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综述

慢性阻塞性肺疾病合并骨质疏松的研究进展

童成文，李 胜*

(十堰市人民医院/湖北医药学院附属人民医院放射影像中心，十堰 442000)

摘要：慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)是一种常见的呼吸系统疾病，主要发生于中老年人，常具有多种肺外并发症，如心血管疾病、骨质疏松、糖尿病、代谢综合征等。COPD的致病因素有长期吸烟、缺少锻炼、有害气体的吸入等，糖皮质激素是主要的治疗方式，而糖皮质激素的长期使用会导致骨质疏松的发生。骨质疏松的特点是骨量低和骨组织微结构恶化，导致骨脆性增加，从而增加骨折风险。骨质疏松引起的骨折可能会增加COPD患者的发病率和死亡率，并导致患者肺功能进一步恶化。故COPD与骨质疏松关系密切，在一定程度上互为因果。COPD患者骨质疏松的高患病率被认为是由常见危险因素(如年龄较大和吸烟)以及COPD特定危险因素(如全身炎症、使用糖皮质激素以及维生素D缺乏等)造成的。目前，临床上针对COPD患者的治疗大多忽略了对其合并症骨质疏松的治疗，且COPD合并骨质疏松的病理机制仍有待进一步研究。因此，本文对COPD合并骨质疏松的发病机制、危险因素及治疗进行综述，以期为COPD合并骨质疏松的治疗提供新的方向。

关键词：慢性阻塞性肺疾病；骨质疏松；骨密度

Research progress of osteoporosis in chronic obstructive pulmonary disease

TONG Chengwen, LI Sheng*

(Department of Radiography Center, the People's Hospital of Shiyan,
Hubei University of Medicine, Shiyan 442000, China)

Abstract: Chronic obstructive pulmonary disease (COPD) is a common respiratory disease, which mainly occurs in the middle-aged and elderly people. It often has many extrapulmonary complications, such as cardiovascular disease, osteoporosis, diabetes, metabolic syndrome and so on. Long-term smoking, lack of exercise and inhalation of harmful gases are the main risk factors for COPD. Glucocorticoids are the main treatment method, and long-term use of glucocorticoids can lead to the occurrence of osteoporosis. The characteristics of osteoporosis are low bone mass and deterioration of bone tissue microstructure, leading to an increase in bone fragility, thereby increasing the risk of fracture. Fractures caused by osteoporosis may increase the incidence rate and mortality of COPD patients, and lead to further deterioration of lung function. Therefore, COPD is closely related to osteoporosis, and to some extent, they are mutually causal. The high incidence of osteoporosis in COPD patients is believed to be caused by common risk factors such as older age and smoking, as well as specific risk factors for COPD such as systemic inflammation, glucocorticoid use, and vitamin D

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第一作者：E-mail: 517119706@qq.com
*通信作者：E-mail: 4016267@qq.com

deficiency. At present, the treatment of COPD patients in clinical practice mostly neglects the treatment of their combined osteoporosis, and the pathological mechanism of COPD combined osteoporosis still needs further research. Therefore, this paper reviews the pathogenesis, risk factors, and treatment of COPD combined with osteoporosis, in order to provide new directions for the treatment of COPD combined with osteoporosis patients.

Key Words: chronic obstructive pulmonary disease; osteoporosis; bone density

慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)是一种以持续性呼吸道症状和气流受限为特征的慢性炎症性疾病，其发病率、致残率、致死率在全球范围内逐年上升，严重威胁着人类健康。随着全球空气污染加剧和老龄化速度加快，COPD有望成为未来人类慢性病的主要经济负担。COPD现在被视为一种全身性疾病，并伴有显著的合并症，如肌肉减少症、骨质疏松、心血管疾病、肺癌、胃食管反流、代谢综合征、焦虑、抑郁等。骨质疏松是一种威胁人类健康的全身性骨病，也是COPD患者的一个重要合并症，涉及骨量减少、骨密度降低和骨微结构退化，并伴有骨脆化和骨折倾向。骨质疏松相关骨折与COPD患者的肺功能恶化、生活质量差、住院率和死亡率增加等不良健康结果相关。这两种疾病往往形成恶性循环，给患者造成了沉重的生活与经济负担。研究表明，COPD患者中骨质疏松的患病率比年龄匹配的健康对照受试者高2~5倍[1]，而骨密度显著降低导致骨质疏松或椎体压缩性骨折的患病率在COPD患者中达到24.6%[2]。骨质疏松患者的胸廓舒张功能受限会抑制呼吸功能并加重COPD。此外，COPD患者的全身炎症反应、全身糖皮质激素应用会诱发骨质疏松甚至导致脆性骨折，提示COPD可能是骨质疏松和骨折的危险因素，因此需要通过骨密度测量定期进行骨质疏松筛查，并预防COPD患者骨折的发生。

