乙型肝炎病毒相关肝性骨营养不良发病因素研究进展

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摘要：乙型肝炎病毒（hepatitis B virus，HBV）感染是我国慢性肝病最常见的病因。随着患者预期寿命的普遍延长，肝性骨营养不良（hepatic osteodystrophy，HOD）已成为HBV相关肝病的常见并发症。为进一步认知和防治HBV相关HOD，本文就HBV相关HOD的发病风险和潜在因素（炎症因子、人口学特征、营养状态、疾病演变、抗病毒药物）等进行综述。

关键词：肝炎病毒；乙型；肝性骨营养不良；发病因素

Research progress on the etiology of hepatitis B virus-related hepatic osteodystrophy

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Abstract: Hepatitis B virus (HBV) infection is the most common cause of chronic liver disease in China. With the general increase of patient life expectancy, hepatic osteodystrophy (HOD) has become a common complication of HBV-related liver disease. To further understand and prevent HBV-related HOD, this article reviewed the risk factors and potential causes of HBV-related HOD, including inflammatory factors, demographic characteristics, nutritional status, disease progression, and antiviral medications.

Keywords: Hepatitis B virus; Hepatic osteodystrophy; Etiology

乙型肝炎病毒（hepatitis B virus，HBV）感染是我国慢性肝病最常见的病因[1,2]。随着临床诊疗水平的不断提升，HBV感染者的预期寿命普遍延长，肝性骨营养不良（hepatic osteodystrophy，HOD）已成为HBV相关肝病常见的并发症[3,4]，但调查资料显示，临床对HOD的诊断率不足为7%，即使发生HOD性骨折，其临床治疗率也仅为30%[4]，为进一步提高对HBV相关HOD的认知、改善HBV相关肝病患者的预后，本文结合相关文献，就HBV相关HOD的发病风险和潜在因素进行综述。

1 HBV 相关 HOD 发病风险

HBV感染与HOD的关系目前尚存在争议。Min等[5]对68 492例骨质疏松患者的Logistic回归分析显示，HBV感染者的骨质疏松风险高于非HBV感染者（*HR* = 1.19，95%*CI*：1.11～1.28，*P* ＜ 0.05）。一项来自韩国国家健康和营养调查的423例乙型肝炎病毒表面抗原（hepatitis B virus surface antigen，HBsAg）阳性感染者，通过双能X线骨密度仪检测股骨骨密度（bone mineral density，BMD），多变量Logistic回归分析表明，HBsAg阳性者股骨颈BMD显著低于HBsAg阴性者 [（0.810 ± 0.010）g/cm^{2}比（0.831 ± 0.002）g/cm^2，*P* = 0.032][6]。Tao等[7]通过美国国家卫生与营养检查调查（national health and nutrition examination survey，NHANES）数据库对1217例HBsAg阳性患者的研究显示，HBsAg阳性患者股骨、脊柱的BMD均显著低于HBsAg阴性者。Chen等[8]对36 146例HBV感染者和144 584例普通人群的对照研究显示，HBV感染者较普通人群的低BMD风险率高1.14倍，发展为骨质疏松的风险高1.13倍，说明HBV感染者患HOD风险和低BMD发生率均高于非HBV感染者，提示HBV是HOD的诱因之一。

2 HBV 相关 HOD 发病因素

HBV相关HOD的发病因素复杂，目前的研究

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多集中于HBV感染所致的炎症因子、人口学特征、营养状态、疾病演变及抗病毒药物等方面。

