

DOI: 10.16781/j.CN31-2187/R.20260059

· 综述 ·

脑-骨轴的调控机制及临床应用前景

杨冠豪¹, 刘登辉², 黄轩¹, 王伟忠³, 刘忠堂^{1*}

1. 海军军医大学(第二军医大学)第一附属医院关节骨病外科, 上海 200433
2. 中国人民解放军联勤保障部队第九〇六医院关节与运动医学科, 宁波 315100
3. 海军军医大学(第二军医大学)海军特色医学中心, 上海 200433

[摘要] 脑-骨轴是神经科学与骨骼生物学交叉领域的新兴概念, 揭示了中枢神经系统与骨骼系统之间复杂的双向调控网络。本文系统综述了脑-骨轴的核心内涵, 深入探讨了大脑通过神经、内分泌及免疫途径对骨骼稳态的调控机制, 以及骨骼作为内分泌器官对大脑功能的反馈调节作用。本文还概述了与脑-骨轴功能紊乱密切相关的疾病谱, 包括神经退行性疾病、精神障碍及代谢性骨病等。此外, 文章聚焦于脑-骨轴理论指导下的潜在临床治疗干预手段, 旨在为相关疾病的跨系统综合治疗提供新的理论依据和策略展望。

[关键词] 脑-骨轴; 中枢神经系统; 阿尔茨海默病; 骨质疏松; 治疗

[引用本文] 杨冠豪, 刘登辉, 黄轩, 等. 脑-骨轴的调控机制及临床应用前景[J]. 海军军医大学学报, 2026, 47(4): 546-552. DOI: 10.16781/j.CN31-2187/R.20260059.

Brain-bone axis: regulatory mechanisms and translational prospects

YANG Guan hao¹, LIU Deng hui², HUANG Xuan¹, WANG Wei zhong³, LIU Zhong tang^{1*}

1. Department of Osteoarthopathy, The First Affiliated Hospital of Naval Medical University (Second Military Medical University), Shanghai 200433, China
2. Department of Joint and Sports Medicine, No. 906 Hospital of Joint Logistics Support Force of Chinese PLA, Ningbo 315100, Zhejiang, China
3. Naval Medical Center, Naval Medical University (Second Military Medical University), Shanghai 200433, China

[Abstract] Brain-bone axis is an emerging concept in the interdisciplinary field of neuroscience and skeletal biology, revealing a complex and bidirectional regulatory network between the central nervous system and skeletal system. This article systematically reviews the core insights of the brain-bone axis, and delves into the mechanisms by which brain regulates skeletal homeostasis through neural, endocrine, and immune pathways and the feedback effects of skeleton (functioning as an endocrine organ) on brain function. This review also outlines the spectrum of diseases closely associated with dysfunction of the brain-bone axis, including neurodegenerative disorders, psychiatric conditions, and metabolic bone diseases. Furthermore, the article focuses on the potential clinical intervention strategies derived from brain-bone axis theory, aiming to provide new theoretical foundation and strategic perspective for integrated cross-system therapeutic approaches to related diseases.

[Key words] brain-bone axis; central nervous system; Alzheimer's disease; osteoporosis; therapy

[Citation] YANG G, LIU D, HUANG X, et al. Brain-bone axis: regulatory mechanisms and translational prospects[J]. Acad J Naval Med Univ, 2026, 47(4): 546-552. DOI: 10.16781/j.CN31-2187/R.20260059.

脑-骨轴 (brain-bone axis) 揭示了大脑与骨骼之间存在着密切且动态的双向分子与功能对话, 打破了传统上将两者视为独立系统的认知局限^[1]。大脑作为“指挥中心”, 可通过下丘脑、交感神经系统等精细调控骨代谢平衡^[2]。与此同时, 骨骼也不再是被动的“支撑结构”, 而是作为活跃的内

分泌器官, 通过分泌多种骨源性因子反作用于大脑^[3]。这种双向通讯紊乱是多种共病的重要病理基础。阿尔茨海默病 (Alzheimer's disease, AD) 与骨质疏松之间形成的恶性循环即为典型例证^[4], 充分凸显脑-骨轴在维持机体整体健康中的核心作用。随着分子生物学、神经影像学及神经调控技术

[收稿日期] 2026-01-27 [接受日期] 2026-03-11

[基金项目] 国家自然科学基金(82172437, 82202730), 浙江省自然科学基金(LMS25H060007)。Supported by National Natural Science Foundation of China (82172437, 82202730) and Natural Science Foundation of Zhejiang Province (LMS25H060007)。

