中国骨质疏松杂志 2011 年 11 月第 17 卷第 11 期 Chin J Osteoporos, November 2011, Vol 17, No. 11
Published online www. wanfangdate. com. cn doi:10.3969/j. issn. 1006-7108. 2011. 11. 020

· 综述 ·

骨质疏松治疗进展

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中图分类号：R681 文献标识码：A 文章编号：1006-7108(2011)11-1019-06
摘要：骨质疏松症是以骨量减少，骨组织细微结构受损，导致脆性骨折等为特征的一种常见疾病，随着我国老年人口的增加，逐渐步入老年社会，患有骨质疏松症的人口数也在逐步增加，对骨质疏松症引起的一系列严重后果是医学界非常重视的一个问题。近年来随着科技的发展，各种新的方法和技术使临床疗效显著提高，现对骨质疏松症的治疗进展做一综述。
关键词：骨质疏松；治疗；进展

Progress in osteoporosis treatment *HUANG Peng, ZHANG Shenqi, GUO Yanmei, et al. General Hospital of Chinese People's Liberation Army, Beijing* 100853, China
Abstract: Osteoporosis is a common disease characterized by bone loss, micro structure damage of bone tissue, and fragility fracture. With the increase of elderly population, China has become an aging society. The number of people with osteoporosis increases gradually. A series of severe complications caused by osteoporosis are emphasized in the medical field. With the development of technology recently, all kinds of new methods and techniques have significantly improved the clinical efficacy. This paper reviews the progress in osteoporosis treatment.
Key words: Osteoporosis; Therapy; Progress

骨质疏松症(osteoporosis, OP)是以低骨量和骨组织微细结构破坏为特征，导致骨脆性和骨折危险性增加的一种全身骨骼性疾病。其最大危害是骨折，骨微结构决定骨质量，骨微结构破坏是骨质疏松性骨折发生直接原因[1]。作为全球性健康问题，其严重性仅次于心血管病[2]。2008 年 2 月，美国国家骨质疏松基金会(National osteoporosis foundation, NOF)公布了 2008 版骨质疏松症防治临床指南，按该指南诊断标准，约 50% 的 50 岁以上白人妇女和 1/6 男性需要药物治疗，这显然是十分沉重的经济负担[3]。OP 病因十分复杂，国内外学者均认为与年龄、性别、体质、营养、运动、生活方式等多因素有关[4]，因而决定了其治疗的多样化。近年来随科技发展，各种新方法和技术使临床疗效显著提高，现对 OP 治疗技术及方法做一综述。

基金项目：全军医药卫生科研基金课题编号：10BJZ16
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1 药物治疗

1.1 钙及维生素 D

钙是维持骨量的基本物质，维生素 D 及其衍生物可促进肠道钙吸收，抑制骨吸收，稳定骨密度，且是骨骼生长及激活成骨细胞和破骨细胞所必需[5]。钙剂和维生素 D 是治疗 OP 最基本的也是必需的药物[6]。血清 25(OH)D 低于 25ng/mL 使 65 岁以上老年男性髋部骨折风险增加[7]。英国一项全国性调查显示，大于 50% 的成人维生素 D 水平偏低，16% 的人冬季和春季维生素 D 严重缺乏[8]。维生素 D 缺乏四肢及背部弥漫性疼痛和肌无力很常见，有时亦被误诊为抑郁症躯体表现[9]。目前成人推荐日摄入剂量为 400IU/天，但仅为防治某些因缺乏维生素 D 引起的疾病的最低剂量，如果没有皮肤合成就不能达到维生素 D 理想水平。专家们认为当达到最佳钙情况和最佳健康状态时，血清 25-OHD 浓度位于 75nmol/L 或更高时是最佳维生素 D 水平[10]。近来许多学者都主张增加维生素 D 推荐摄入量[11]。既往认为维生素 D3 优于维生素 D2，Bonura 认为二者一样好[12]。一天中血钙浓度最低

