

肠道炎症状态下骨代谢调节的稳态与失衡

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摘 要

肠道炎症性疾患(Inflammatory Bowel Disease)是一种慢性全身性炎症疾病, 主要包括溃疡性结肠炎(Ulcerative Colitis, UC)以及克罗恩病(Crohn's Disease, CD)特征是肠道黏膜受到广泛的炎症破坏。此外, 其可涉及全身各个系统, 形成系统性合并症, 骨骼系统便是其中之一。肠道炎症患者或各式各样的动物模型中均可观察到骨质破坏以及骨量丧失的现象, 而这其中的病因机制却涉及各个方面, 包括营养状况、炎症因子、肠道激素类信号分子以及肠道菌群等。总的来说骨代谢的平衡主要依赖于成骨与破骨作用之间的平衡, 外界或内部因素倘若打破这一平衡, 便会引起宏观方面的骨骼系统的变化, 肠道炎症状态下亦是如此。本文将从肠道炎症状态出发, 对这一病理环境下骨代谢异常的表现以及病因机制以及相关治疗策略做一综述。

关键词

肠道炎症, 骨代谢, 炎症性肠道疾病

Homeostasis and Imbalance of the Bone Metabolism Regulation in the State of Intestinal Inflammation

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Abstract

Inflammatory Bowel Disease, as a chronic systemic inflammatory disease that includes Ulcerative Colitis (UC) and Crohn's disease (CD), is characterized by extensive inflammatory destruction of the intestinal mucosa. In addition, it involves various systems throughout the body, leading to systemic comorbidities, especially the skeletal system. Bone destruction and bone loss have been observed in patients with intestinal inflammation or in various animal models, and the etiological mechanism of this phenomenon involves various aspects, including nutritional status, inflammatory factors, intestinal hormone signaling molecules, and intestinal flora. In general, the balance of bone metabolism mainly depends on the balance between osteogenesis and osteoclastogenesis. If external or internal factors break this balance, it would cause changes in the skeletal system in the macro aspect, and this is also the case in the state of intestinal inflammation. Starting from the state of intestinal inflammation, this article will review the manifestations, etiological mechanisms and related treatment strategies of abnormal bone metabolism in this pathological environment.

Keywords

Intestinal Inflammation, Bone Metabolism, Inflammatory Bowel Disease

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1. 序言

炎症性肠道疾病(又称为 Inflammatory Bowel Disease, IBD)包括溃疡性结肠炎及克罗恩病[1], 在全世界范围内大约有 360 万人患有炎症性肠道疾病, 在 IBD 人群中, 约有高达 40% 的患者同时出现肠道外症状, 累及包括骨骼肌肉系统、皮肤黏膜系统、视觉系统、呼吸循环系统等全身诸多系统[2]。研究表明 IBD 人群常常会出现骨密度的降低与骨量不足[3] [4], 这导致了 IBD 患者出现骨质疏松与骨折的概率较正常人更高, 这一数值据统计可达 14%~42% [5]。由于 IBD 的高发病率以及高危害性, 对于临床医生而言, 额外关注 IBD 患者全身骨质状态尤为重要, 对于患者骨质状态, 可通过双能 X 线骨密度测量仪(DXA)检测腰椎及股骨近端来反映单位面积或体积的骨量, 即骨密度(BMD)。然而, 目前而言对于 IBD 患者骨量丧失的具体病理机制尚未完全明确, 其潜在风险因素主要涉及营养状况方面, 药物使用方面、系统性炎症因子以及肠道内信号调节因子和微生物及代谢物质等方面[5]-[8]。本文将从骨代谢生理及病理过程出发, 结合现有证据从以上各个方面对 IBD 患者骨量丧失的潜在因素进行分析, 同时合并针对各个方面的现有改善手段做一综述。

生理状态下骨骼系统维持于一个动态改建的状态下, 这一状态是骨代谢得以保持稳态的必要条件, 包括了以成骨细胞(Osteoblasts, OBs)发挥主要作用的骨形成过程以及以破骨细胞(Osteoclasts, OCs)发挥主要作用的骨吸收过程[9] [10]。