[作者简介] 杨冠豪, 硕士生。E-mail: jointyoung@163.com

*通信作者 (Corresponding author)。E-mail: surgeon_liu@163.com

的快速发展,研究者们对脑-骨轴相关信号通路和细胞机制的认识不断深化^[5],为开发针对神经系统与骨骼系统共病的创新疗法开辟了新方向。本文综述了与脑-骨轴相关的临床疾病及治疗进展。

1 脑-骨轴的双向调控机制

1.1 脑-骨轴的核心概念与理论框架 脑-骨轴概念源于2002年Gérard Karsenty团队的重要发现,该团队首次证实中枢神经系统可通过瘦素通路远程调控小鼠骨密度^[6],标志着脑-骨轴研究正式开启。脑-骨轴的核心内涵是中枢神经系统与

骨骼之间经由神经、体液及免疫途径构成的双向调节网络^[7]。一方面,大脑通过下丘脑及自主神经系统自上而下主动调控骨代谢^[8];另一方面,骨骼并非大脑指令的被动接受者,而是通过自下而上反馈机制分泌的骨源性因子穿越血脑屏障影响中枢神经系统功能^[9]。这种双向通讯使机体能够整体应对激素波动、应激事件等内外变化,维持骨骼稳态与整体生理功能的协调^[10]。因此,脑-骨轴理论超越了传统局部骨骼疾病视角,为骨质疏松等疾病的发病机制提供了全新的系统性解释框架(图1)。

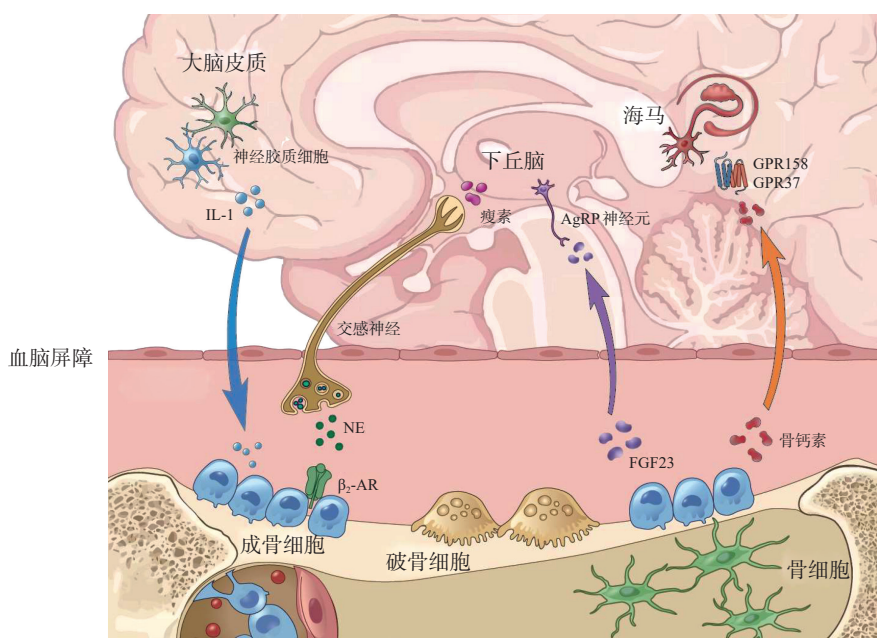


图1 脑-骨轴的双向调控机制

IL-1:白细胞介素1;NE:去甲肾上腺素; β_2 -AR: β_2 肾上腺素能受体;AgRP:刺鼠基因相关蛋白;FGF23:成纤维细胞生长因子23;GPR158:G蛋白偶联受体158;GPR37:G蛋白偶联受体37。

1.2 大脑对骨骼的调控途径 大脑主要通过神经、内分泌及免疫途径调控骨骼。其中,交感神经系统扮演关键角色,其释放的去甲肾上腺素与成骨细胞表面 β_2 肾上腺素能受体结合,升高环腺苷酸水平并激活蛋白激酶A,进而上调NF- κ B受体活化因子配体表达,抑制骨形成;同时通过成骨细胞分泌的NF- κ B受体活化因子配体间接激活破骨细胞的NF- κ B受体活化因子信号,促进破骨细胞分化与骨吸收^[11-12]。下丘脑作为高级整合中枢,通过分泌瘦素、神经肽Y等调控骨代谢^[13]。此外,中枢神经系统的多种细胞(包括神经胶质细胞和神经元)可产生IL-1,该促炎细胞因子通过乙酰胆碱作用于表达烟碱型乙酰胆碱受体的成骨细胞和破骨细胞,