1 COPD合并骨质疏松的发病机制

骨组织中的骨相关细胞通过复杂的相互作用参与骨重塑。在骨重塑过程中，破骨细胞的骨吸收和成骨细胞的骨形成不断重复，并且二者在数量和功能上保持动态平衡，而二者的功能失衡则会导致骨质疏松。骨质疏松的发病机制是体内成骨细胞凋亡和破骨细胞增生，导致骨代谢紊乱和骨质流失，进而导致骨形态恶化[3]。成骨细胞在其表面表达核因子-κB配体受体激活剂(receptor activator of nuclear factor-κB ligand，RANKL)，当其与破骨细胞前体表达的核因子-κB受体活化因子(receptor activator of nuclear factor -κB，RANK)结合时，可激活破骨细胞分化和功能来启动骨重塑周期，抑制破骨细胞的凋亡。骨保护素(osteoprotegerin，OPG)是一种由成骨细胞和骨髓基质细胞表达的可溶性糖蛋白，为可溶性RANKL诱饵受体，可通过阻止RANK与其受体RANKL的结合来抑制破骨细胞分化和骨质流失。有研究已发现，OPG与RANKL的结合亲和力比RANK高约500倍[4]。因此，RANKL/OPG比率在破骨细胞分化、激活和存活的调节中起关键作用，被认为是骨质疏松发生的关键因素。在多种条件下可以增加该比率以促进骨吸收。

骨质疏松的形成和发展在分子水平上受多种骨相关转录因子和遗传因子调控，包括转化生长因子β、骨形态发生蛋白(bone morphogenetic protein，BMP)、甲状旁腺激素、成纤维细胞生长因子[5,6]。这些骨相关生长因子通过自分泌/旁分泌机制对破骨细胞的分化以及成骨细胞和破骨细胞的活性具有直接或间接的生理和病理调节作用[7]。正常的调节功能受阻，会导致骨形成和骨吸收失衡，最终诱发骨质疏松。如在骨形成和吸收过程中，转化生长因子β从骨基质中释放出来，促进成骨细胞前体的增殖和成熟，抑制破骨细胞的分化和形成，从而抑制骨吸收，同时还可刺激骨髓基质细胞和成骨细胞中OPG的产生[5,8]。研究发现，长期BMP-2刺激人类前成骨细胞，可诱导促炎介质的释放以及破骨细胞生成调节蛋白RANKL的分泌，进而促进破骨细胞的分化和和骨重塑[9]。Wnt/

β-catenin通路是调控骨形成和骨重建的关键通路。Wnt和BMP蛋白可通过协同作用参与骨再生的调节、促进干细胞增殖和成骨分化[10]。研究表明，*Wnt*基因与骨髓间充质干细胞的生长、分化和凋亡有关，从而影响骨形成和发育并调节骨质疏松的信号转导[11]。骨质疏松通过激活Wnt/β-catenin信号通路诱导骨髓间充质干细胞的募集并刺激成骨细胞的增殖和分化，促进成骨细胞中OPG的表达，抑制破骨细胞分化，从而减少破骨细胞形成和骨吸收，而抑制Wnt信号则可诱导破骨细胞分化并促进骨吸收，进而导致骨质疏松[12]。此外，Wnt信号通路在COPD患者的炎症和气道重塑中发挥着重要的免疫调节作用，影响COPD的进展[13]。