成骨细胞由位于骨髓的间充质干细胞(MSCs)分化, 间充质干细胞在不同微环境条件下亦可分化为脂肪细胞及软骨细胞[11]。其向成骨细胞的分化经历了骨-软骨祖细胞、成骨祖细胞、成骨前体细胞的中间过程, 并受到多种信号分子的调控, 主要包括骨形态蛋白(Bone Morphogenic Proteins, BMPs)以及无翅相关整合位点(Wingless-related integration site, Wnt pathways), 此外还包括核因子 κ B (NF- κ B), 这些因子调

控着 MSC 向骨 - 软骨祖细胞分化。接着, 随着主要成骨转录因子的激活, 包括 runt-related transcription factor 2 (RUNX2)、osterix (OSX), 骨 - 软骨祖细胞分化形成骨祖细胞, 并随着早期成骨基因的转录(包括碱性磷酸酶, ALP 以及胶原 $\alpha 1$ 链, Col-1)形成成骨前体细胞, 后者依次表达成骨细胞的其他表面标志物, 如骨桥蛋白(OPN)、骨唾液蛋白 II (BSP II)和骨钙素(OCN)。破骨细胞来源于造血干细胞骨髓系的单核前体细胞。

破骨细胞可受巨噬细胞集落刺激因子、骨保护素(osteoprotegerin, OPG)、核因子- κ B 配体受体激活剂(RANKL)等影响。在骨吸收过程中, 破骨细胞通过分泌酸和蛋白水解酶(如 cathepsin K 和抗酒石酸酸性磷酸酶(TRAP))降解骨, 分别溶解骨的无机和有机成分[12]。在骨生长和重塑过程中, 成骨细胞与破骨细胞的平衡决定了骨稳态的生理状态能否维持。此外, 成骨细胞还会产生核因子- κ B 配体受体激活因子(RANKL)和骨保护素(OPG), 来直接对破骨细胞的形成起到一定调控作用。

2. 肠道稳态与肠道炎症状态下骨代谢异常的表现与机制

肠道稳态是指肠道菌群、肠上皮屏障与免疫细胞以及营养和代谢产物相互作用所形成的一个动态平衡状态。肠道稳态对于肠道局部以及全身各个系统, 包括免疫系统、呼吸系统、循环系统、内分泌系统及骨骼系统具有十分重要的生理意义[13]-[15]。肠道稳态的失衡将会引起肠道发生病理性改变, 逐步发展成为炎症性肠道疾病(IBD), 继而直接或间接对全身各个系统产生不利影响, 尤其是骨骼系统[16] [17]。

2.1. 营养状况与营养物质对骨代谢的影响

营养因素往往是 IBD 人群出现全身性骨破坏的重要因素之一, IBD 患者的营养状况往往处于一种受损状态, 这点在疾病的始发期及缓解期均可以存在[18] [19]。导致这一现象的原因涉及多个方面, 包括食物摄入量的减少, 肠道吸收功能的减弱, 肠道屏障破坏导致的蛋白质等营养物质丢失以及高代谢水平伴随的能量需求增加等[20]。这些原因往往通过单一或协同作用影响机体内多种营养物质(如钙磷等微量元素、维生素 D、维生素 K、蛋白质等[21]-[23])的有效浓度从而影响骨骼系统的代谢与稳态的维持。