值在晚上，为提高生物利用度，补钙应在晚饭后、睡前服用。当维生素D浓度大于500nmol/L时易发生中毒，服用时亦应注意不可盲目加量[13]。

1.2 二磷酸盐类

这类药是人工合成的非生物降解性焦磷酸盐类似物，能抑制破骨细胞介导的骨吸收。有效增加骨密度[14]。具有抑制骨吸收和抑制钙化两个基本作用[15]，从而减少绝经后和其他原因OP患者骨折风险[16]。口服双膦酸盐利塞一年后发现：脊椎和股骨近端的骨密度增加，且椎体压缩性骨折发生风险降低[17]。但有报道唑来膦酸治疗后患者总骨质疏松性骨折发生率和病死率降低，而髋部骨折发生率并未降低[18]。Bonnick等[19]报道阿仑膦酸钠单用与联合钙制剂均能增加患者BMD，而单用钙尔奇D对患者BMD影响不大。二磷酸盐作为一类重要的防治OP的药物，治疗（特别是2型OP）机理主要是作用于破骨细胞，抑制骨吸收，降低骨转换，并通过改变使破骨细胞活化的骨基质性质抑制新生破骨细胞形成[20]。Romanello等[21]认为二磷酸盐是通过激活成骨细胞核酸受体信号和表达热休克蛋白Hsp90，促使其增殖分化。难以记住用药时间，且服用药物要求的限制（餐前或餐后快速口服，体位直立30～60min等），使其依从性差，限定了其真正的临床有效率及临床应用[22]。与每周服用1次相比，患者更加偏爱每月服药1次，同时76.6%的患者认为每月服药1次更为方便，依从性更好[23]。静脉应用双膦酸盐给药方便、依从性好、安全性高[24]。作为广泛使用的骨吸收抑制剂，它的副作用不容忽视[25]，长期应用可过度抑制骨转换，影响骨强度，而且部分患者消化道反应比较严重，长期使用要慎重。

1.3 锶盐

随着雷尼酸锶（Strontium ranelate）的研制成功及其在提高骨强度、降低骨质疏松性骨折发生率等方面的作用，锶盐在OP药物干预中的应用前景获得广泛重视[26,27]。雷奈酸锶是一种不同于其他任何药物的新的抗OP药物，通过激活钙敏感受体和潜在的未知受体发挥作用[28]，同时增加成骨细胞的前列腺素E生成水平，来刺激骨形成，可能通过调节细胞核因子-KB受体活化因子配体（RANKL）/骨保护素比率来减少破骨细胞形成和骨吸收[29]。与双膦酸盐抑制骨吸收、减低骨转换不同，雷尼酸锶中活性成分——锶原子进入体内发挥抑制骨吸收、刺激骨形成双向调节作用[30]。锶可干扰破骨细胞分化成熟及其骨吸收活性[31]，还可促进骨髓基质于细胞向成骨细胞分化，刺激成骨细胞增殖和骨基质蛋白表达和增加骨形成[32]。该作用可能与通过钙敏感受体（calcium-sensing receptor）或其他受体激活cox-2，刺激PGE表达有关[33]。Chattopadhyay等[34]认为雷尼酸锶刺激成骨细胞的作用与经由HEK293细胞介导的钙感知受体有关。雷奈酸锶能够增加前成骨细胞增殖、加速成骨细胞分化、增加I型胶原合成、加速骨矿化[35]。Reginster等[36]报道雷奈酸鳃治疗绝经后OP 3年，降低脊椎骨骨折风险41%，降低髋部骨折危险度36%；治疗5年，髋部骨折危险度降低43%，脊椎骨骨折危险度降低24%。骨中锶的增加增强了骨的x线削减作用，可导致估高的骨密度值，但雷尼酸锶治疗有效提高骨强度的作用是肯定的[37]。但服用雷奈酸锶可引起静脉血栓形成和肺栓塞，其他不良反应有精神心理、意识、记忆力的障碍[38]。