从而调控骨吸收过程,在骨骼局部营造促吸收炎症微环境,加速骨质流失^[14]。上述多层次下行通路共同构成大脑对骨骼的调控网络。

1.3 骨骼对大脑的反馈调控机制 骨骼作为内分泌器官,可通过分泌多种骨源性因子对大脑进行反馈调控。其中骨钙素(osteocalcin)的作用尤为突出,它能穿越血脑屏障,靶向作用于大脑皮质、海马体、下丘脑等关键脑区,并通过与G蛋白偶联受体158、37等中枢特异性受体结合调控认知功能、情绪状态及应激反应等核心中枢活动^[15-16]。成纤维细胞生长因子23(fibroblast growth factor 23, FGF23)除调节磷代谢外,也可作用于下丘脑神经元参与能量调节。研究证实,FGF23分布于大鼠下

丘脑(包括弓状核、正中隆起等)、第三脑室室管膜及脉络丛等,且脑室内注射 FGF23 可增强下丘脑能量代谢相关刺鼠基因相关蛋白神经元的活性^[17]。此外,脂联素、骨桥蛋白等因子可通过相应中枢受体参与食欲、认知功能调控^[18]。这些骨源性因子构成骨骼到大脑的上行反馈,可使骨骼代谢与负荷状态实时传递至中枢神经系统^[19]。

2 脑-骨轴功能紊乱相关疾病

2.1 神经退行性疾病与骨骼健康 AD 与骨骼健康状况密切相关,AD 患者常伴骨密度降低和骨折风险增加。一项纳入 1 772 名老年人的 meta 分析表明,与无痴呆的老年人相比,AD 患者的骨密度显著降低,尤其是在股骨颈部位^[20]。其潜在机制涉及多方面:(1)脑内病理改变可通过神经内分泌和炎症通路影响骨骼。研究表明,股骨颈骨密度降低与 AD 易感脑区(如左楔前叶)皮质减少显著相关^[21]。(2)骨钙素在 AD 进程中发挥重要作用。研究发现,男性早期 AD 患者血清骨钙素水平异常升高,且与认知评分呈负相关^[22]。(3)AD 相关病理蛋白质可直接影响骨骼。动物模型实验显示,AD 模型小鼠骨组织中存在淀粉样蛋白异常沉积^[23]。而通过自噬途径特异性清除淀粉样蛋白不仅能改善认知功能障碍,还可有效恢复骨代谢稳态^[24]。

帕金森病患者同样高发骨质疏松和骨折,此类风险由多种因素共同介导。帕金森病的核心运动症状(如震颤、运动迟缓和姿势不稳)可直接导致患者活动减少、跌倒风险增高,这是骨折的重要外部诱因^[25]。而骨骼脆弱的内在因素同样关键,帕金森病患者常有维生素 D 缺乏,这与接受日照不足、维生素 D 摄入减少等有关,可导致骨密度降低^[26]。临床中帕金森病患者的骨骼健康常被忽视,研究显示,即便新诊断的帕金森病患者中脆性骨折的发生率较高,但接受骨密度检测和抗骨质疏松治疗患者的比例仍较低^[27]。因此,优化筛查策略以提高帕金森病患者的骨质疏松检出率至关重要,应初步评估患者用药情况、肌肉力量、活动能力及营养状况,若存在多项危险因素则建议行髋骨/脊柱骨密度检测以明确诊断^[28]。

2.2 精神心理障碍与骨骼疾病 抑郁症与骨骼疾病之间存在超越行为层面的病理生理双向关联。一

方面,重度抑郁症可导致神经内分泌紊乱与免疫异常,从而干扰骨代谢。临床可见未服药的抑郁症患者骨形成标志物(如 I 型胶原氨基末端前肽)代偿性升高,抑郁相关行为改变(如食欲减退、日照与活动减少)及部分抗抑郁药物(如文拉法辛、氟伏沙明、氟西汀等)长期使用也会进一步抑制骨重塑,增加骨质疏松风险。另一方面,骨质疏松也是抑郁症的独立危险因素,骨细胞与神经细胞的相互作用可反向加剧抑郁、焦虑等情绪障碍,甚至影响物质依赖性渴求症状,而情绪障碍与物质滥用又进一步破坏骨代谢平衡,最终形成恶性循环^[29]。