2.1.1. 钙、磷、镁等微量元素

钙元素对于人体骨骼正常发育至关重要, 作为羟基磷灰石的组成部分, 其在维持骨骼强度方面发挥着必不可少的作用。多项研究表明, 在幼年期及青春期的受试者中, 相较于钙缺乏及未额外补充钙的对照组, 额外补充钙元素能够显著增加骨矿物质的获取率[24]-[27], 例如对平均年龄为 11.9 岁的青少年女性受试者给予 18 个月的钙元素补充处理(以柠檬酸 - 苹果酸钙的形式, 每天补充约 500 mg 钙盐)之后, 测量他们的腰椎骨密度(18.7% vs 15.8%; $P = 0.03$)、腰椎骨矿化量(39.4% vs 34.7%; $P = 0.06$)以及全身骨骼总密度(9.6% vs 8.3%; $P = 0.05$)均高于安慰剂对照组[25]。磷元素作为骨代谢过程中重要的一环, 对于软骨或骨样组织的矿化起到不可或缺的作用[28]。而镁元素作为一系列酶促反应的阳离子辅助因子, 在甲状腺激素分泌和钾稳态中起作用, 镁摄入不足与髋关节骨密度减低存在一定相关性[29]。在 IBD 患者中, 由于疾病活性、饮食摄入等原因, 往往出现上述微量元素的丢失, 且这一状况出现的概率大约在 11%~82.5% 不等[19] [23]。这对于全身骨骼稳态的维持无疑是个不利因素, 将会造成骨密度减低并出现骨质疏松症。

2.1.2. 维生素类

维生素作为人体必需的基本营养元素之一, 在骨生长发育代谢中也起到重要作用。其中, 维生素 D 在体内通过转化为活性形式骨化三醇从而增加肠道对钙以及磷酸盐的吸收作用[30]。种种证据表明[31]维生素 D 缺乏会引起幼儿佝偻病以及成人骨软化病的发生, 同时, 在联合补充维生素 D 与钙时能够减少继

发性甲状旁腺功能亢进,降低髌部骨折的风险,特别是对住在养老院的老年人[32]。Giorgia 等人[22]的研究显示 IBD 人群相较于健康志愿者维生素 D 的含量显著减低;且 IBD 人群中维生素 D 缺乏者的比例也显著高于健康志愿者。此外,维生素 K 在维持骨骼健康状态方面也发挥着重要作用,具体来讲,其作为 g-谷氨酰羧化酶的辅因子,促进其对骨钙素(osteocalcin, OCN)和基质 Gla 蛋白(Matrix Gla Protein, MGP)的羧化过程,从而促进骨骼钙化并抑制软组织钙化。同时,维生素 K 能够通过抑制核因子 κ B (NF- κ B)以及 RANKL 从而抑制破骨细胞发生。

2.1.3. 蛋白质类

蛋白质的摄入影响着胰岛素样生长因子-1 (IGF-1)的产生,后者作为一种重要营养激素,对骨骼、软骨起到促进生长的作用,此外,IGF-1 能够调节磷酸盐在肾脏中的再吸收,并通过刺激肾脏合成 1,25-二羟基维生素 D3 (骨化三醇)来刺激肠道对钙和磷酸盐的主动摄取[33]。IBD 人群常常由于多种因素,如有效能量摄取不足、疾病引起的全身炎症反应以及炎症触发的特定细胞因子等出现蛋白质-能量营养不良,继而对骨代谢产生不利影响。

2.2. 肠道炎症因子对骨代谢的影响

IBD 的特点之一是较为严重的胃肠道炎症,而这一炎症状态往往会波及全身各个系统造成机体处于一个系统性炎症状态。B. Hugle 等人的研究以及 M. Leppkes 等人[34] [35]的结论表明 IBD 人群相较于健康人群,体内 IL-1 β 、IL-33 以及 TNF α 等炎症因子的表达显著升高,而这些炎症因子通过对骨代谢相关细胞(成骨细胞与破骨细胞)产生多种作用从而构成骨质流失的一个潜在机制。

2.2.1. 系统性炎症因子对骨代谢中成骨细胞的影响

正如上文所提到的,由 BMSC 分化而成的成骨细胞,在炎症因子的刺激下受到不利影响(如增殖和分化的抑制),从而引起骨量的丧失。在多种模拟 IBD 的动物模型中,DSS 诱导啮齿类动物的肠道炎症模型被认为接近人体溃疡性结肠炎(UC)的表现[36],因此较为广泛地被应用于对 IBD 的相关研究中。多项研究表明 DSS 诱导的小鼠 IBD 模型中,均出现不同程度的骨量丧失[37]-[39],在 IBD 小鼠中,出现了 IL-1a, IL-1b, TNF-a, IL-6, 和 IL-33 等炎症因子的表达增高,通过观察 IBD 小鼠体内分离 BMSC 的染色结果表明,其更多地分化为成脂细胞而非成骨细胞;此外,RNA 测序结果也反映出成骨基因的表达抑制与成脂肪相关基因的表达增多。这表明了 IBD 通过增加体内的炎症因子从而抑制骨代谢中的成骨作用。同时在 DSS 诱导的大鼠 IBD 模型中,也观察到了伴随炎症因子上调的骨细胞凋亡的增加以及骨骼相关参数比如骨量及骨质强度的降低[40]。