1.4 护骨素

护骨素（osteoprotegerin，OPG）由成骨及骨髓基质细胞分泌而产生，OPG-RANKL-RANK系统是近年来发现的在破骨细胞分化过程中的一个重要信号传导通路。该系统调控成骨细胞与破骨细胞平衡，从而改变骨形成和骨吸收的动态平衡关系。RANKL与破骨细胞前体细胞表达的RANK结合后，进破骨细胞前体细胞的生长、活化和存活，而OPG与RANK竞争性结合RANKL，阻止RANKL与RANK之间的结合，从而在早期阶段即抑制破骨细胞前体细胞向成熟破骨细胞分化及生长[39]。动物研究显示，OPG基因敲除鼠模型表现为严重骨质疏松，髋部缺乏骨小梁，破骨细胞数量增加及骨转换效率高，而过度表达OPG转基因鼠则表现为严重的骨硬化症[40]。OPG为防治绝经后骨质疏松症开辟了新途径，特别是重组人OPG（rhOPG）和OPG基因治疗已成为研究热点[41]。针对RANKL的完全人源化单克隆抗体药物狄诺塞麦（denosumab）已获批准上市，它可模拟内源性OPG效应，阻断RANKL与RANK结合的相互作用，使破骨细胞生成减少，可用于绝经后OP的骨丢失治疗，以抑制破骨细胞分化和活化，减少骨吸收，增加骨密度，降低患者骨折的风险[42]。另外DKK1（Dickkopf-1）的反义寡核苷酸可以增加成骨细胞的数量，降低RANKL的表达，减少破骨细胞的发生，增强去卵巢大鼠股骨的骨矿含量和骨密度。靶向DKK1的治疗仍然要解决特异性的问题，其对骨骼外其它器官的毒副作用是今后研究的关键[43]。

1.5 雌激素

雌激素是维持人体骨吸收、骨形成平衡的重要因素，长期以来雌激素一直被视为保护绝经后妇女的标准制剂[44]。当血中雌激素浓度低于 40pmol/L 时，骨质疏松症和骨质疏松性骨折发生率大大提高[45]。相关研究证实，雌激素缺乏亦可导致男性骨量丢失[46]。对去睾丸大鼠的研究也表明，雌激素升高骨密度的作用优于雄激素。雌激素在调节骨吸收方面起主导作用[47]。绝经后 OP 患者随着雌激素水平降低，除通过细胞受体途径外，还可通过细胞因子途径促进成骨细胞的分化及破骨细胞的凋亡[48]。雌激素对骨代谢的作用机制可能通过以下途径起作用：①影响骨代谢局部调节因子，如 IL-1、TNF、TGF-β 等，从而影响骨代谢；②降低骨骼对甲状旁腺素的敏感性；③增加降钙素合成；④增强肾脏 1-α 羟化酶的作用，促进肠钙吸收，降低肾排钙量；⑤直接通过骨细胞上的雌激素受体起作用[49-50]。绝经后 OP 防治中备受关注且疗效确切的治疗方案是雌激素替代疗法，但雌激素替代疗法的副作用使其在临床上的应用仍存疑虑。

1.6 降钙素

降钙素是由甲状腺 c 细胞分泌的一种抑制破骨细胞活性的激素，能特异性地直接作用于破骨细胞的受体，减弱破骨细胞的活性及数量，减慢破骨细胞成熟过程，从而抑制骨吸收[51-52]，还可作用于神经中枢特异性受体，升高 β-内啡肽水平，阻止钙离子进入神经细胞，抑制疼痛介质前列腺素的合成及刺激内源性镇痛物质内啡肽释放，从而减轻疼痛[53]。该类制剂可作为高转换型 OP 患者腰背痛（特别是椎体急性骨折时）的首选治疗药物。Karsdal 等认为饭前 10min 口服鲑鱼降钙素比饭后服用生物利用度更高[54]。