2.1 炎症因子 炎症因子是HBV相关HOD最热点的研究领域。HBV感染人体后，HBV免疫损伤和HBsAg以剂量依赖性的诱导方式刺激机体产生大量炎症因子，如肿瘤坏死因子α（tumor necrosis factor α，TNF-α）、白细胞介素1（interleukin 1，IL-1）、IL-6和IL-10等[9,10]。Shi等[9]研究显示，TNF-α具有影响和调控成骨细胞产生的核因子-κB活化体受体配体（receptor activator of nuclear factor-κB ligand，RANKL）和破骨细胞前体细胞上的核因子-κB活化体受体（receptor activator of nuclear factor-κB，RANK）的作用，可激活核因子-κB（nuclear factor kappa-B，NF-κB）信号系统，导致骨吸收增加和骨形成减少而诱发HOD。同时TNF-α还具有促进破骨细胞形成、增加骨髓中破骨细胞池的大小、加速破骨细胞分化和成熟的作用[10]，也将进一步增加HOD发生的风险。IL-1β是一种强力刺激骨吸收的炎症因子，通过增加RANKL的分泌促进破骨细胞形成，导致HOD。Ruiz-Gaspà等[11]通过动物实验证实IL-1β缺失与小鼠股骨BMD、骨小梁和骨皮质厚度呈显著负相关。IL-6是HOD的促进因子，具有直接或间接激活破骨细胞的作用[9,12]，可导致骨量减少，出现HOD。Wang等[13]通过动物骨质疏松实验证实，降低血清IL-6、TNF-α水平能够有效抑制细胞外调节蛋白激酶1/2（extracellular regulatory kinase，ERK1/2）和磷酸化ERK1/2蛋白的表达，显著改善大鼠骨丢失和骨微结构的破坏，提示有效降低TNF-α、IL-1、IL-6和IL-10等炎性因子水平是降低HBV相关HOD发生率的重要一环。

2.2 人口学特征 有研究表明HOD与年龄、性别具有显著相关性[14,15]。国内学者通过城镇职工基本医疗保险（Urban Employee Basic Medical Insurance，UEBMI）、城市居民基本医疗保险（Urban Resident Basic Medical Insurance，URBMI）和新型农村合作医疗（New Rural Cooperative Medical Scheme，NRCMS）数据库，对2013年14 545例和2016年11 648例慢性乙型肝炎（chronic hepatitis B，CHB）患者的队列研究表明，年龄＞ 45岁的HBV相关肝病患者由2013年的40.3%增长至2016年49.0%[14]。Zhang等[8]对我国HBV感染者的大样本研究显示，HOD发病率随年龄增长而增加（年龄49岁：*HR* = 1；年龄50～64岁：*HR* = 5.67，95%*CI*：5.09～6.32；年龄65岁：*HR* = 13.3，95%*CI*：11.8～14.9）。另有文献明确指出，年龄是CHB患者发生HOD的独立危险因素（*OR* = 1.108，95%*CI*：1.026～1.196，*P* = 0.009）[4]。性别方面，一项韩国全国性大样本的队列研究显示，女性HBV感染者的骨质疏松患病率显著高于男性[5]。女性HBV感染者，特别是绝经女性HOD风险更高[15]，提示对于HBV相关肝病患者，临床应高度重视人口学对HOD的影响。

2.3 营养状态 HBV相关肝病特别是肝硬化患者普遍存在营养不良。营养不良易诱发或加重HOD，目前研究较多的领域是维生素D和肌少症、低握力。

维生素D缺乏是影响骨营养不良的首要因素[16,17]。维生素D是维持骨骼健康的重要物质，作用于小肠黏膜细胞和肾小管可促进钙、磷吸收；作用于骨骼可降低RANKL/RANK比值，抑制滑膜成纤维细胞产生的RANKL与破骨前体细胞以及破骨细胞表面的RANK结合而抑制破骨活动[18]，维持骨组织的动态平衡。大量研究表明，维生素D缺乏在HBV相关肝病患者中普遍存在。Hu等[19]对7篇涉及814例CHB患者和696例健康人群文献的Meta分析显示，CHB患者维生素D水平显著低于对照组，且与HBV DNA载量呈负相关（*r* =－0.41，95%*CI*：0.54～0.27）。Banerjee等[20]通过PubMed、Google Scholar和Scopus等平台，对33篇文献共计6360例HBV相关肝病患者进行的Meta分析表明，无论HBV携带者还是CHB患者，其血清25-羟维生素D [25-hydroxy vitamin D，25（OH）D] 水平均显著低于健康对照组（*P* ＜ 0.01），且与乙型肝炎病毒e抗原（hepatitis B virus e antigen，HBeAg）阳性和肝纤维化程度显著相关。说明HBV病毒载量、HBeAg阳性、肝纤维化程度是影响HBV相关肝病患者维生素D水平的重要因素，提示积极降低HBV DNA载量，缓解病情进展是提高维生素D水平、减少HBV相关HOD发生发展的手段之一。