2.2.2. 系统性炎症因子对骨代谢中破骨细胞的影响

肠道炎症与破骨细胞之间的交联反应也影响着这一状态下的骨代谢。Peek 等人[6]通过化学诱导、T 细胞驱动以及病原菌感染三种不同方法分别构建小鼠结肠炎模型。首先观察到伴随肠道炎症的加重,出现了骨小梁的丢失,并且在造模的第 7 天,发现了单位骨面积破骨细胞数目的显著增多。这一现象的出现与肠道炎症改变了骨骼内细胞因子的丰富度有密切关系,包括 TNF- α , G-CSF, IL-12p40 等。经过进一步研究发现,这些改变的细胞因子通过引起破骨细胞前体细胞表面髓系 dap-12 相关凝集素-1 (MDL-1)的表达增多导致了破骨细胞前体的扩张,从而引起骨代谢的失衡。此外, M Stanisławowski 等人[41]报道长期患有溃疡性结肠炎(UC)的受试者表现出骨密度的降低,并且相较于健康受试者,UC 受试者血清中具有较高水平的 I 型胶原交联 C-末端肽(CTX),同时在 mRNA 水平检查到炎症因子 IL-33 的表达增高,而后者能够促进刺激肥大细胞产生促炎因子 TNF- α , 这些结果提示 UC 患者的肠道炎症环境通过促进炎症因子的产生使得破骨细胞骨吸收活性加强,从而引起骨丧失。

2.3. 肠道激素类分子对骨代谢的影响

近年来关于肠道信号分子对全身骨代谢影响的相关研究愈来愈丰富,其中由肠道嗜铬细胞(enterochromaffin cells, EC cells)分泌的血清素在肠道局部功能及全身各个系统,尤其是骨骼系统方面得到了较多的研究[42]-[45]。血清素别称五羟色胺((5-hydroxytryptamine, 5-HT), 因其在中枢神经系统中发挥神经递质的作用而广为人知。然而由于其在常规情况下无法穿透血脑屏障, 机体内的血清素可被划分为中枢系统血清素及外周系统血清素, 而后者绝大部分产生于肠道, 被称为肠源性血清素[46]。肠源性血清素来源于肠道黏膜中的肠嗜铬细胞(enterochromaffin cells, EC cells), 由其内的色氨酸羟化酶 1 (TPH1)作为限速酶而合成, 这同中枢神经系统来源的血清素不同, 后者源自神经元内的色氨酸羟化酶 2 (TPH2) [42]。肠道血清素在微观方面通过对成骨细胞及破骨细胞产生多种影响从而引起宏观方面的骨丧失, 这一途径也将肠道炎症同骨代谢稳态的失衡紧密连接在一起。这一结论源自 Yadav 等人的研究[45], 在对小鼠基因组进行低密度脂蛋白受体家族成员 Lrp5 特异性敲除后, 检测到了 TPH1 表达的显著增加, 进而引起循环当中血清素水平的显著增加并通过激活于小鼠成骨细胞前体细胞表面的 5-HT1B 受体来抑制其增殖从而引起骨量的丧失。此外, 通过进一步对转录因子的研究发现, FOXO1 对肠源性血清素影响小鼠成骨细胞增殖能力起到关键作用[47], 这也为“肠道-血清素-骨”轴的出现奠定了一定的基础, 这一途径在肠道炎症应激状态下则引起骨代谢的失衡。例如, B Lavoie 等[48]通过化学药物葡聚糖硫酸钠(DSS)构建小鼠 IBD 模型, 观察到了肠源性血清素的合成增多, 同样地, 他们发现这些进入血循环的大量血清素通过作用于骨骼系统成骨细胞表面 5-HT1B 受体从而抑制其增殖最终使得骨量丧失。此外, 吴船课题组的研究表明[49]在肠道炎症状态下, 炎症因子 IL-33 通过结合 EC 细胞表面受体 ST2 使下游磷脂酶 C- γ (PLC- γ) 磷酸化继而引起细胞内钙离子增加从而增加 EC 细胞合成及释放血清素, 这些肠源性血清素随着血液循环抵达骨骼系统对成骨细胞发挥不同的作用而引起骨代谢失衡并导致骨丧失。