慢性应激与焦虑症个体的交感神经系统持续激活,是应激性骨质疏松的重要发病机制。基于慢性不可预测轻度应激模型的动物研究显示,模型小鼠不仅出现焦虑、抑郁样行为,也伴随骨代谢显著紊乱,表现为骨密度降低,骨小梁数量减少、分离度增加,皮质骨厚度变薄,破骨细胞活性显著增强^[30]。此外,慢性应激诱导的全身性低度炎症与氧化应激亦参与其中,促炎因子如 IL-6、TNF- α 等升高可刺激骨吸收;海马体神经炎症及下丘脑-垂体-肾上腺轴过度激活与骨代谢异常相关,而抗炎干预可同时改善神经与骨骼状态^[31]。社会隔离等强烈心理应激同样可导致实验小鼠骨形成减少与骨量丢失^[32]。

2.3 代谢性骨病与中枢神经系统改变 原发性骨质疏松症与中枢神经系统功能密切相关,共同构成脑-骨共病恶性循环。临床研究表明,骨质疏松患者常伴有认知功能下降和抑郁情绪,且骨密度降低与卒中后认知功能损害程度独立相关^[33]。当骨质疏松合并骨少肌症(osteosarcopenia)时,对认知的负面影响较单独患病更显著,其协同机制涉及慢性低度炎症、氧化应激与营养不足等^[34]。此外,骨质疏松还可能通过减少骨钙素分泌削弱其对大脑的支持作用,从而加剧认知衰退^[35]。

肥胖与代谢综合征构成连接代谢、骨骼与大脑健康的病理网络。在肥胖状态下,脂肪组织功能紊乱,瘦素、脂联素等脂肪因子分泌异常,既影响骨代谢,也作用于大脑食欲中枢^[36]。同时,肥胖诱导的慢性低度炎症导致大量促炎因子产生,这些因子可透过血脑屏障加剧神经炎症,潜在损害认知功能^[37]。2 型糖尿病合并骨质疏松患者的静息态功能 MRI 研究提示,左中颞回、右枕上回、右顶

上小叶、右角回及左楔前叶等多个脑区自发活动显著异常,局部一致性(ReHo值)明显升高,且右顶上小叶自发活动的异常程度与骨钙素水平呈负相关^[38]。

3 基于脑-骨轴的临床治疗干预策略

目前,针对脑-骨轴功能紊乱相关疾病已形成与疾病特征相匹配的干预策略与方案。例如,对帕金森病患者,高度重视并系统评估非运动症状,尤其是自主神经功能障碍表现,有助于骨质疏松的早期识别与全程管理^[39];对抑郁症患者,补充n-3多不饱和脂肪酸可作为辅助治疗途径,其能在改善抑郁症状的同时对骨代谢产生积极影响^[40];对肥胖症患者,靶向向下丘脑神经元的免疫蛋白酶体已成为治疗肥胖和代谢紊乱的新策略^[41]。

3.1 针对神经调控通路的干预 针对神经调控通路的干预策略旨在通过调节中枢神经系统与骨骼之间的神经通讯来防治脑-骨轴相关疾病。交感神经系统是连接大脑与骨骼的关键通路,使用 β 受体阻滞剂(如普萘洛尔)阻断该通路为治疗神经源性骨质疏松提供了潜在方向,但目前仍以动物实验为主,亟待开展临床试验以评估其安全性、有效性与用药方案^[42]。下丘脑作为代谢与内分泌整合中枢,其分泌的瘦素、神经肽Y对骨稳态有重要调控作用,靶向这些通路为恢复能量与骨代谢平衡、治疗相关骨病提供了新思路。其中,瘦素通路受瘦素抵抗制约,仅适用于特定代谢疾病的补充治疗;神经肽Y通路靶向性强且无天然抵抗现象,具有更高的临床转化优先级,值得开展更多的研究验证其临床价值^[43]。此外,下丘脑-垂体轴功能完整性对骨骼健康至关重要,其损伤可间接影响骨代谢,提示在相关疾病治疗中应进行整体评估与干预^[44]。

3.2 靶向骨源性因子的治疗策略 靶向骨源性因子为治疗脑-骨共病提供了新思路。补充骨钙素或其类似物可同时发挥保护认知功能和促进骨形成的双重效益,为AD合并骨质疏松患者提供了潜在治疗策略。然而,骨钙素的临床应用仍面临多重限制:一是骨钙素存在多受体结合特性,易引发信号通路交叉干扰,影响治疗效果;二是骨钙素的疗效呈现显著剂量差异,难以形成普适性治疗方案;三是骨钙素广泛参与能量代谢、生殖调控等生理过程,长期使用可能扰乱内分泌稳态^[45-46]。此外,