COPD患者的全身炎症反应以及糖皮质激素的使用等，导致COPD患者骨质疏松的发生或加重，而骨质疏松患者通常存在与代谢紊乱和免疫相关的炎症因子功能障碍，这会加剧COPD的病程。基于对COPD患者的骨代谢监测，研究人员发现，随着COPD严重程度的增加，这些患者的骨形成和骨转换能力明显减弱、成骨功能障碍[14]。而随着COPD全身炎症反应的发展，常导致炎症细胞因子如白细胞介素-6(interleukin-6，IL-6)、IL-1β和肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)的血清水平升高[15]。这些细胞因子使OPG/RANK/RANKL轴的平衡向RANKL倾斜来增强破骨细胞的形成并刺激骨吸收[16]，从而导致COPD患者发生骨质疏松。而升高的RANKL可以上调IL-6和TNF-α的表达，这可能会加剧COPD患者的炎症环境[17,18]。此外，RANKL还可以通过激活核因子-κB信号转导刺激细胞增殖和/或减少细胞死亡来促进肺组织上皮修复[19]。因此，COPD合并骨质疏松的调节因素众多，机制较为复杂。

2 COPD合并骨质疏松的危险因素

COPD患者发生骨质疏松的危险因素较多，包括一般风险因素和疾病特异性风险因素，如吸烟、缺氧、维生素D水平低、炎症反应、氧化应激、糖皮质激素等。

2.1 吸烟

吸烟是COPD的主要致病因素，同时吸烟也被认为是骨质疏松发展的独立危险因素。吸烟者的肺部特异性变化与COPD引起的骨质疏松性骨折的发病率和死亡率密切相关[20]。骨质疏松研究表明，长期吸烟者的骨密度明显低于非吸烟者，伴有Ⅰ型胶原蛋白沉积减少及成骨细胞的凋亡增加，累积骨质流失可导致骨转换失衡和骨脆性增加，进而增加骨折风险[21,22]。这可能是因为烟草中的尼古丁直接或间接增加了破骨细胞的活性，使血钙和尿钙浓度升高，导致骨质疏松[23,24]。同时，尼古丁抑制芳香酶活性并发挥抗雌激素作用，促进雌激素的分解和代谢，使钙调节激素失调，导致消化道钙吸收减少和血清钙水平降低，从而导致骨密度减低[25,26]。此外，慢性香烟烟雾暴露可增强破骨细胞的活性并诱导骨吸收，从而抑制成骨细胞的分化，同时香烟烟雾提取物可诱导破骨细胞中核因子NF-κB介导的RANKL激活，进而损害骨重塑[27]，并通过降低破骨细胞前体中活性氧(reactive oxygen species，ROS)的产生和抑制破骨细胞凋亡来增加体外破骨细胞的数量，从而增加骨吸收[28]。因此，吸烟与骨代谢和骨质疏松发生发展关系密切，预防吸烟引起的骨质疏松具有积极意义。

2.2 缺氧

COPD患者存在气道阻塞、肺泡通气和血流比例失调、肺功能下降，而肺通气功能障碍会导致肺泡缺氧和二氧化碳潴留，从而引起不同程度的低氧血症和高碳酸血症。缺氧条件下细胞发生应激反应增强和抗氧化功能降低，导致ROS的产生。缺氧不仅会通过增加细胞内的ROS直接破坏骨平衡，还会诱发炎症反应，进一步增强骨吸收[29]。缺氧还可以降低成骨细胞的分化和活性，并增加破骨细胞的生成和骨吸收能力，同时可以减少骨形成和成骨细胞基质矿化，进而改变骨重塑[30]。缺氧也能通过激活NF-κB配体和巨噬细胞集落刺激因子促进破骨细胞分化[31]。缺氧诱导因子-1α(hypoxia inducible factor-1α，HIF-1α)是细胞缺氧反应的关键转录调节因子，也是一种在骨再生过程中受生物力学和促炎信号调节的适应性蛋白。HIF-1α一方面通过调节血管生成-成骨细胞偶联促进骨再生，另一方面通过诱导成骨细胞代谢重编程，促进细胞无氧糖酵解，保证缺氧条件下成骨细胞的能量供应，进一步促进骨再生和修复[32]。破骨

细胞中HIF-1α的特异性缺失可减轻废用性骨质疏松中骨吸收的减少[33]，而抑制ROS/HIF信号通路则可促进成骨细胞生成，改善高原缺氧引起的骨质疏松[34]。因此，明确缺氧以及缺氧通路与骨质疏松的关系具有重要意义。

