·综述·

特殊人群骨质疏松症研究进展

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中图分类号: R681 **文献标识码**: A **文章编号**: 1006-7108(2015) 06-0737-05

摘要: 骨质疏松症是老年人常见的一种疾病,其最大的危害是增加了骨折的风险。随着人口的老龄化,骨质疏松性骨折的发病率也显著增高,引起了医学研究者的普遍关注。近年来许多研究表明骨质疏松的发生常与一些慢性疾病相关。本文通过分析强直性脊柱炎、慢性炎症、肾病综合征、精神分裂症及智力障碍这几类人群中骨质疏松症的研究进展,探讨骨质疏松症与这些疾病的关系。在以上几种疾病中,引起骨质疏松的因素包括:①TNF-α 和 IL-6 等炎症因子可通过抑制 Wnt/β-catenin 信号通路、引起 OPG/RANKL/RANK 系统平衡失调等途径产生一系列反应从而影响骨代谢,抑制成骨活动,促进破骨活动,加重骨质流失。②由于其他疾病引起的器官功能障碍影响导致钙、维生素 D、雌激素等一些骨代谢相关因子的不足,使得成骨活动受到抑制,导致骨质疏松。③糖皮质激素、抗癫痫药物等影响了骨的代谢。④不良生活习惯、缺乏光照、缺少劳动锻炼、营养不良、体质指数下降等因素在骨质疏松的发生中同样扮演了重要的角色。综上所述,骨质疏松症的发生与多种因素相关,对于老年人,尤其是合并其他慢性疾病的老年人,应当加强骨密度的监测,早诊断,早治疗。

关键词: 骨质疏松;特殊疾病;骨代谢

Osteoporosis in special populations

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Abstract: Osteoporosis is a common disease in the elderly, and its greatest damage is the increased risk of fractures. Along with the population ageing, the incidence of osteoporotic fracture has increased significantly, which draws general attention by medical researchers. In recent years, many studies show that osteoporosis is often associated with some chronic diseases. In this paper, the advance in the research of osteoporosis in special population, who are with ankylosing spondylitis, chronic inflammation, nephrotic syndrome, schizophrenia, and dysgnosia, are summarized in order to further clarify the relationship between osteoporosis and these diseases. In these diseases, the factors to induce osteoporosis include: 1) Inflammatory factors such as TNF-α and IL-6 that suppress bone formation and promote loss of bone mass by suppressing Wnt/β-catenin pathway and unbalancing OPG/RANKL/RANK system; 2) The lack of Ca2 +, Vit D, estrogen, and some cytokines that participate bone metabolism caused by organ dysfunction has been associated with osteoporosis. 3) The use of glucocorticoid, antiepileptics, etc affects bone metabolism. 4) Unhealthy lifestyle, lack of sunshine and exercise, malnutrition, and low body mass index also play an important role in osteoporosis. Osteoporosis is associated with many factors. In the elderly, especially in elderly with other chronic diseases, it is necessary to monitor bone mineral density in order to have early diagnosis and treatment.

Key words: Osteoporosis; special populations; Bone metabolism

骨质疏松症是一种以低骨量和骨组织微结构破坏为特征,导致骨质脆性增加的全身性骨代谢性疾病。影响骨质疏松的因素包括遗传、钙和维生素 D 的缺乏、雌激素不足及老年退行性改变等。许多研究显示骨质疏松的发生与诸多慢性疾病存在关联。本文选取了强直性脊柱炎、慢性炎症、肾病综合征、精神分裂症及智力障碍几种人群,对这几类人群中的骨质疏松症研究进展进行综述,探讨骨质疏松与上述疾病之间的关系。

1 强直性脊柱炎与骨质疏松

强直性脊柱炎(ankylosing sporidylitis, AS)是一

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种主要侵犯脊柱,并累及骶髂关节和周围关节的慢性进行性炎性疾病,与人类白细胞抗原-B27(Human Leucocyte Antigen, HLA-B27)呈强关联。骨质疏松及骨量减少在 AS 患者中普遍存在。在 AS 早期(<10 年)即可通过双能 *X* 线吸收测定法(dualenergy X-ray absorptiometry, DXA)发现腰椎骨密度减低。而在 AS 晚期(≥10 年)患者中以 DXA 测得其腰椎骨密度(Bone mineral density, BMD)与早期组相比增高,可能是与韧带骨赘、椎体韧带骨化有关。以定量计算机断层扫描(quantitative computed tomography, QCT)测得晚期患者的腰椎骨矿物含量仍明显降低,说明在 AS 晚期患者腰椎仍存在骨量流失[1]。