肝硬化患者维生素D水平下降更明显，存在维生素D不足或缺乏者高达88.3%[21]。Ahmed等[22]研究表明，HBV相关肝硬化患者血清25（OH）D水平为（40.63 ± 19.90）nmol/L，Child-Pugh A级、B级、C级患者25（OH）D水平分别为（67.80 ± 15.28）nmol/L、（39.93 ± 13.50）nmol/L和（23.93 ± 2.88）nmol/L，25（OH）D水平与Child-Pugh评分呈负相关，肝硬化严重程度是影响HBV相关肝病患者维生素D水平的重要因素，提示积极控制病情，改善病情状态也是延缓HBV相关HOD进展的有效手段。

肌少症、低握力是肝硬化营养不良最典型的临床表现，也是HBV感染者高HOD风险的重要影响因素[23]。研究显示肌少症是肝硬化HOD的独立危险

因素[24,25]。资料显示，肝硬化合并肌少症患者HOD发生率可高达95%[26]。Saeki等[24]研究显示，肝硬化肌少症患者的HOD比例显著高于无肌少症的肝硬化患者（63.3%比18.3%，$P < 0.001$），多因素分析显示，肌肉减少是肝硬化患者发生HOD的独立危险因素（$OR = 6.510$，$P = 0.001$）[25]。同时Santos等[27]对129例肝硬化患者手握力的检测显示，低握力是肝硬化患者HOD的有效预测指标，文献倡议可将手握力检测作为所有肝硬化患者骨骼健康监测的第一指标。此外，肝硬化患者长期蛋白质摄入不足、维生素K缺乏、睡眠障碍也是诱发或加重HOD的相关因素[15,28,29]。

2.4 疾病演变 HBV感染在无临床干预下呈隐匿进展。HBV相关性肝病发展至不同时期，其HOD发生率也不同，HOD发生率随病情的加重而增高[30,31]。Menekşe等[32]对11 125例CHB患者的研究显示，HOD发生率为12.1%～17.7%。Chen等[30]采用双能X线吸收法（dual energy X-ray absorptiometry，DXA）检测3754例非肝硬化且ALT正常的CHB患者腰椎和股骨颈的BMD，结果表明低BMD患者达53.0%。HBV相关肝硬化患者HOD发生率高达66.7%～78.4%[31,33]，是HBV肝硬化患者的重要肝外表现[8,31,34]。Child-Pugh评分和肝脏硬度检测可反映肝硬化严重程度，与HOD发生率具有显著相关性[8,34,35]。Zhang等[35]对189例HBV相关肝硬化患者HOD的多因素分析显示，高肝硬度值、高Child-Pugh评分是HOD的独立危险因素。

高胆红素血症和胆汁淤积症是肝硬化患者的常见表现，既往研究认为高胆红素血症与HOD无明显相关性[36]。随着研究的深入，高胆红素血症对骨的危害越来越受到重视。有研究证实高胆红素血症可加速成骨细胞的凋亡而使骨形成减少[37,38]。Ruiz-Gaspa等[11,28]研究进一步明确了胆红素与HOD间的相关机制，即胆红素导致RANKL、护骨素基因（osteoprotegerin，OPG）表达明显上调，下调Runt相关转录因子2（runt-related transcription factor，RUNX 2），减少骨形成蛋白因子（bone morphogenetic protein，BMP）的表达，使骨吸收增加和骨形成减少而诱发或加重HOD，因此降低胆红素水平也是改善HBV相关HOD的有效途径。

