

· 综述 ·

抑郁症和骨质疏松症关系的研究进展

赫明超^{1,2} 张勇³ 连音³ 王拥军^{1,2} 张岩^{1,2*}

1. 上海中医药大学附属龙华医院, 上海 200032
2. 教育部筋骨理论与治法重点实验室, 上海 200032
3. 深圳平乐骨伤科医院, 广东 深圳 518000

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摘要: 抑郁症是骨质疏松症的重要危险因素之一。抑郁症患者的骨密度比正常人低, 更易发生骨量减少、乃至骨质疏松症。抑郁症患者骨量减少可能与交感神经系统、下丘脑-垂体-肾上腺轴、免疫系统、维生素 D、瘦素、抗抑郁药有关。本文将对抑郁症和骨质疏松症关系的研究进展进行综述。

关键词: 抑郁症; 骨质疏松症; 交感神经系统; 维生素 D; 瘦素

Research progress on the association between depression and osteoporosis

HE Mingchao^{1,2}, ZHANG Yong³, LIAN Yin³, WANG Yongjun^{1,2}, ZHANG Yan^{1,2*}

1. Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200032
2. Key Laboratory (Theory and Therapy of Muscles and Bones) of Ministry of Education, Shanghai 200032
3. Shenzhen Pingle Orthopedic Hospital, Shenzhen 518000, China

* Corresponding author: ZHANG Yan, Email: medicineyan@163.com

Abstract: Depression is one of the important risk factors for osteoporosis. Bone mineral density was lower in patients with depression than that of healthy people, thus, osteopenia, and even osteoporosis are more prone to occur in patients with depression. Osteopenia in patients with depression may be attributed to sympathetic nervous system, hypothalamus-pituitary-adrenal gland, immune system, vitamin D, leptin, and drugs for anti-depression. This review summarized the research progress on the relationship of depression and osteoporosis.

Key words: depression; osteoporosis; sympathetic nervous system; vitamin D; leptin

抑郁症是以持续的心境低落和认知功能障碍为主要临床特征的一种疾病^[1]。抑郁症的终生患病率高达 10%~15%, 据世界卫生组织统计显示, 目前全球抑郁症患者达 3.22 亿人, 到 2020 年, 抑郁症可能成为人类第二大疾病^[2]。

骨质疏松症是骨强度下降导致骨折危险性升高的一种骨骼疾病^[3]。2016 年我国 60 岁以上老年人骨质疏松症的患病率高达 36%^[4], 严重威胁着患者的健康与生命。据预测到 2030 年, 中国大陆地区骨质疏松性骨折发生率将达 436 万例次/年, 至 2050 年达 599 万例次/年, 相应的医疗支出分别为 178 亿

美元和 254 亿美元^[5], 给家庭和社会带来沉重的负担。

1 抑郁症和骨质疏松症的关系

早在 1994 年, Schweiger 等^[6]通过单能定量 CT 扫描抑郁症患者的脊柱骨质情况, 发现抑郁症患者的骨密度比正常人低 15%。后续大量研究^[7-8]也表明抑郁症是骨质疏松症的重要危险因素之一, 高达 15% 的抑郁症患者会出现骨质流失^[9]。绝经后女性抑郁症患者, 骨质疏松症的发病率比没有抑郁症状的女性高 2 倍^[10]。骨质疏松症患者抑郁症的发病率也明显增加, 3 例患有脊柱骨折的患者出现抑郁症的几率增加了 3 倍^[11]。越来越多的研究结果表明, 抑郁症和骨质疏松症之间存在着紧密联系。近年来, 二者之间的作用机制逐渐成为研究的热点。

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* 通信作者: 张岩, Email: medicineyan@163.com