FGF23-Klotho轴异常与慢性肾脏病密切相关,调控该轴可能有助于延缓肾性骨病进展。具体而言,慢性肾脏病1~2期患者需以预防FGF23失衡为核心,阻断代谢轴早期紊乱;慢性肾脏病3~4期患者需针对性纠正激素异常,控制FGF23升高;慢性肾脏病5期患者则需强化毒性因子清除与保护性因子维持,通过降低FGF23毒性减少不良事件发生风险^[47]。靶向骨桥蛋白、硬化蛋白等其他骨源性因子亦是潜在的研究方向^[48]。

3.3 生活方式调整 生活方式调整作为调节脑-骨轴最安全的干预策略,核心在于通过多模式整合协同促进脑与骨骼健康。制定个体化运动处方是实现双重获益的有效手段,规律有氧运动(如每周3次、每次30min的跑步、骑行、游泳等)及阻力训练(如每周2次、每次60min的哑铃训练、弹力带训练、器械力量训练等)可机械刺激骨骼、促进骨形成,同时提高脑源性神经营养因子水平,改善认知与情绪^[49-50]。在营养物质摄入方面,钙与维生素D是维持骨骼正常功能的基础,成年人钙推荐摄入量800mg/d,最高摄入量2000mg/d^[51]¹⁹⁴⁻¹⁹⁹;维生素D推荐摄入量10 μ g/d,最高摄入量50 μ g/d^[51]³³⁴⁻³⁴³。补充特定营养素(如短链脂肪酸)可调控食欲、情绪等中枢行为,但目前尚未形成统一推荐剂量^[52]。值得注意的是,不同神经活性药物对骨骼的影响存在差异,临床用药应权衡神经获益与骨骼风险^[53]。总体来说,综合生活方式干预可通过改善血管功能、减轻炎症等多重机制协同保护脑与骨骼,是应对增龄相关脑-骨共病的重要研究方向^[54]。

4 结语

脑-骨轴理论将脑与骨骼视为双向调控的整体,突破了传统器官孤立研究的局限。该领域研究已从现象关联逐步深入至机制解析,初步勾勒出“神经-内分泌-免疫”调控过程的基本轮廓。然而,脑-骨轴是高度复杂且情境依赖的动态网络,不同信号在不同病理状态下的作用存在差异。此外,如何将实验室发现转化为临床有效疗法,仍需设计严谨的临床试验进行研究。

展望未来,以脑-骨轴为指导的精准医学与个体化综合治疗有赖于神经科、骨科、内分泌科等多学科深度融合与协作,也需要从基础研究、临床实

践及技术驱动等层面进行更深入的探索。在基础研究层面,应持续深化对 β_2 肾上腺素能受体、骨钙素及瘦素等经典靶点的机制解析,同时积极拓展骨源性外泌体、非编码RNA等新兴方向;在临床实践层面,可探索建立联合门诊、多学科病例讨论等一体化诊疗模式,同时推动生物样本库与临床数据平台共建共享;在技术驱动层面,需深度融合人工智能与多模态组学数据,系统挖掘脑-骨交互的潜在机制,构建以机器学习和动态建模为核心的计算研究体系。通过从上述层面的系统性推进,有望开发出能同步维护“脑”与“骨骼”健康的系统性干预策略,最终从根本上改善脑-骨共病患者的整体生活质量与长期预后。

[参考文献]