2.3 维生素D缺乏

维生素D是一种脂溶性物质，经肝肾激活后转化为有活性的1,25-$(OH_2)D_3$，可增加肠道对钙的吸收和骨吸收，并减少肾脏对钙和磷酸盐的排泄，在钙稳态和骨代谢中起重要作用。低维生素D水平会导致血液中钙水平降低，从而刺激甲状旁腺激素分泌增加，进而导致继发性甲状旁腺功能亢进，这会增加骨质疏松、跌倒和骨折的风险[35]。而维生素D和甲状旁腺激素会影响OPG/RANK/RANKL轴，使RANKL/OPG比率显著升高，破骨细胞分化和活化增加，骨吸收增强[36,37]。同时，维生素D参与成骨细胞和破骨细胞的骨生长和骨重塑，其缺乏会加速骨转换、骨质流失和骨质疏松[38,39]。低维生素D水平还与慢性肌肉骨骼疼痛、肌肉无力和跌倒风险增加有关，这进一步增加了骨折的风险[40]。维生素D缺乏在COPD患者中很常见。随着肺功能的恶化和COPD的加重，维生素D显著下降[41]。研究发现，血清维生素D与COPD患者急性加重之间呈负相关，而补充维生素D可降低中度和重度恶化的风险[42]，改善患者肺功能，有效促进细胞免疫功能恢复，从而提高患者的免疫力[43]。

2.4 全身炎症反应

慢性气道炎症是COPD的主要特征，而全身炎症反应被认为是COPD患者诱发骨质疏松的关键。炎症细胞诱导的许多细胞因子包括IL-1β、IL-6、IL-8、IL-17、TNF-α等作为破骨细胞诱导剂，可增强破骨细胞的形成和活化，并通过调节OPG/RANK/RANKL轴参与骨质疏松的发展[44]，而干扰素-γ、IL-4、IL-10则可以抑制破骨细胞的形成[45]。高水平的IL-6诱导RANKL表达增加，能够在体内和体外直接抑制成骨细胞的成熟和分化，增加破骨细胞生成和骨质流失[46]，而TNF-α可增加成骨细胞凋亡和RANKL的表达，间接导致破骨细胞分化和活性增强并抑制成骨细胞的功能和骨的形成[47]，二者可协同促进破骨细胞的生成。体内外研究发现，COPD患者肺组织中RANKL-RANK和IL-17A的表达增加[48]，而IL-17A缺失可减少暴露于香烟烟雾中小鼠COPD模型骨组织中破骨细胞数量和RANKL表达，并使促破骨细胞炎症细胞因子下调，骨密度增高，骨质流失减弱[49]。上述研究表明，细胞因子网络在维持破骨细胞和成骨细胞之间的骨吸收和形成平衡方面起着关键作用，而细胞因子的失调可能导致骨质疏松等骨骼疾病。

2.5 氧化应激

氧化应激是COPD发病的主要驱动机制。由于香烟烟雾和空气污染中的外源性氧化剂以及肺部炎症和细胞产生的内源性ROS，COPD患者的肺部氧化应激增加[50]。氧化应激可以增加破骨细胞生成，减少成骨细胞向成骨细胞谱系的分化，并降低成骨细胞活性和分化，增加成骨细胞和骨细胞凋亡，从而导致骨质流失[51]。而ROS的过量产生会增加破骨细胞生成，并减少成骨细胞的生成和活性的降低，导致骨结构改变和骨丢失[52]。此外，破骨细胞产生的超氧化物可直接导致骨质退化，这些都促进了骨质疏松的进展。NF-κB激活是一种氧化应激驱动的机制。研究发现，抑制NF-κB可改善COPD患者呼吸功能障碍并减轻氧化应激和炎症反应[53]。而通过抑制氧化应激介导的骨代谢则可以促进成骨细胞的分化并防止骨质疏松的发展[54]。

2.6 糖皮质激素

骨质疏松糖皮质激素目前是治疗COPD的有效方法，但也是诱发继发性骨质疏松的首要原因。全身暴露剂量和糖皮质激素治疗持续时间，以及年龄、低体重指数、基础疾病和低骨密度都是糖皮质激素诱发骨折的危险因素。糖皮质激素使用时间越长、剂量越高，骨折的风险就越高。即使长期糖皮质激素剂量<5 mg/天也会导致骨质流失和骨折[55]。全身性糖皮质激素治疗可增强破骨细胞活性并抑制成骨细胞成熟，从而促进骨吸收并抑制骨形成[56]。糖皮质激素可直接作用于骨组织，通过Wnt信号通路诱导成骨细胞凋亡，通过胰岛素样生长因子-1(insulin-like growth factor-1，IGF-1)抑制成骨细胞前体分化和成骨细胞成熟[57]。另一方面，糖皮质激素通过影响RANKL/RANK/OPG轴、甲状旁腺激素、巨噬细胞集落刺激因子等细胞因子诱导破骨细胞的分化和活性的增强，从而增加骨吸收[58,59]。糖皮质激素还可增加血清甲状旁腺激