2 理疗

物理疗法主要包括体外冲击波疗法（ESWT）、低强度脉冲超声（LIPUS）、振动疗法等。体外冲击波治疗仪产生高能震荡波经特殊介质将压力和能量集中于局部，局部微循环血流加速，加速局部代谢反应[55]。微循环改善后，渗出物吸收与消散加快，降低了组织间的张力，消除水肿，解除了对神经末稍的机械性压迫，ESWT 还可以损伤疼痛感受器，影响疼痛信号传递，进而治疗疼痛症状[56]。Ma 等[57]报道高能震波能上调骨形态发生蛋白（BMP）和血管内皮生长因子（VEGF）基因在骨组织中的表达。进而诱导血管化发生，增强膜内化骨及加速软骨化骨。Tischer 等[58]的实验也验证了上述观点并发现使用较大能量时，诱导的新骨形成在背侧骨皮质也能够观察到，而且产生皮质骨破裂和骨膜分离。Hofmann 等[59]离体细胞培养实验显示，体外震波能产生的牵张应力和流体剪切应力能够作用于骨细胞、成骨细胞等应力感受细胞，引起与骨生长和成骨细胞相关的多种基因增量调节，显著刺激来源于正常人类松质骨的成骨细胞的增殖和分化，并呈剂量依赖关系。Appleford 等[60]认为体外震波通过刺激成骨祖细胞对应力信号的传导，启动细胞内的化学信号传递过程，同时激活细胞膜表面的整合素受体，增加粘附蛋白的合成以利于细胞在骨小梁表面的附着。体外实验发现，人的骨髓基质于细胞在诱导分化过程中，经 LIPUS 作用后明显加速向软骨细胞表型分化，同时相关糖蛋白和胶原含量也增加[61]。Bandow 等[62]报道随着成骨细胞的成熟，LIPUS 明显促进其 RANKLmRNA 表达，而后者对刺激破骨细胞分化调节起着最重要的作用。Gilsanz 等[63]认为采用高频低能全身振动能增强低 BMD 的青年女性承重骨与肌肉的发育。且在成年期维持较高增长水平，可预防老年时 OP。Xie 等[64]通过动物实验发现全身振动疗法可使骨膜骨面积、骨髓面积、骨皮质面积和该治疗部位惯性矩明显增大，但破骨细胞活性无显著差异；并推测这种效应如果维持至成年期，松质骨、皮质骨及肌肉良性结构改变可减少 OP 性骨折的发病率。实验结果证明，短期高频（90Hz）全身垂直振动（WBVV）显著提高 BMD，其对松质骨的效应相对皮质骨更明显，从而提高骨生物力学性质[65]。Rubinacci 等[66]推测成骨潜力局限于骨皮质并与振动振幅大小呈依赖关系。以上各种疗法直接或间接诱导血管化发生，增强膜内化骨及加速软骨化骨，成骨作用和血管发生作用发生耦联，从而促进骨形成和骨修复[67]。与药物治疗相比，其最大优点是患者无不良反应无创伤、无感染、费用低廉，是一种有较好应用前景的治疗 OP 的方法。但其镇痛作用的有效维持期尚缺乏远期随访。

3 运动疗法

目前的研究显示，在一定强度范围内的力量训练是提高骨骼 BMD 的有效锻炼方式[68]。Kam 等认为 1 年以上负重或有氧运动的肌肉锻炼才可增强 BMD，从而降低骨折的发生[69]。不同运动项目中，运动负荷通过不同途径对骨骼产生影响，其中起重

要作用的是骨骼受力方向，纵跳等高强度冲击性运动对骨的刺激，改变了骨的内外部结构和形状[70]。应力刺激也会引起骨组织电力学作用，产生负压电位，易于结合胶原和羟磷灰石等阳性钙离子，促进骨形成[71]。Renno 等[72]通过动物实验证明跳跃运动对骨质疏松大鼠的骨骼和肌肉都有刺激效应，肌肉的过度生长能刺激骨质含量。Buer 等[73]认为运动或机械负荷的力学刺激时成骨细胞增殖和分化增加，引起骨形成增加。运动疗法与钙、维生素 D 均有协同效应，三者结合能协同减少骨丢失、促进钙的吸收和新骨形成，其影响主要发生在松质骨[74]。

4 总结

综上所述，随着人们对 OP 病因、病理机制的认识及分子生物学研究的进一步深入，新疗法会不断涌现。理想的疗法应具有抗骨吸收和促骨形成的双向作用，有待进一步研发。因此，目前 OP 治疗可联合各种方法，使其更加系统化、规律化。

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(收稿日期: 2011-06-30)

骨质疏松治疗进展

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刊名： 中国骨质疏松杂志ISTIC
英文刊名： Chinese Journal of Osteoporosis
年，卷(期)： 2011,17(11)