·综述·

骨质疏松症的治疗及柚皮苷抗骨质疏松的研究进展

刘朝晖[1,2] 马剑雄[1] 马信龙[1*]
1.天津市天津医院骨科研究所,天津 300050
2.天津医科大学,天津 300070

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摘要: 骨质疏松症是一种常见的代谢性疾病,典型的病理改变是全身骨量降低以及骨微结构的退化和破坏,骨质疏松性骨折是其严重的并发症。随着人口老龄化进展,骨质疏松症,尤其是最常见的绝经后骨质疏松,给全球公共卫生事业带来极大的经济负担,同时也严重影响了患者自身的生活质量。当前普遍认为治疗骨质疏松的关键在于恢复机体内骨代谢的动态平衡,而细胞之间的信号通路是研究的关键。随着新的信号通路不断出现,以其为作用靶点的新型药物也层出不穷,本文初步综述了近年来骨质疏松症的流行病学特点、目前的主要诊断技术、经典药物及新型药物的作用机制,以及从中药骨碎补中提取的单体化合物柚皮苷治疗骨质疏松症的研究进展。

关键词: 骨质疏松症;治疗方法;中药;柚皮苷

Treatment of osteoporosis and research progress of naringin

LIU Zhaohui[1,2], MA Jianxiong[1], MA Xinlong[1*]
1. Institute of Orthopaedics, Tianjin Hospital, Tianjin 300050, China
2. Tianjin Medical University, Tianjin 300070, China
* Corresponding author: MA Xinlong, Email: maxinlong8686@sina.com

Abstract: Osteoporosis is a common metabolic disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility. With an ageing population, osteoporosis, especially the most common postmenopausal osteoporosis has brought great economic burden to the global public health, and also seriously affects the quality of life of patients. It is generally believed that the key to the treatment of osteoporosis is to restore the dynamic balance of bone metabolism, and the signal pathway between cells has become a key to research. With the emergence of new signaling pathways, new types of drugs targeting them are also emerging. This paper reviews the epidemiology, current main diagnostic technologies, mechanism of action of classical drugs and new drugs, and the research progress of naringin extracted from Rhizoma Drynariae for the treatment of osteoporosis.

Key words: osteoporosis; treatment; Chinese Traditional Medicine; naringin

骨质疏松症(osteoporosis,OP)是一种全身性骨代谢疾病,特征是患者骨量降低和骨组织微结构退化及破坏,骨质脆性增加,日常生活中轻微外力导致的骨折风险上升[1]。随着全球老龄化进程的发展,骨质疏松症的发病率显著上升,已经成为老年人致死致残的主要疾病之一[2]。当前药物治疗主要是通过恢复骨代谢的动态平衡达到治疗目的,本文主要综述了该病的流行病学、诊断技术、经典药物的作用机制以及中药提取物柚皮苷对骨代谢的积极作用。

1 流行病学

目前全球约有 2 亿人患骨质疏松症,骨折是其最严重的并发症。2015 年我国骨质疏松性骨折约为 269 万例次,预计 2035 年达到 483 万例次,2050 年将达到 599 万例次;我国在 2015 年、2035 年和 2050 年用于治疗骨质疏松性骨折的费用将分别达到 720 亿元、1 320 亿元和 1 630 亿元[3]。从 2005 年到 2025 年美国骨质疏松性骨折相关医疗费用将累计达 4 740 亿美元。预计 2025 年美国骨质疏松性骨折将高达 300 万人次[4]。随着人口老龄化进程

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* 通信作者: 马信龙,Email:maxinlong8686@sina.com

的加剧，骨质疏松症的医学和社会学意义将进一步提高[5]。

2 诊断与治疗

2.1 诊断标准

骨质疏松症的诊断以骨密度为主要标准，主要包括双能 X 线吸收检测法、定量计算机断层扫描技术、外周定量计算机断层扫描技术和定量超声等。目前公认的诊断标准仍然是双能 X 线吸收检测法[3]，世界卫生组织规定：骨密度低于峰值 1 至 2.5 个标准差为骨量低下；骨密度低于峰值 2.5 个标准差及以下为骨质疏松症[6]。

2.2 治疗方法

目前常用药物包括：双膦酸盐类、核因子 κB 受体活化因子配体抑制剂（RANKL inhibitor）、激素替代治疗（HRT）、选择性雌激素受体调节剂（SERM）、特立帕肽、新型药物阿巴洛帕肽（Abaloparatide）和 EVENITY ™（romosozumab-aqqg）[7]。