2 抑郁症患者骨量减少的可能诱发因素

2.1 交感神经系统

交感神经系统是自主神经系统的重要组成部分,广泛分布于外周组织器官,其中骨生长板和长骨干骺端密度最大,并主要通过肾上腺素能受体在骨代谢中发挥抑制作用^[12]。基础研究^[13]中,小鼠的双侧前庭病变导致交感神经过度激活,出现骨形成减少和骨吸收增加的低骨量表现,而 β_2 -肾上腺素能受体敲除和给予 β 受体阻滞剂普萘洛尔的小鼠则可预防这种现象。在应激状态下,交感神经的激活对机体功能的调节发挥着重要作用。但抑郁症患者的交感神经系统活性过度增高,去甲肾上腺素分泌增加,通过抑制成骨细胞的骨形成和促进破骨细胞的骨吸收而影响骨重建。Bab等^[14]使用慢性温和刺激(CMS)模型小鼠证明了抑郁样行为和骨质流失之间的因果关系。CMS小鼠出现糖水偏爱百分比下降,嗅探、追逐时间减少等抑郁样行为,同时伴有腰3椎体及股骨远端干骺端骨小梁数量及体积密度的减少、成骨细胞减少、破骨细胞增加等骨质量和结构的实质性损害。抑郁症引起的骨质流失与骨骼去甲肾上腺素和血清皮质酮水平的增加有关, β 受体阻滞剂可以预防CMS模型小鼠的骨质流失,说明抑郁症确实能够通过兴奋交感神经系统,影响骨吸收和骨重建,诱发骨质疏松症。

2.2 下丘脑-垂体-肾上腺轴

下丘脑-垂体-肾上腺(HPA)轴是神经内分泌系统的重要组成部分,参与应激反应的控制及身体活动的调节,适应机体需求的变化,维持机体内环境稳定与健康状态。长期以来,压力和严峻的挑战被认为是抑郁的危险因素。抑郁可导致压力系统持续性激活,抑郁时HPA轴的变化反映压力的变化,调节着抑郁症状的表现。应激时,下丘脑分泌促肾上腺皮质激素释放因子,进而激活垂体分泌促肾上腺皮质激素,最终刺激肾上腺皮质分泌糖皮质激素(主要是皮质醇)^[7]。Lopez-Duran等^[15]对115名(35例抑郁症患者和80名健康人)青少年进行了社会性评价冷压测试,通过结合热应激和社会评价引发皮质醇应激反应。通过对测试前后唾液皮质醇水平的监测发现,在接触应激刺激后,抑郁症患者唾液皮质醇水平的增加程度明显高于普通人。一项包括1354名抑郁症患者和1052名健康对照者的Meta分析^[16]显示,与对照组相比,抑郁症患者的唾液皮质醇平均增加了2.58 nmol/L(95% CI: 0.95~4.21)。

研究表明,女性青春期皮质醇分泌水平升高可作为后期重度抑郁症发病的预测指标^[17]。皮质醇是激活应激反应的关键生理标志物,但过量的皮质醇却是骨质疏松症的重要诱发因素,这是抑郁症诱发骨质疏松的重要原因之一。

2.3 免疫因素

抑郁症与免疫失调有关,特别是与白细胞介素-1 β (IL-1 β)和肿瘤坏死因子- α (TNF- α)等炎症因子增高有关。研究发现^[18]IL-1 β 可以增加骨保护素(OPG)和RANKL的mRNA表达,导致破骨细胞活化,增加骨吸收。TNF- α 可直接活化破骨细胞或通过激活RANKL系统活化破骨细胞,增加骨吸收^[19]。与健康人相比,抑郁症患者的IL-1和TNF- α 水平升高^[20-21],也有大量证据^[22-24]表明细胞因子和炎症反应与氧化应激状态密切相关,氧化应激水平的增加可能是抑郁症诱发骨质疏松症的另一个潜在途径^[25]。

2.4 维生素D

维生素D是一种调节钙磷代谢的脂溶性维生素,与骨质疏松的发病密切相关。维生素D缺乏会引起继发性甲状旁腺功能亢进,增加骨质疏松症和骨折的风险,严重者可能因此降低骨质量并导致骨软化^[26]。补充维生素D可改善骨密度(bone mineral density, BMD)^[27],每天补充>400 IU的维生素D3可以使非椎骨骨折或髌部骨折的风险减少约10%~20%^[26,28]。一项针对52228名韩国人的研究^[29]表明,抑郁症患者的平均血清维生素D水平 $[(16.29 \pm 6.73) \text{ ng/mL}]$ 显著低于非抑郁患者 $[(17.37 \pm 6.64) \text{ ng/mL}]$,血清维生素D水平与抑郁症发病率呈负相关。Sepehrmanesh等^[30]将40例抑郁症患者分为维生素D组($n=20$)和安慰剂组($n=20$),维生素D组患者每周给予一次50 kIU维生素D治疗。8周后对所有患者进行贝克抑郁量表(BDI)评估,发现服用维生素D后,抑郁症患者BDI下降幅度(-8.0)明显大于安慰剂组(-3.3),说明补充维生素D有利于改善患者抑郁症状。因此,抑郁症患者维生素D水平降低是抑郁症诱发骨质疏松症的重要原因之一。

