·文献综述·

抗骨质疏松药物对骨折愈合的影响

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骨质疏松性骨折(Osteoporotic Fracture,OPF)[1]常见于老年人,出现再骨折风险高,严重影响患者的生活质量,增加其社会、家庭的经济负担。在临床治疗过程中,除常规进行骨折复位、固定外,仍需进行抗骨质疏松治疗,目前以药物为主。为同时治疗骨质疏松与骨折,了解抗骨质疏松药物对骨代谢的影响至关重要。抗骨质疏松药物不仅通过抑制骨吸收或促进骨形成来抵消骨丢失,还对骨折愈合进程有一定影响。本研究将抗骨质疏松药物从骨代谢作用角度分类,综述其对骨折愈合方面的影响,以期对后续研究及临床治疗骨质疏松性骨折提供参考。

1 降低骨吸收药物

1.1 双磷酸盐类药(Bisphosphonates,BPs)

双磷酸盐类药在骨修复和骨折动物模型中的作用是肯定的,大多数研究表明,其对骨痂组织的大小、数量和矿化程度没有负面影响并可改善骨机械性能,提高生物力学强度,降低骨折风险,提高软骨钙化后骨痂组织成熟的延迟率[2-4]。

双磷酸盐类药的预防骨折功效已有临床证据充分证明,阿仑膦酸钠(Alendronate Sodium,AS)显著降低骨折风险,对脊椎和髋部骨折风险降低分别超过70%和50%[5-6]。Clement等[7]和Duckworth等[8]均得出早期给予阿仑膦酸钠不会对骨折愈合或临床结果产生不利影响的结论。另外有研究从影像学角度评估阿仑膦酸钠给药时机对骨折愈合的影响,同样发现早期给药不影响临床结果[9-10]。但双磷酸盐类药的给药时间和方案可能对骨痂性质有显著影响,双磷酸盐类药优先沉积在通过软骨内骨化愈合的骨折部位,促进骨痂形成[11]。相比每周给药,延迟1~2周的单次给药有助于产生更大体积、更高强度及更好机械性能的骨痂[12-13],这提示临床可通过延迟给药调节控制愈合过程中的骨重塑。在动物实验中,观察到双磷酸盐类药对改善植入物固定和松质骨愈合方面的正面影响[14-21]。植入物稳定性增加表现在骨-植入物接触、植入物周围骨体积和植入物固定强度等方面改善,这可能是由于双磷酸盐类药的抗吸收作用导致骨量增加,从而增加植入物与骨的接触。Lin等[22]的临床研究也发现双磷酸盐类药显著减少关节置换术后假体周围骨丢失,尤其术后的前3个月和12个月后最明显。

双磷酸盐类药的不良反应率一般较低,但在大剂量或长期使用后,也观察到颌骨坏死和股骨不典型骨折等并发症的发生[23-24]。另外双磷酸盐类药对脊椎骨折愈合的影响没有很好的评估结果,Ha等[25]的研究显示,双磷酸盐类药没有显著影响临床结果,但使用双磷酸盐类药治疗的患者出现椎间裂隙,这可能是双磷酸盐类药影响脊椎骨折愈合的一个指标。

1.2 肿瘤坏死因子(RANK)配体抑制剂

地舒单抗(Denosumab)虽抑制骨重塑,但未见其对动物骨折愈合不利的报道。Gerstenfeld等[26]发现地舒单抗与阿仑膦酸钠均不影响骨折愈合或骨痂组织形成,得出两者对骨折短期修复均无负面影响的结论,且地舒单抗组只有29%发生骨痂再骨折,而阿仑膦酸钠组和对照组分别为57%和87%。Flick等[27]虽发现使用肿瘤坏死因子配体抑制剂减少骨折愈合期间的骨吸收,但同样得出其不损害骨折愈合的结论,提示地舒单抗有助于形成更高强度的骨痂,更可能有助于机械性能的恢复,这可能是由于地舒单抗作为高活性肿瘤坏死因子受体配体(RANKL)靶向抑制剂,阻止肿

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瘤坏死因子受体配体与肿瘤坏死因子结合，抑制破骨细胞形成与活化，从而减少骨吸收，增加骨量并提高骨密度，促进骨痂形成，提高机械性能。

多项临床研究表明，长期应用地舒单抗可降低脊椎、非脊椎及髋部骨折风险[28-29]。Bilezikian 等[30]研究发现其能增加前臂骨密度，降低上肢骨折风险。区别于双磷酸盐类药，地舒单抗不仅增加骨痂组织骨矿物含量，还增加骨密度。地舒单抗与特立帕肽（Teriparatide，TPTD）联合使用被证明在增加骨密度方面比单独使用其他疗法更有效[31]。地舒单抗还通过减少皮质孔隙度影响小梁和皮质骨微结构来增加骨强度[32]。在接受地舒单抗治疗的绝经后妇女中观察到，骨吸收标志物血清 C-末端肽（CTX）在给药后迅速下降，随后在下一次给药前回到基线水平，而骨形成标志物血清 1 型前胶原（P1NP）延迟下降[28,33-35]，这表明地舒单抗对骨吸收标志物的影响是可逆的。但在一项临床Ⅱ期研究中，发现用地舒单抗治疗 24 个月并停药后，出现短暂的血清 C-末端肽和尿 1 型胶原氨基末端肽（NTX）的增加，其临床意义尚不清楚[36]。