- [1] HANSDA S, DAS H. Unraveling the bone-brain communication network[J]. *Biology*, 2025, 14(9): 1279. DOI: 10.3390/biology14091279.
- [2] LIANG T Z, JIN Z Y, LIN Y J, et al. Targeting the central and peripheral nervous system to regulate bone homeostasis: mechanisms and potential therapies[J]. *Mil Med Res*, 2025, 12(1): 13. DOI: 10.1186/s40779-025-00600-8.
- [3] HE T, QIN L, CHEN S, et al. Bone-derived factors mediate crosstalk between skeletal and extra-skeletal organs[J]. *Bone Res*, 2025, 13(1): 49. DOI: 10.1038/s41413-025-00424-1.
- [4] GAO S, QI L, LI N, et al. The role of the brain-bone axis in skeletal degenerative diseases and psychiatric disorders. A genome-wide pleiotropic analysis[J]. *Prog Neuropsychopharmacol Biol Psychiatry*, 2025, 139: 111388. DOI: 10.1016/j.pnpbp.2025.111388.
- [5] ZHAO S, UMPIERRE A D, WU L J. Tuning neural circuits and behaviors by microglia in the adult brain[J]. *Trends Neurosci*, 2024, 47(3): 181-194. DOI: 10.1016/j.tins.2023.12.003.
- [6] TAKEDA S, ELEFTERIOU F, LEVASSEUR R, et al. Leptin regulates bone formation via the sympathetic nervous system[J]. *Cell*, 2002, 111(3): 305-317. DOI: 10.1016/s0092-8674(02)01049-8.
- [7] SHI H, CHEN M. The brain-bone axis: unraveling the complex interplay between the central nervous system and skeletal metabolism[J]. *Eur J Med Res*, 2024, 29(1): 317. DOI: 10.1186/s40001-024-01918-0.
- [8] HOUWELING P, KULKARNI R N, BALDOCK P A. Neuronal control of bone and muscle[J]. *Bone*, 2015, 80: 95-100. DOI: 10.1016/j.bone.2015.05.006.
- [9] GUAN Q, CAO Y, ZOU J, et al. Bone-derived factors: regulating brain and treating Alzheimer's disease[J]. *Biology*, 2025, 14(9): 1112. DOI: 10.3390/biology14091112.
- [10] ABEYNAYAKE N, ARTHUR A, GRONTHOS S. Crosstalk between skeletal and neural tissues is critical for skeletal health[J]. *Bone*, 2021, 142: 115645. DOI: 10.1016/j.bone.2020.115645.
- [11] CHAMOUNI A, SCHREIWEIS C, OURY F. Bone, brain & beyond[J]. *Rev Endocr Metab Disord*, 2015, 16(2): 99-113. DOI: 10.1007/s11154-015-9312-5.
- [12] ELEFTERIOU F. Impact of the autonomic nervous system on the skeleton[J]. *Physiol Rev*, 2018, 98(3): 1083-1112. DOI: 10.1152/physrev.00014.2017.
- [13] HUANG S, LI Z, LIU Y, et al. Neural regulation of bone remodeling: identifying novel neural molecules and pathways between brain and bone[J]. *J Cell Physiol*, 2019, 234(5): 5466-5477. DOI: 10.1002/jcp.26502.
- [14] QUIROS-GONZALEZ I, YADAV V K. Central genes, pathways and modules that regulate bone mass[J]. *Arch Biochem Biophys*, 2014, 561: 130-136. DOI: 10.1016/j.abb.2014.06.005.
- [15] KHRIMIAN L, OBRI A, RAMOS-BROSSIER M, et al. Gpr158 mediates osteocalcin's regulation of cognition[J]. *J Exp Med*, 2017, 214(10): 2859-2873. DOI: 10.1084/jem.20171320.
- [16] LI J, LOU S, BIAN X. Osteocalcin and GPR158: linking bone and brain function[J]. *Front Cell Dev Biol*, 2025, 13: 1564751. DOI: 10.3389/fcell.2025.1564751.
- [17] URSEM S R, DIEPENBROEK C, BACIC V, et al. Localization of fibroblast growth factor 23 protein in the rat hypothalamus[J]. *Eur J Neurosci*, 2021, 54(4): 5261-5271. DOI: 10.1111/ejn.15375.
- [18] CHEN H, SHANG D, WEN Y, et al. Bone-derived modulators that regulate brain function: emerging therapeutic targets for neurological disorders[J]. *Front Cell Dev Biol*, 2021, 9: 683457. DOI: 10.3389/fcell.2021.683457.
- [19] WAN Q Q, QIN W P, MA Y X, et al. Crosstalk between bone and nerves within bone[J]. *Adv Sci (Weinh)*, 2021, 8(7): 2003390. DOI: 10.1002/advs.202003390.
- [20] CEZAR N O C, DA SILVA S G, AILY J B, et al. Older adults with Alzheimer's disease have lower bone mineral density compared to older adults without dementia: a systematic review with meta-analysis of observational studies[J]. *J Geriatr Phys Ther*, 2023, 47(3): 162-170. DOI: 10.1519/JPT.0000000000000386.
- [21] TAKANO Y, TATEWAKI Y, MUTOH T, et al. Voxel-based morphometry reveals a correlation between bone mineral density loss and reduced cortical gray matter volume in Alzheimer's disease[J]. *Front Aging Neurosci*, 2020, 12: 178. DOI: 10.3389/fnagi.2020.00178.