2.5 瘦素

瘦素是由脂肪组织分泌的蛋白质类激素,具有调控骨代谢的生物学作用。瘦素水平的代谢失衡能够诱发骨代谢紊乱^[31]。一项关于206名受试者(103名健康人和103例抑郁症患者)的调查研究^[32]显示,抑郁症患者的血清瘦素水平 $[(10.9 \pm$

12.0) ng/mL] 明显低于健康人 (20.3 ± 24.0) ng/mL。抑郁症患者血清瘦素水平低下是抑郁症患者诱发骨质疏松症的重要原因之一。然而,不同科研团队关于抑郁症患者血清瘦素水平的报道还存在着一定的差异。Chen 等^[33]检测了 407 名孕妇分娩时的血清瘦素水平,并在产后 3 个月使用爱丁堡产后抑郁量表评估其抑郁症状。研究发现,产后抑郁的女性患者分娩时的血清瘦素水平(36.5 ng/mL)明显高于无产后抑郁症状女性(14.5 ng/mL),分娩时高血清瘦素水平可作为出现产后抑郁症状的预测标志物。因此,抑郁症患者血清瘦素水平的改变以及其在抑郁症诱发骨质疏松症病理过程中的生物作用还有待深入探索。

2.6 抗抑郁药

研究表明在治疗剂量下,抗抑郁药的使用与骨矿物质密度降低和骨折风险增加有关。一项涉及 117 494 名瑞典人的队列调查^[34]显示,50 岁以上且在 1 年内有过髌部骨折史的患者中,髌部骨折的发生风险与抗抑郁药物使用显著相关 $[RR = 1.90 (1.55 \sim 2.32)]$, $RD = 3.1 (2.0 \sim 4.3)$ 。

选择性 5-羟色胺再摄取抑制剂(SSRIs)作为临床中广泛使用的抗抑郁药,能抑制突触前神经元对 5-羟色胺的再摄取,从而维持突触间隙更高水平的 5-羟色胺并增加突触后神经传递。但是,大量文献报道 SSRIs 的使用与骨折风险增加有关。一项涉及 906 422 名挪威人的队列调查^[35]显示,原发性髌部骨折患病率为 4.4%,接触抗抑郁药物且伴有髌部骨折的患者为 4.7%。研究还发现,SSRIs 增加髌部骨折的风险($SIR = 1.8$, 95% CI : 1.7~1.8)明显高于三环类抗抑郁药($SIR = 1.4$, 95% CI : 1.3~1.5)。虽然关于使用 SSRIs 和骨折风险之间的关联性可能因药物剂量、用药时间、患者年龄或性别有所不同,但在停止使用 SSRIs 后,髌骨、股骨骨折的 OR 值从 2.31(95% CI : 1.94~2.76)显著降低为 1.64(95% CI : 1.14~2.35)^[36]。

3 总结

大量研究表明,抑郁症是骨质疏松症的重要危险因素。抑郁症患者的骨密度比正常人低,更易诱发骨质疏松症,可能与交感神经系统兴奋性增强、下丘脑-垂体-肾上腺轴激活、IL-1 β 和 TNF- α 等炎症因子增高、血清维生素 D 水平较低、瘦素水平变化及抗抑郁药的使用有关(图 1)。无论具体原因如何,抑郁症患者都应考虑进行骨质疏松症的筛查,并且

在抑郁症合并骨质疏松症患者的用药开发方面尚有很大的研究与创新空间。

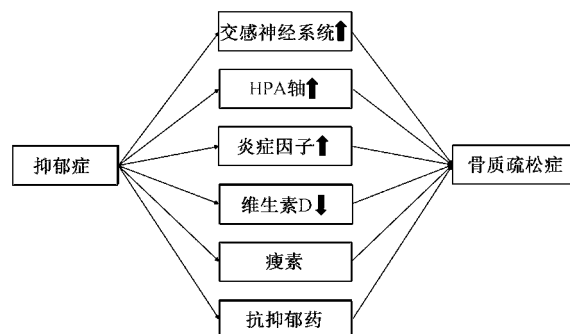


图 1 抑郁症诱发骨质疏松症的可能因素

Fig.1 Possible factors involved in osteoporosis induced by depression

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