除了对成骨细胞产生影响, 肠源性血清素还能作用于破骨细胞, 从骨代谢另一方面引发骨丧失。Yasmine Chabbi-Achengli 等人在其的研究中[50]证明在敲除了肠源性血清素合成限速酶基因 TPH1 (TPH^{-/-})的生长发育及成年小鼠中骨吸收显著减少, 具体而言, 从其体内分离出的造血前体多核细胞在 RANKL 及巨噬细胞集落刺激因子 CSF 的作用下表现出了破骨分化的减少, 且这一现象在添加了血清素后被逆转。

2.4. 肠道微生物及代谢产物对骨代谢的影响

在炎症性肠道疾病中, 肠道菌群往往处于一个失调的状态, 并且作为其特征性的表现之一[51]。此外, Sternes 等人报道[52]健康受试者与 IBD 受试者可观察到肠道菌群 α 及 β 丰富度的改变。肠道微生物作为机体代谢调节的关键一环, 对宿主包括免疫稳态、血液循环、内分泌、功能在内的各个生理方面产生调节作用, 对于骨骼系统与骨代谢也是如此。目前肠道菌群对机体骨代谢的影响具有一定争议性, 例如 Klara 等人的研究[53]表明肠道菌群能够激活破骨细胞的骨吸收作用从而引起骨丧失; 而另有证据[54]表明在使用抗生素抑制肠道菌群并使肠道菌群结构紊乱后, 其代谢产物短链脂肪酸(SCFA)以及血清中胰岛素样生长因子 1 (IGF-1)出现降低, 且出现骨质形成的抑制作用; 这一现象在补充了短链脂肪酸(SCFA)后出现了逆转, 血清中 IGF-1 的水平及骨量的丧失得到了恢复。

3. 结论与展望

肠道炎症对于骨代谢及骨重塑影响的相关研究仍不失为当下的热点, 尽管目前尚无法明确其二者之间产生联系的具体机制, 但是种种证据皆指向一个共同点, 即这一联系涉及肠道局部微环境及全身系统

的多方面影响。同时,针对上述各方面因素,目前已形成了很多十分有效的干预及治疗措施。首先针对绝大部分 IBD 人群可能伴随的营养失衡状况,健康规律的饮食并及时补充蛋白质、维生素以及有利于骨骼生长的微量元素能够达到显著降低 IBD 相关骨骼并发症(如髌关节骨折、骨质疏松、类风湿关节炎等)的风险[5]。其次,适当使用双磷酸盐、雌激素以及雌激素受体选择性调节剂、降钙素等成骨、破骨细胞调节剂除了应对于一般情况下的骨质疏松外,也被证明对肠道炎症引起的骨丧失具有一定疗效[55] [56]。除此之外,越来越多的新型信号分子调节剂也展现出了其巨大的潜力,Yadav [57]等人报道了一种 Tph-1 酶抑制剂 LP533401 通过抑制肠源性血清素的产生从而缓解了骨丧失;Lavoie 等报道[48]在建立了 DSS 诱导的小鼠 IBD 模型下,分别使用肠源性血清素合成酶抑制剂、再摄取抑制剂以及成骨细胞表面作用靶点 5-HT1B 受体抑制剂,均出现了骨量丧失的缓解。种种结果表明,特异性针对肠道内激素类信号分子的调节剂,可能成为未来潜在的治疗方案。无论如何,肠道炎症状态与骨代谢失衡之间的关联,目前是需要特别重视的,未来的研究也应集中于二者的发病机制与治疗措施方面,以期获得更深入的了解。

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