肠道菌群失调是近年的研究热点。动物实验表明，肠道菌群紊乱可导致BMD降低[39]。肝硬化门静脉高压可使肠黏膜屏障受损，肠道通透性增加，细菌发生移位，同时肝硬化胆汁排泄障碍，肠道内环境破坏，易出现肠道菌群紊乱。肠道菌群失调会导致肠道中短链脂肪酸（short-chain fatty acid，SCFA）减少。Lucas等[40]研究表明，SCFA是抑制破骨细胞分化和骨吸收的有效调节剂，可显著增加实验小鼠的骨量[39,40]，因此有学者指出，维持肠道菌群稳态将有望成为改善肝硬化患者BMD水平的新靶点[41]。

2.5 抗病毒药物 抗HBV治疗是临床诊疗HBV相关肝病的首选措施，也是阻断病情进展的根本手段[42,43]。富马酸替诺福韦酯（tenofovir disoproxil fumarate，TDF）是国内外指南推荐的抗HBV一线药物，广泛应用于临床中[43,44]。既往研究认为使用TDF出现的HOD与维生素D缺乏相关，与TDF无关[44]。随着研究的深入，大量临床证据显示长期使用TDF抗HBV后出现的HOD与TDF直接相关。Hajiania等[45]对TDF治疗的CHB患者进行12个月的追踪观察显示，TDF组HOD发生率显著高于对照组（60.43%比21.43%）。同时Viganò等[46]对使用TDF的CHB患者进行了为期70（14～121）个月的观察，结果显示52.2%（24/46）基线BMD正常的患者出现了HOD。Zhang等[47]为进一步明确TDF诱发HOD的机制，通过体外实验证实TDF不仅可抑制MC3T3-E1细胞的成骨分化和矿化，减少成骨细胞数量和骨组织新血管体积，长期使用还可抑制骨膜蛋白和β-连环蛋白的表达，减少骨的形成，抑制骨的修复，因此欧洲肝脏研究协会建议对于年龄＞ 65岁或有骨质疏松、肾损伤风险的患者，宜选用富马酸丙酚替诺福韦（tenofovir alafenamide fumarate，TAF）治疗[1]。临床为进一步明确更换TAF对HOD的影响，有学者将接受TDF治疗达到病毒学应答的488例CHB患者按1∶1随机继续使用TDF和更换TAF治疗，48周后TAF组CHB患者髋关节和脊柱的BMD得到了改善[48]。Li等[49]通过多中心、前瞻性研究发现，使用TDF治疗的CHB患者改为TAF治疗24周后，腰椎BMD得到明显改善 [（1.03 ± 0.11）g/cm^{2}比（0.97 ± 0.12）g/cm^2，$P = 0.001$]，提示采用TDF抗病毒治疗的患者，特别是存在HOD风险的患者，宜及早更换TAF，以减少HOD的发生发展。此外，HBV相关肝病是一种进行性疾病，肝硬化特别是失代偿期肝硬化患者，病情复杂，并发症多，许多药物如干扰素、利尿剂、皮质类固醇、质子泵抑制剂等也会诱发或加重HOD，需引起重视[50,51]。

3 小结

随着患者预期寿命的普遍延长，HOD成为了HBV相关肝病的常见临床表现，且HOD发生率与HBV相关肝病的进展密切相关，呈现随病情加重

而增加的态势。HBV相关HOD的诱因和发病机制十分复杂，目前尚缺乏统一观点。HBV免疫损伤和HBsAg诱导的炎症因子是导致HOD的重要机制。年龄、女性雌激素低下、低体重指数、高肝硬度值、高Child-Pugh评分是HBV相关HOD的独立危险因素[4,25,35]。长期蛋白质摄入不足、营养缺乏、高HBV DNA载量、高胆红素血症、肠道菌群失调、抗HBV药物也是诱发或加重HBV相关HOD的重要因素。因此，针对HBV相关HOD，应采取全面、个体化评估和管理[50]，尽早减轻或消除HOD的相关因素，以预防或减少脆性骨折的发生，提高患者的生活质量。

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