2.2.1 骨吸收抑制剂

双膦酸盐类药物与羟基磷灰石亲和力高，与骨重建活跃的骨表面特异性结合，抑制破骨细胞，减缓骨量流失[3]。其安全性已经得到了广泛认可，但长期服用仍然有一些不良反应，包括胃肠道反应、肾脏毒性、甚至是罕见的下颌骨坏死及非典型骨折。考虑到该类药物半衰期长，与骨质亲和力较强，为了减少不良反应，治疗一段时间后可以考虑停药。停药后体内的残余药量仍继续发挥治疗作用。建议口服阿仑膦酸钠的治疗期为 5 年[8]，唑来膦酸为 3～6 年[9]，之后考虑停药进入药物假期（drug holiday）。

RANKL 抑制剂，如狄诺塞麦，是破骨细胞关键信号通路 RANKL 的人源化单克隆抗体[10]，骨代谢受 OPG/RANK/RANKL 信号通路调控，成骨细胞分泌 OPG 和 RANKL，破骨细胞前体细胞表达 RANK，OPG 与 RANK 结合能抑制破骨细胞分化，而 RANKL 和 RANK 结合能促进破骨细胞的分化[10-11]。一项历时 10 年纳入 7 808 名受试对象的研究显示狄诺塞麦是安全有效的[12]，如果患者治疗前骨折风险较低，症状缓解后可以停药[9]，相比双膦酸盐类，停药后患者会出现较明显的骨量流失[13]。

雌激素可以抑制破骨细胞活性、促进破骨细胞凋亡，也有促进成骨细胞合成胶原的作用[14]。北美更年期协会 2017 年激素治疗声明表示雌激素替代治疗可以增加患者罹患子宫内膜癌的风险，但是没有明确的数据表明会增加乳腺癌和卵巢癌的风险[15]，如果采用激素替代治疗建议在绝经早期使用。

雌激素受体调节剂（SERM）与雌激素受体结合，激动或拮抗雌激素。第一代 SERM 他莫西芬最初用于治疗乳腺癌，但有较严重的不良反应，如子宫内膜癌、下肢深静脉血栓及脑卒中[16]。他莫昔芬能明显降低血浆脂蛋白，对降低心血管疾病具有积极作用[17]。第三代 SERM 雷洛昔芬，在骨组织中发挥雌激素样作用，在乳腺、子宫发挥拮抗作用[18]，不增加罹患乳腺癌[19]和子宫内膜癌[20]风险。研究表明，雷洛昔芬可以明显降低 60 岁以上女性盆腔器官脱垂的风险[21]，但一项纳入 24 523 名绝经妇女的研究表明长期使用雷洛昔芬可以使下肢深静脉血栓和肺水肿的发生率增加 62%[22]

2.2.2 骨形成促进剂

特立帕肽是一种促合成代谢药物，本质是重组人甲状旁腺素（human parathyroid，hPTH）。PTH 是哺乳动物钙稳态的重要调节因子[23]，钙离子浓度上升抑制 PTH 释放。PTH 能增加肾脏 1α 羟化酶的活性，促进合成 $1,25(OH)_2D_3$，促进胃肠道钙吸收。PTH 作用于肾脏远端小管增强原尿中钙的重吸收。在成骨细胞中，PTH 激活 PTH Ⅰ型受体，既能活化环磷酸腺苷依赖的蛋白激酶 A，又能激活钙依赖的蛋白激酶 C/磷脂酶 C[24]，前者的成骨作用更为重要[23]。

阿巴洛帕肽是抗骨质疏松的新型药物，本质是人甲状旁腺素相关蛋白类似物，阿巴洛帕肽能更高效的激活环磷腺苷通路，改善骨质疏松，降低骨重建和高血钙症这两个特立帕肽常见的不良反应[25-26]。动物实验发现长期使用该药会增加大鼠骨肉瘤的发生率，但还没有相应的队列研究[27]。美国 FDA 于 2017 年 4 月批准该药上市[28]。2018 年 3 月欧盟 EMA 人用药委员会拒绝该药进入欧洲市场，认为该药的部分临床试验未严格遵循药品临床试验管理规范，不能证明获益大于风险[29]。

EVENITY ™（romosozumab-aqqg）是一种人源化骨硬化蛋白（Sclerostin）的单克隆抗体，美国 FDA 于 2019 年 4 月 9 日批准上市，尤其适用于高骨折风险的绝经妇女[7]。Sclerostin 作用于 Wnt 通路，促进胞内 β-catenin 降解，抑制成骨[30]；增加骨细胞 RANKL 的表达，提高 RANKL/OPG 的比例，刺激破骨细胞吸收骨质[31]。