AS 引起骨质疏松的原因尚不明确。关于炎症因子对骨质疏松的影响方面研究较多。肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)可促进 Dickkopf-1(DKK-1)的表达,诱导硬骨素(sclerostin, SOST)的产生,DKK-1 及 SOST 竞争性与 Wnt 的受体 LRP5/6 结合,抑制 Wnt/β-catenin 通路,使骨形成减少[2]。TNF-α 与基质细胞(stromal cells)上的 TNF-α 受体结合,分泌核因子 κ B 受体活化因子配体(receptor activator for nuclear factor-κ B ligand, RANKL)等,促进破骨细胞形成[3]。在炎症刺激下,骨钙素(bone gla protein, BGP)的活性降低,导致骨碱性磷酸酶(bone alkaline phosphatase, BALP)、甲状旁腺素(parathyroid hormone, PTH)、I 型胶原羧基端前肽(collagen type I carboxyterminal propeptide, CICP)活性降低,抑制骨形成。同时,BGP 活性降低使环磷酰胺(cyclophosphamide, CTX)、尿脱氧吡啶酚(deoxypyridinoline, DPD)活性增强而促进了骨破坏,造成骨量减少。HLA-B27 可通过抑制骨胶原蛋白的合成、促进其分解加速骨破坏[4]。而 AS 疾病的活动与 1,25-二羟维生素 D_3($1,25(OH)_2D_3$)的下降也具有相关性[5]。

抗肿瘤坏死因子药物被认为可以对抗骨密度的下降,有研究表明用英夫利昔单抗治疗 AS 患者后,其脊椎及髋关节骨密度较对照组均有提高[6]。在近 6 月内使用过非甾体抗炎药的 AS 患者中,其椎骨骨折风险明显降低,其机制仍不明确。可能因为非甾体类抗炎药可以减少韧带骨赘的形成,减缓脊柱强直的进程,而降低其易损性,并通过减少炎性疼痛及僵硬改善身体功能而帮助维持骨量,减少跌倒风险,进而降低骨折风险[7]。

2 慢性炎症与骨质疏松

许多慢性炎症与骨质疏松有着密切的联系,其中炎症的活动是骨密度下降的重要原因,炎症控制得越好,骨质疏松的治疗效果越好。在髋部骨密度下降的绝经后妇女中,口服维生素 C 降低炎症因子后可使髋部骨密度上升 2%[8]。在不少慢性炎性疾病患者中 TNF-α、IL-1、IL-6、IL-10 和 IL-4 等指标均与骨质疏松有关,每种炎症因子对于骨代谢的作用及炎症因子间的互相影响等还需进一步研究。

慢性炎症导致器官功能障碍也是引起骨质疏松的原因之一。炎性肠病患者因伴有腹泻、纳差、肠营养吸收不良,可导致患者营养状况低下,造成骨量减少。慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)患者因长期慢性缺氧,细胞线粒体氧化过程出现障碍,肾皮质细胞羟化酶功能降低,钙吸收不足,致使患者继发骨质疏松,病情严重者还可能出现高碳酸血症,抑制肾小管排酸,促使患者通过排尿将 H^+ 等排出体外,增加了钙的流失[9]。各种疾病引起的活动减少、长期卧床、光照不足、体重下降等原因同样可能加重骨量的丢失。