素水平，降低肠黏膜钙转运功能，减少肠道钙吸收，并抑制肾小管钙重吸收。另外，糖皮质激素会抑制促性腺激素释放，导致性腺机能减退，还会减少IGF-1，两者都会导致骨质流失增加[60]。IGF-1能刺激Ⅰ型胶原合成促进骨形成，同时抑制骨胶原降解和成骨细胞凋亡。此外，IGF-1诱导的甲状旁腺激素受体磷酸化也增强了成骨细胞到骨细胞的转变[61]。总之，糖皮质激素通过多种方式影响骨代谢，导致骨质流失，诱发骨质疏松。因此，COPD患者接受永久性全身性糖皮质激素治疗后发生骨质疏松的风险很高。

3 COPD合并骨质疏松的预防和治疗

COPD合并骨质疏松的机制复杂，应实施有效和可持续的多学科治疗干预措施，通过针对COPD患者定制个性化的营养干预措施，改善患者不健康的生活方式并结合药物治疗来降低COPD患者的骨折风险。在COPD患者中，戒烟是阻止疾病进展、提高总体生存率和降低长期并发症风险的主要干预措施。除了戒烟之外，还应指导患者减少久坐行为，尤其是老年COPD患者。减肥和日常锻炼也可以逆转骨质疏松。药物治疗是骨质疏松治疗管理的基石，用于预防和治疗脆性骨折风险较高的患者。批准用于治疗骨质疏松的药物包括抗再吸收药物，如双膦酸盐(阿仑膦酸钠、利塞膦酸钠、伊班膦酸钠、唑来磷酸)、狄诺塞麦，合成代谢剂特立帕肽。抗再吸收药物主要靶向并阻断破骨细胞活性，以减少骨吸收和骨密度损失，而合成代谢药物可短暂刺激甲状旁腺激素受体，从而刺激成骨细胞和骨形成[62]。双膦酸盐是目前COPD并发骨质疏松患者的首选药物，其预防和治疗骨质疏松的功效已被广泛研究，并且可在每周口服给药(阿仑膦酸钠70 mg/周或10 mg/天，利塞膦酸钠35 mg/周或5 mg/天)以及静脉注射唑来膦酸盐(5 mg/年)的基础上使用[63]。研究证明，双磷酸盐可显著增加骨质疏松患者腰椎、全髋和股骨颈的骨密度，降低椎骨骨折的风险[64]。狄诺塞麦是一种RANKL抑制剂，是治疗骨质疏松最有效的抗骨吸收药物之一，经FDA批准用于治疗骨折高危男性和女性。每6个月皮下注射60 mg狄诺塞麦，几乎可完全抑制骨转换，减少骨质流失并增加骨密度，从而减少所有骨骼部位的脆性骨折[64]。此外，根据疾病特点和严重程度合理制定糖皮质激素的使用剂量和频率，有助于预防骨质疏松的发生。在剂量和持续时间方面尽量减少口服糖皮质激素的使用，并在最短时间内使用最低有效剂量。维生素D是COPD患者改善骨量的重要补充剂，其不仅可以改善骨骼健康状况，还可以提高整个骨骼肌系统的身体机能。骨质疏松指南建议每日最佳总钙摄入量为1 200~2 000 mg，维生素D3每日摄入量为800~1 000单位，以达到50~125 nmol/L(20~50 ng/mL)的25-羟基维生素D总目标水平[63]。

4 小结

骨质疏松是COPD患者中最常见的骨代谢疾病。骨脆性增加和灵活性降低会降低胸廓活动度，导致呼吸运动受限，进而会抑制呼吸功能并加重COPD。这种恶性循环的形成大大降低了生活质量，增加了患者的死亡率。COPD患者骨质疏松的发生和发展受多种复杂因素的调控，需要创新治疗方法，开发更有效的药物来预防和治疗骨质疏松，以期提高COPD患者的生活质量。此外，COPD作为骨质疏松和骨折的独立风险因素，应加强对COPD患者进行定期骨质疏松筛查和骨密度测量，以预防骨质疏松和骨折的发生、发展。

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