- [22] PU Z, TANG X, FEI Y E, et al. Bone metabolic biomarkers and bone mineral density in male patients with early-stage Alzheimer's disease[J]. *Eur Geriatr Med*, 2020, 11(3): 403-408. DOI: 10.1007/s41999-020-00289-z.
- [23] SURYADEVARA V, KREHBIAL C J, VALIYA A K, et al. Presenilin L166P mutation, a model of familial Alzheimer's disease, leads to early onset bone loss[J]. *Compr Physiol*, 2026, 16(1): e70097. DOI: 10.1002/cph4.70097.
- [24] DUAN R, HONG C G, CHEN M L, et al. Targeting autophagy receptors OPTN and SQSTM1 as a novel therapeutic strategy for osteoporosis complicated with Alzheimer's disease[J]. *Chem Biol Interact*, 2023, 377: 110462. DOI: 10.1016/j.cbi.2023.110462.
- [25] Ó BREASAIL M, SINGH K P, LITHANDER F E, et al. Management of osteoporosis in Parkinson's disease: a systematic review of clinical practice guidelines[J]. *Mov Disord Clin Pract*, 2025, 12(3): 285-295. DOI: 10.1002/mdc3.14311.
- [26] CAN N U, ALAGÖZ A N. The relationship among bone mineral density, bone biomarkers and vitamin D levels in patients with Parkinson's disease[J]. *Clin Lab*, 2020, 66(8). DOI: 10.7754/Clin.Lab.2019.190615.
- [27] FLEET J L, CARTER B, CADARETTE S M, et al. Fracture incidence and osteoporosis treatment in Parkinson's disease: a population-based cohort study[J]. *Osteoporos Int*, 2026, 37(2): 459-467. DOI: 10.1007/s00198-025-07802-9.
- [28] TAN Y J, LIM S Y, YONG V W, et al. Osteoporosis in Parkinson's disease: relevance of distal radius dual-energy X-ray absorptiometry (DXA) and sarcopenia[J]. *J Clin Densitom*, 2021, 24(3): 351-361. DOI: 10.1016/j.jocd.2020.07.001.
- [29] TSAO H M, HUANG M C, LIU T H, et al. Association of bone turnover markers and craving reduction in patients with alcohol use disorder during withdrawal: exploring the role of bone-brain axis[J]. *Alcohol Clin Exp Res (Hoboken)*, 2024, 48(12): 2294-2302. DOI: 10.1111/acer.15472.
- [30] ZHANG J, LI J, HUANG J, et al. Psychological stress disturbs bone metabolism via miR-335-3p/Fos signaling in osteoclast[J]. *eLife*, 2025, 13: RP95944. DOI: 10.7554/eLife.95944.
- [31] HE M C, XIA S H, PAN H, et al. Chaihu-Shugan-San ameliorated osteoporosis of mice with depressive behavior caused by chronic unpredictable mild stress via repressing neuroinflammation and HPA activity[J]. *Drug Des Devel Ther*, 2024, 18: 5997-6015. DOI: 10.2147/DDDT.S480077.
- [32] MOUNTAIN R V, LANGLAIS A L, HU D, et al. Social isolation through single housing negatively affects trabecular and cortical bone in adult male, but not female, C57BL/6J mice[J]. *Bone*, 2023, 172: 116762. DOI: 10.1016/j.bone.2023.116762.
- [33] LEE S H, PARK S Y, JANG M U, et al. Association between osteoporosis and cognitive impairment during the acute and recovery phases of ischemic stroke[J]. *Medicina (Kaunas)*, 2020, 56(6): 307. DOI: 10.3390/medicina56060307.
- [34] CHOU Y Y, LIN C F, LEE Y S, et al. The associations of osteoporosis and possible sarcopenia with disability, nutrition, and cognition in community-dwelling older adults[J]. *BMC Geriatr*, 2023, 23(1): 730. DOI: 10.1186/s12877-023-04431-x.
- [35] SCHATZ M, SARAVANAN S, D'ADESKY N D, et al. Osteocalcin, ovarian senescence, and brain health[J]. *Front Neuroendocrinol*, 2020, 59: 100861. DOI: 10.1016/j.yfrne.2020.100861.
- [36] REBOLLEDO-SOLLEIRO D, SOLLEIRO-VILLAVICENCIO H, VELASCO M, et al. Obesity, metabolic syndrome and olfactory perception[J]. *Rev Neurol*, 2020, 70(2): 53-66. DOI: 10.33588/rn.7002.2019204.
- [37] KORAC B, KALEZIC A, PEKOVIC-VAUGHAN V, et al. Redox changes in obesity, metabolic syndrome, and diabetes[J]. *Redox Biol*, 2021, 42: 101887. DOI: 10.1016/j.redox.2021.101887.
- [38] LIU M, LI J, LI J, et al. Altered spontaneous brain activity in patients with diabetic osteoporosis using regional homogeneity: a resting-state functional magnetic resonance imaging study[J]. *Front Aging Neurosci*, 2022, 14: 851929. DOI: 10.3389/fnagi.2022.851929.
- [39] ZHANG F, LU J, ZHANG Y, et al. Significance of non-motor symptoms and development of a screening tool for osteoporosis in Parkinson's disease[J]. *Clin Neurol Neurosurg*, 2024, 239: 108181. DOI: 10.1016/j.clineuro.2024.108181.
- [40] WANG F, YUAN H, JIN K, et al. Effects of fish oil supplementation on bone turnover markers in depression: a pilot study[J]. *Front Nutr*, 2024, 11: 1464526. DOI: 10.3389/fnut.2024.1464526.
- [41] ALBORNOZ N, ÁLVAREZ-INDO J, DE LA PEÑA A, et al. Targeting the immunoproteasome in hypothalamic neurons as a novel therapeutic strategy for high-fat diet-induced obesity and metabolic dysregulation[J]. *J Neuroinflammation*, 2024, 21(1): 191. DOI: 10.1186/s12974-024-03154-z.
- [42] LIU M, LIU Y, YU J, et al. Molecular mechanisms and therapeutic implications of the sympathetic nervous system in bone-related disorders: a brain-bone axis perspective[J]. *Bone Res*, 2025, 13(1): 98. DOI:

