业界的高度关注。本文就VitD在NAFLD的发病机制及作用做一系统综述,为早期诊治NAFLD提高新策略。

[关键词] 非酒精性脂肪性肝病;维生素D;相关研究

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Advances in research on the relationship between nonalcoholic fatty liver disease and vitamin D

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[**Abstract**] With the rapid development of economy, the dietary structure and lifestyle of Chinese residents have changed. As a result, the incidence of non-alcoholic fatty liver disease has also shown a significant upward trend, and the age of onset is showing a younger trend. It has brought new challenges to the prevention and treatment of this disease in China. Therefore, understanding the pathogenesis of non-alcoholic fatty liver disease is of great practical significance for the prevention and treatment of the disease. At present, a large number of studies have shown that the pathogenesis of non-alcoholic fatty liver disease is very complicated, but the pathogenesis of vitamin D in non-alcoholic fatty liver disease has received great attention from the industry. In view of this, this article makes a systematic review of the pathogenesis and role of vitamin D in non-alcoholic fatty liver disease, so as to improve new strategies for the early diagnosis and treatment of non-alcoholic fatty liver disease.

[**Key words**] Nonalcoholic fatty liver disease(NAFLD);Vitamin D(VitD);Related research

非酒精性脂肪性肝病(nonalcoholic fatty liver disease,NAFLD)是指以肝细胞脂肪变性和脂质沉积为特征的临床病理综合征,其后期可出现肝硬化、肝功能衰竭及原发性肝癌等一系列肝脏损害的临床表现,并与心血管疾病、糖尿病、慢性肾脏病、阻塞性睡眠呼吸暂停综合征及胃肠道肿瘤的发生密切相关,严重危害人类健康[1]。据一项荟萃分析统计发现,NAFLD在全球患病率高达25.24%,患病率最高的地区是中东(37.19%)和南美洲(30.45%),其次是亚洲(27.17%)、北美洲(24.13%)、欧洲(23.17%)和非洲(13.48%)[2]。随着我国经济发展,居民生活方式的改变,NAFLD患者的增加已成为主要的公共卫生问题之一。有研究指出,我国NAFLD的患病率高达29.2%,这提示防治该病面临严峻形势[3]。目前,有关NAFLD的发病机制至今仍不明确,但近年来大量的研究表明(vitamin D,VitD)的抗炎、抗氧化以及抗纤维化作用参与了NAFLD的发生和发展,补充VitD也可以辅助治疗NAFLD[4]。本文就VitD与NAFLD的相关关系做系统综述,为临床医师初步了解VitD在NAFLD的作用价值提供参考依据。

1 VitD缺乏与NAFLD的相关性

越来越多的实践研究证据发现,VitD缺乏与NAFLD具有一定的相关性。Stein等[5]在动物实验研究中发现血清25-羟维生素D[25(OH)D]水平下降不仅会使体质指数增加,而且会导致缺乏VitD肥胖大鼠的NAFLD进展加快。同样有学者研究也发现,血清低VitD水平与NAFLD发病相关。黄金华等[6]发现NAFLD患者存在25(OH)D缺乏,且低25

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(OH)D水平与NAFLD显著相关。Wang等[7]也同样发现,NAFLD受试者的25(OH)D水平降低,VitD缺乏患者患有NAFLD的风险高于VitD水平正常的人群。另外研究还发现,NAFLD肝纤维化的发生和发展与血清25(OH)D关系紧密。血清25(OH)D水平越低,老年NAFLD肝纤维化程度越高[8]。