3 柚皮苷的研究进展

中药骨碎补治疗骨质疏松历史久远,效果显著。柚皮苷是骨碎补的主要活性成分,具有抗炎、抗氧化和改善循环的作用[32]。近年来柚皮苷的药理机制已经形成比较全面的理论体系。

Liu等[33]检测不同浓度柚皮苷干预下人羊水干细胞的增殖分化情况,用Wnt信号通路抑制剂DDK-1做对照,发现翻译生成BMP4, RUNX2, β-catenin和Cyclin D1的mRNA明显升高,表明柚皮苷能通过BMP和Wnt信号通路来促进成骨细胞分化;Li等[34]在研究柚皮苷缓解椎间盘髓核退化从而缓解腰痛的研究中发现BMP-2的含量随柚皮苷浓度上升而增加,Habauzit等[35]通过研究给与老年大鼠柚皮苷干预,发现其BMP含量增加,骨密度增加,证明柚皮苷具有促进BMP表达,增加骨量的作用;Shangguan等[36]通过给予去势大鼠不同浓度的柚皮苷灌胃,分析血清内皮素和一氧化氮的差异,同时用不同浓度的柚皮苷体外培养血管内皮细胞,检测线粒体膜电位、胞内内皮素和一氧化氮的差异,表明柚皮苷通过内质网应激和线粒体介导的通路抑制血管内皮细胞凋亡;Lin等[37]研究表明,柚皮苷通过IHH信号通路上调Foxc2,促进骨髓间充质干细胞成骨分化;An等[38]综述了柚皮苷、淫羊藿、圣草苷、枸橘甙等多种天然化合物治疗骨质疏松的机制,涉及OPG/RANKL信号系统、MAPK信号系统、BMP信号系统、雌激素受体介导通路、氧化应激介导通路、一氧化氮介导通路等多种途径,以及碱性磷酸酶、Ⅰ型胶原蛋白、骨唾液蛋白、骨钙素、骨调素等多种骨特异性基质蛋白;Wang等[39]研究氧化应激条件下脂肪诱导的间充质干细胞的成骨分化情况,发现氧化应激抑制碱性磷酸酶活性、降低RUNX2和OSX的转录水平、降低β-catenin and clyclin D1蛋白的表达量,从而抑制脂肪诱导的间充质干细胞的成骨分化,柚皮苷可以解除这种抑制作用;Wong等[40]发现中药骨碎补的活性成分对去势大鼠有雌激素样保护作用;Ang等[41]发现柚皮苷可以抗维甲酸诱导的骨质疏松,通过抑制RANKL介导的NF-κB和ERK信号干扰破骨细胞形成和骨吸收;抑制关键破骨细胞标记基因的表达,通过抑制RANKL介导的IκB-α降解来抑制RANKL诱导的NF-κB活化;抑制RANKL介导的ERK磷酸化;Zhang等[42]通过检测人骨髓间充质干细胞在不同浓度柚皮苷作用下的增殖分化情况,发现在一定浓度范围内,促进成骨的作用和柚皮苷的浓度呈计量依赖关系,但200 μg/mL的柚皮苷对细胞存在毒副作用。以上研究证实柚皮苷可以通过很多经典的信号通路协同调节体内骨代谢,具有很好的应用潜力。

4 总结与展望

随着世界老龄化进程的发展,骨质疏松症已经成为威胁公共健康的第二大全球性疾病。骨质疏松症的高发病率、高致残率和高致死率给全世界卫生事业带来了巨大的压力。然而它的危害不仅仅止于骨量的丢失、慢性疼痛以及骨折,更会给患者带来恐惧、焦虑、抑郁及丧失自信等不良心理,影响到患者的情感、认知以及社会功能。骨质疏松症是一种慢性疾病,需要长期干预,但因药物潜在的不良反应难以进行数年乃至数十年的长期服用,影响前期的治疗效果。针对这种情况1979年Frost就提出了"序贯治疗"的理念[43],近年来多项队列研究结果证明序贯治疗比传统单一用药或联合用药效果更好[44-47]。除此之外,许多传统中药具有不良反应小,可长期服用,并且作用机制多样,能从各个角度协同调节改善骨代谢的失衡,研发潜力巨大,相信未来中医中药会在治疗骨质疏松的医疗中发挥越来越重要的作用。

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