- 10.1038/s41413-025-00494-1.
- [43] ZHOU R, GUO Q, XIAO Y, et al. Endocrine role of bone in the regulation of energy metabolism[J]. *Bone Res*, 2021, 9(1): 25. DOI: 10.1038/s41413-021-00142-4.
- [44] VANKOEVERING K K, SABETSARVESTANI K, SULLIVAN S E, et al. Pituitary dysfunction after radiation for anterior skull base malignancies: incidence and screening[J]. *J Neurol Surg B Skull Base*, 2020, 81(1): 75-81. DOI: 10.1055/s-0039-1679893.
- [45] SHAN C, ZHANG D, MA D N, et al. Osteocalcin ameliorates cognitive dysfunctions in a mouse model of Alzheimer's disease by reducing amyloid β burden and upregulating glycolysis in neuroglia[J]. *Cell Death Discov*, 2023, 9(1): 46. DOI: 10.1038/s41420-023-01343-y.
- [46] LOSKUTOVA N, HONEA R A, VIDONI E D, et al. Bone density and brain atrophy in early Alzheimer's disease[J]. *J Alzheimers Dis*, 2009, 18(4): 777-785. DOI: 10.3233/JAD-2009-1185.
- [47] TAKASHI Y, KAWANAMI D. The role of bone-derived hormones in glucose metabolism, diabetic kidney disease, and cardiovascular disorders[J]. *Int J Mol Sci*, 2022, 23(4): 2376. DOI: 10.3390/ijms23042376.
- [48] DU Y, ZHANG L, WANG Z, et al. Endocrine regulation of extra-skeletal organs by bone-derived secreted protein and the effect of mechanical stimulation[J]. *Front Cell Dev Biol*, 2021, 9: 778015. DOI: 10.3389/fcell.2021.778015.
- [49] JINICH-DIAMANT A, SIMPSON S, ZUNIGA-HERTZ J P, et al. Neural and molecular changes during a mind-body reconceptualization, meditation, and open label placebo healing intervention[J]. *Commun Biol*, 2025, 8(1): 1525. DOI: 10.1038/s42003-025-09088-3.
- [50] REN J, XIAO H. Exercise for mental well-being: exploring neurobiological advances and intervention effects in depression[J]. *Life (Basel)*, 2023, 13(7): 1505. DOI: 10.3390/life13071505.
- [51] 中国营养学会. 中国居民膳食营养素参考摄入量: 2023版[M]. 北京: 人民卫生出版社, 2023.
- [52] MA K, WANG F, ZHANG X, et al. Acupuncture and nutritional parallels in obesity: a narrative review of multi-pathway modulation of the microbiota-gut-brain axis[J]. *Front Nutr*, 2025, 12: 1610814. DOI: 10.3389/fnut.2025.1610814.
- [53] MÖDDER U I, ACHENBACH S J, AMIN S, et al. Relation of serum serotonin levels to bone density and structural parameters in women[J]. *J Bone Miner Res*, 2010, 25(2): 415-422. DOI: 10.1359/jbmr.090721.
- [54] THUNBORG C, WANG R, ROSENBERG A, et al. Integrating a multimodal lifestyle intervention with medical food in prodromal Alzheimer's disease: the MIND-AD_{mini} randomized controlled trial[J]. *Alzheimers Res Ther*, 2024, 16(1): 118. DOI: 10.1186/s13195-024-01468-x.

[本文编辑] 杨亚红