药物对骨质疏松的影响不容忽视,糖皮质激素性骨质疏松症是最常见的药物性骨质疏松。糖皮质激素(glucocorticoid, GC)通过调高细胞外因子 DKK1、分泌型 Frizzled 相关蛋白(secreted frizzled related proteins, SFRPs)的表达水平抑制 Wnt/β-catenin 信号通路,从而抑制骨细胞形成;通过增强成骨负性因子 SOST、过氧化物酶体增生物激活受体 γ2(peroxisome Proliferator-activated receptor, PPARγ2)的活性,弱化成骨活性因子核心结合因子(core binding factor alphal-1, Cbfa1)、胰岛素样生长因子-1(insulin-like growth factots-1, IGF-1)的表达来抑制骨形成。同时通过调节 OPG/RANKL/*RANK* 途径促进骨吸收[10]。长期质子泵抑制剂(proton pump inhibitor, PPI)治疗可导致骨密度降低,骨折风险增加[11],原因可能是近端十二指肠的胃酸和酸性环境有利于钙离子的吸收,抑酸剂影响了钙的吸收[12]。非甾体类抗炎药的使用虽然对骨密度没有明显的影响,但却可能影响骨折的愈合。前列腺素不仅可通过增强破骨细胞的活性,加快骨折断端坏死骨以及机化组织的吸收,有利于新生血管的长入,还能刺激血管及成骨细胞增殖,促进骨折愈合。非甾体类抗炎药抑制前列腺素的合成可能是其影响骨折愈合的一个原因。环氧化酶-2(cyclo-oxyge-nase-2, *COX-2*)

的转录调节是骨代谢强有力的调节因子,抑制 COX-2 可影响骨形成减少和骨吸收增多[13]。

3 肾病综合征与骨质疏松

肾病综合征(nephrotic syndrome, NS)中引起骨质疏松的因素也是多方面的。在 NS 活动期血清 IL-1、IL-6、IL-8 和 IL-10 水平明显增加,抑制成骨细胞胶原合成,增强破骨细胞功能,促进骨吸收。NS 患者肾小球滤过膜通透性增高,可导致生长激素(growth hormone, GH)、胰岛素样生长因子-1(insulin like growth factor-1, IGF-1)、胰岛素样生长因子结合蛋白(insulin-like growth factor binding proteins, IGFBPs)、I 型前胶原羧基端肽(procollagen type I carboxyterminal propeptide, PICP)、BGP、维生素 D、钙等物质从尿中丢失增加,导致成骨细胞功能降低。

糖皮质激素是 NS 的首选治疗药物,NS 患者并发骨质疏松与长期使用激素的关系密不可分。而糖皮质激素性骨质疏松在停止了糖皮质激素治疗之后是可逆的,肾病综合征患者停用激素骨密度可以逐渐恢复[14]。双膦酸盐在骨质疏松症的治疗中应用广泛,但其副反应较多。有案例报道骨质疏松患者在口服双膦酸盐 4 月后出现全身水肿,蛋白尿,低蛋白血症,高胆固醇血症等肾病综合征表现,但其血清肌酐正常,电镜下仅有轻度系膜及间质增生。停用双膦酸盐,仅予以利尿剂而未予其他特殊治疗后,症状改善,40 天后蛋白尿消失[15]。一项研究评估了唑仑膦酸对绝经后骨质疏松患者肾功能的影响,虽然短时间内可引起肌酐水平的升高,但经过 3 年的长期观察,肌酐清除率没有明显的变化[16]。目前缺少明确的证据证明双膦酸盐可造成严重的肾功能损害,但对于肾功能不全患者仍应慎用。

4 精神分裂症与骨质疏松

精神分裂症患者骨密度显著低于健康对照者,同时骨质疏松的发生率亦显著增高。这可能与疾病本身和抗精神病药物所致的内分泌紊乱有关。有研究显示,精神分裂症患者中同型半胱氨酸(homocysteine, Hcy)水平升高可以使女性的骨密度水平降低,与男性无关[17]。但同样也有研究认为青年男性精神分裂症患者骨密度降低与血浆 Hcy 升高有关[18]。Hcy 可抑制抗氧化酶的表达,促进细胞内钙超载及氧化应激,通过细胞毒性作用破坏神经细胞,并抑制甲基化代谢,引起中枢神经系统内生物胺神经递质的平衡紊乱,被认为与精神分裂症发病有关。Hcy 在骨及骨胶原的形成和吸收方面也发挥着作用。Hcy 可通过 RANKL 促进破骨细胞的形成,抑制破骨细胞的程序性凋亡;Hcy 可使 αvβ3 mRNA 表达水平升高而增加破骨细胞的活性;Hcy 增加骨髓细胞内活性氧(ROS)产生,而活性氧增加了破骨细胞的数量和活性[19]。Hcy 能够抑制初级成骨细胞的活性,减少骨髓间质干细胞(hBMSCs)分化,促进 hBMSCs 和骨髓间质细胞株(HS25cells)的程序性凋亡。Hcy 增加成骨细胞的氧化应激,通过及线粒体途径诱导成骨细胞的程序性凋亡[20]。Hcy 通过增加破骨细胞数量及活性,使基质金属蛋白酶-21(MMP-21)增加,胶原过度地降解;通过促进成骨细胞凋亡,减少胶原合成。高 Hcy 还可减少赖氨酸介导的胶原连接,影响骨胶原网状结构的形成,使骨骼脆性增加[21]。