2 VitD的来源、代谢及生理作用

人体的VitD来源可以分为两条途径:①内源性途径(主要来源),其合成途径是人体皮肤被紫外线照射以后,皮肤中7-脱氢胆固醇经光化学作用转化为$VitD_3$;②外源性途径(次要来源),通过人体摄取一些含钙丰富的食物,如动物肝脏、蛋黄、牛奶等。$VitD_3$经过肠道淋巴管吸收进入人体血液循环,皮肤合成的$VitD_3$直接进入血液循环,再通过血浆中的VitD结合蛋白(vitamin D binding protein, VDP)结合被转运到肝脏,在肝脏内被25-羟化酶羟基化合成25-羟基维生D_3(25-OHD_3),后者与α球蛋白结合后转运至肾脏,经1-羟化酶再次羟化合成1,25(OH)$2D_3$。1,25(OH)$2D_3$与VitD受体(vitamin D receptor,VDR)结合最终发挥生物学效能[9]。VitD通过在肝脏表达的VDR介导细胞内信号[10]。据不完全统计,VDR参与调节超过200个基因,包括葡萄糖和脂质代谢、炎症、细胞增殖与分化和凋亡[11]。Barchetta等[12]发现,人类肝脏VDR表达和NAFLD组织学严重程度负相关,独立于其他代谢参数,如体质指数(BMI)、胰岛素抵抗或脂联素。因此,VitD在NAFLD中发挥的独特作用机制为进一步干预该病的发生具有一定的价值。

既往的研究表明,VitD的生理作用主要是参与血钙及骨盐代谢稳态的调节。VitD主要用于组成和维持骨骼的强壮。其被用来防治儿童的佝偻病、成人的软骨症及关节痛等。患有骨质疏松症的人通过添加合适的VitD和镁可以有效的提高钙离子的吸收度。最近的研究表明VitD有广泛而十分重要的生理作用,VitD缺乏与冠心病、慢性阻塞肺疾病、支气管哮喘、糖尿病及恶性肿瘤有关[13-17],由此可见,VitD具有十分广泛的作用,值得引起研究者的关注及深入探讨。

3 NAFLD的经典发病机制

目前世界上公认的NAFLD的发病机制是“多次打击”理论[18]:第1次打击是胰岛素抵抗主导的肝脏脂肪蓄积和肝脏细胞变性;第2次打击是各种氧化代谢产物。在脂肪细胞因子、脂质过氧化、炎症因子等参与下,导致脂肪变性的肝细胞发生炎症、坏死甚至纤维化;第3次打击是肝脏免疫系统紊乱导致肝脏纤维化、肝硬化。近年大量的研究表明VitD参与了NAFLD的发病和发展。因此,研究清楚VitD参与NAFLD的发病机制具有重要的临床意义。

4 VitD在NAFLD发病机制中的作用

4.1 VitD参与免疫炎症反应影响NAFLD的发病机制 研究表明,低水平VitD作为独立因素加重NAFLD的脂肪变形、组织炎症及纤维化的程度[19]。VitD在抑制免疫炎症的途径可能有调节自噬功能、降低氧化应激、减少白细胞分化和激活[20-22]。VitD可以增强保护性固有免疫反应和调节适应性免疫性反应[23-24]。具体分3个途径:①VitD可以通过直接或间接作用影响T淋巴细胞、树突状细胞和巨噬细胞来调节免疫应答。VitD影响T淋巴细胞的作用主要是调节Th1细胞(分泌IL-2)和Th2细胞(分泌IL-4,IL-5)的增值分化。②VitD能抑制Th-17细胞分泌促炎因子IL-17,进而降低炎症反应[25]。③树突状细胞(dendritic cells,DC)作为抗原提呈细胞,在启动$CD4^+$T细胞应答方面发挥重要作用,而VitD作用于DC,是通过抑制其分化产生炎症因子(如IL-12)发挥抑制炎症反应作用的。另外,其它一些炎症因子也在NAFLD中发挥一定的作用。如核因子-κB (nuclear factor-κB, NF-κB) 是一种细胞核转录因子,在动物实验中发现高脂饮食或蛋氨酸与胆碱缺乏饮食诱导的NAFLD小鼠肝脏组织中,均发现NF-κB的表达增加[26-27]。Crespo等[28]在肥胖型非酒精性肝炎患者的研究中发现,非酒精性肝炎患者肝脏TNF-α及TNF-α受体的基因表达增加,且与肝脏炎症严重程度相关。因此,未来的药物研发可以通过靶向干扰发病的一个或多个环节,为治疗全球发病率最高的NAFLD治疗带来新突破。

4.2 VitD参与胰岛素抵抗影响NAFLD发病机制 有文献报道,几乎所有NAFLD患者的周围组织和肝脏均存在胰岛素抵抗,且不一定伴有糖耐量异常或者肥胖,其严重程度与NAFLD的病情进展有关[29]。因此,胰岛素抵抗参与了NAFLD的发生发展,其在NAFLD的具体发病机制有可能是不同的。有研究证实,通过补充VitD可以改善胰岛素抵抗,提高胰岛素敏感性。1,25(OH)$2D_3$可以直接抑制3T3-L1前体脂肪细胞向脂肪细胞的分化,从而发挥其抗脂肪形成的作用,减少周围组织的胰岛素抵抗[30]。Maestro等[31]对U-937人幼单核细胞的研究发现,1, 25-(OH) $2D_3$ (1×10^{-8} mmol/L) 可增加人胰岛素受体基因转录活性,强化了胰岛素对葡萄糖的氧化作用,改善胰岛素抵抗。Norman等[32]研究发现,VitD缺乏影响胰腺β的胰细胞岛素分泌功能而影响胰岛素抵抗。总之,VitD及其活性成份能抑制脂肪细胞分化形成、增加胰岛素受体基因转录活性及影响胰细胞岛素分泌功能等,从而改善胰岛素抵抗作用。

4.3 VitD参与肠道菌群影响NAFLD发病机制 肠道菌群是人体最复杂而微妙的微生态系统,在人体中发挥着免疫保护、吸收营养、维持肠道黏膜屏障、防癌抗癌等重要作用[33],调控着人体的能量代谢和脂肪沉积,进而会影响相关代谢性疾病的发生发展[34]。肠道菌群失调会导致代谢综合征和NAFLD的发生,而VDR在回肠中高表达。因此,VitD通过调节肠道微生态来影响NAFLD的发生,具体机制是由VitD与VDR结合上调小肠潘氏细胞特异性的α-防御素5、小肠紧密连接相关基因的表达、调节肠道菌群屏障完整性,实现肠道微生态系统菌群的多样性[35]。可见,VitD是通过参与肠道微生态稳态而参与到影响NAFLD发病过程中。因此,未来有待进一步深入研究VitD和肠道菌群是如何协同调控代谢性疾病的发生发展。

5 补充VitD对NAFLD患者的影响

有流行病学研究证实,NAFLD患者相比一般人群而言,更容易缺乏VitD,且游离VitD水平与肝脏纤维化程度成正比[36]。研究表明,补充日常剂量VitD可以改善NAFLD患者的胰岛素抵抗并对心血管系统有积极作用[37-38]。Della Corte等[39]对NAFLD患儿的单中心研究发现,VitD可改善NAFLD患儿胰岛素抵抗、脂质代谢,降低肝星状细胞活性与纤维状胶原含量,表明VitD可能对NAFLD患者具有潜在治疗作用。也有研究与上述报道结论相反,认为低风险与高风险的NAFLD患者VitD水平之间没有差异,不会影响到NAFLD[40]。由此可见,补充VitD是否对NAFLD患者有影响仍然存在一定的分歧,有待未来开展更高质量的循证医学证据进一步阐明两者关系。

6 小结与展望

目前,有大量文献报道VitD在NAFLD发病机制中发挥着一定的作用,同时也受到越来越多业界学者们的关注,但是具体发病机制仍然不是很明确。另外,通过补充VitD对于防治NAFLD的发生作用也存在争议,但这些研究对于未来深入了解VitD在NAFLD的作用具有重要意义。随着VitD参与NAFLD发病机制的研究不断深入,VitD将在防治NAFLD中发挥越来越重要的临床价值。

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（上接第349页）

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