抗精神病药物阻断下丘脑多巴胺受体,使泌乳素分泌增加,雌激素水平降低,也可导致骨密度下降,引起骨质疏松[22]。对于精神分裂症患者,因其长年脱离社会、孤独、生活无规律以及缺乏必要的劳动、运动锻炼、依赖他人而生存同样加重其骨质流失。而保持一定时间的运动量,骨矿物质含量会保持相对稳定,反之,骨矿物质含量会迅速下降。

5 智力障碍与骨质疏松

在智力障碍患者,生活方式,营养不良,缺乏光照及劳动锻炼是引起骨质疏松的一个重要因素。神经系统的发育不良可能导致的内分泌紊乱,性腺、甲状腺功能减低,也可引起骨质疏松,而甲状腺功能减低等疾病本来就同时影响骨质及智力的发育。

癫痫发作可引起智力损伤,而颅脑损伤引起智力障碍的患者也可合并癫痫。抗癫痫药物的应用被认为可加重骨质的流失,其机制尚不明。目前比较公认的是肝酶诱导学说,苯妥英钠等肝酶诱导剂促进 Vit D 及甲状腺激素的分解,使骨形成减少[23]。而作为肝酶 P450 的抑制剂,丙戊酸的剂量也与骨密度呈负相关,可能是它增强破骨细胞活动,导致骨形成障碍,使骨量减少[24]。奥卡西平大剂量应用时能降低活性维生素 D,影响骨密度[25],托吡酯可导致代谢性酸中毒,骨组织内蓄积过多的酸性物质,Ca^{2+}、P^{5+}减少,Na^{+}、H^{+}及枸橼酸增多,加速骨组织溶解[26]。值得注意的是,在这一类人群中,由于可能出现癫痫发作、精神行为异常等,故跌倒、外伤风险较正常人高,而发生骨折的风险也高于常人。

6 结论

骨质疏松是一种全身性骨代谢性疾病,可合并多种疾病,其发病、治疗之间存在复杂的联系。在以上几种疾病中,一方面 TNF-a、IL-6 等细胞因子可通过一系列反应影响骨代谢,抑制成骨活动,促进破骨活动,加重骨质流失。另一方面,由于其他全身性疾病影响导致消化道、肾功能障碍,而使得钙、磷等元素,维生素 D、雌激素、甲状旁腺激素、生长激素等激素,以及一些骨代谢相关因子的摄入或吸收减少、丢失过多,致使骨代谢过程中一些重要的原料或中间产物不足,使得成骨活动受到抑制。对于慢性疾病的患者,药物对骨密度的影响不容忽视,糖皮质激素、抗癫痫药物、非甾体类抗炎药、PPI、精神类药物等与骨质疏松均存在关联,其作用及机制仍需进一步研究。另外,不良的生活习惯、缺乏光照、缺少劳动锻炼、营养不良、体质指数下降等,同样也是骨质疏松的危险因素。诊断上目前仍以 DXA 为金标准,但应密切结合临床,根据临床表现、风险因数及辅助检查结果综合判断。治疗上除常规抗骨质疏松治疗外,应结合其他基础疾病的治疗。预防为主,不仅包括脆性骨折的预防,也包括骨量减低的预防。骨质疏松症在老年人中发病率较高,在合并其他慢性疾病时,更应注意骨质疏松危险因素,加强锻炼,改善生活习惯,密切随访,早诊断早治疗,同时警惕骨质疏松药物可能引起的不良反应。对于已经存在骨质疏松的患者,需警惕骨折发生,尤其是对于自主生活能力较差,跌倒风险高的患者。脊柱骨折易并发神经损伤,死亡率及致残率较高,及时的诊断及治疗可以有效地改善患者的预后及生存质量。

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(收稿日期:2014-08-06,修回日期:2014-09-23)

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(收稿日期:2013-10-24,修回日期:2014-01-12)