Adami 等[37]报道地舒单抗未出现类似长期服用阿仑膦酸钠相关的股骨干异常骨折，另外，该团队观察 199 例使用地舒单抗的非脊椎骨折患者后，发现地舒单抗与骨折或手术治疗后的延迟愈合或并发症无关。同样，研究发现在骨折前后给药地舒单抗不会延迟骨折愈合或导致其他并发症[38-39]。这些结果均表明，地舒单抗治疗具有更好的适用性和更低的不良反应率，并且不影响骨折愈合进程，降低了并发症风险。

2 增加骨形成药物

2.1 甲状旁腺激素类药（Parathyroid Hormone Analogue，PTH）

动物研究表明，超生理剂量的甲状旁腺激素类药增加骨折部位的强度，改善骨痂组织的质量和数量；相对于对照组，甲状旁腺激素类药组形成更大、更致密和更成熟的骨痂组织；骨痂组织的矿化速度也更快，并显著改善刚度、抗扭强度等生物力学特性[40-44]。Friedl 等[45]研究表明，甲状旁腺激素类药促进骨表面的骨形成，包括骨内膜骨、骨膜骨和小梁，增加小梁的连通性和皮质骨的厚度，改善骨骼的微结构和生物力学特性。特立帕肽通过增加软骨细胞募集和分化率来增强软骨内早期骨修复，促进软骨细胞的再生和分化，增加骨折或融合部位的软骨形成[46]。O'Loughlin 等[47]从组织学和影像学角度评估经过甲状旁腺激素类药处理后的标本，发现其有更多的骨和软骨形成，这表明甲状旁腺激素类药对骨愈合的影响不仅体现在成骨作用，还影响软骨的增殖和分化过程。阿巴洛肽（Abaloparatide）在动物实验中同样表现出改善骨折愈合的作用，Bernhardsson 等[48]研究了不同剂量阿巴洛肽和特立帕肽对骨折愈合的影响，发现两种药物作用下产生的骨痂密度无明显差异，且均改善骨折愈合。阿巴洛肽促进骨痂发育、成骨和骨折桥接等方面的作用也在 Lanske 等[49]的研究中证实。

多项临床证据表明，特立帕肽显著降低脊柱和髋部的骨折风险，但是否对上肢等其他部位有同样积极作用，需要新的临床证据证明[50-51]。在动物研究中观察到甲状旁腺激素类药改善骨折愈合的作用，但在临床证据中却观察到矛盾的结果，这可能是由于多数动物研究中的剂量远高于人类使用的剂量。许多临床证据表明，甲状旁腺激素类药因其合成代谢作用，可积极促进骨愈合，特别是在桡骨远端、骨盆和脊柱等部位[52-59]。例如对急性骨质疏松性脊柱骨折（Osteoporotic Spinal Fracture，OSFs）患者而言，使用甲状旁腺激素类药可显著促进骨折愈合，减少进行性塌陷，缓解疼痛[60]。另外特立帕肽可加快骨折愈合速度，缩短愈合时间[61-62]，但并未出现预期的在降低术后并发症、二次手术率、死亡率、骨折愈合畸形率、影像学表现、疼痛评分等方面的显著差异[62-63]。

在对骨盆、股骨转子、桡骨远端等部位骨折的研究中发现，特立帕肽不同程度地缩短愈合时间并改善骨折愈合，其与减轻疼痛和缩短功能恢复时间也相关[57,64-67]。在接受股骨近端固定治疗的粗隆间骨折患者中，特立帕肽组也表现出更短的骨折愈合时间、更好的疼痛和功能评分结果[68]。Johansson 等[69]的研究中，通过研究肱骨近端骨折，却发现特立帕肽没有促进骨折愈合，也未改善疼痛，这可能可以解释为特立帕肽在对骨折愈合或功能恢复方面具有选择性优势。

2.2 选择性雌激素受体调节剂（Selective Estrin Receptor Modulators，SERMs）

选择性雌激素受体调节剂对骨修复和骨折愈合的确切影响仍不清楚，但多项动物实验显示雷洛昔芬（Raloxifene，Rlx）改善骨折愈合的所有阶段，增强骨痂组织质量和生物力学特性，缩短愈合时间。Spiro 等[70]通过研究标准化股骨截骨模型小鼠应用雷洛昔芬后的影像学和组织学变化，发现雷洛昔芬对骨折全期都有显著改善，主要体现在显著增加的骨痂组织矿化度、小梁厚度和缩短的愈合时间，这提示雷洛昔芬可能成为一种增强骨折愈合且避免雌激素副作用的药物。

Stuermer 等[71]通过建立大鼠胫骨骨折模型，发现雷洛昔芬及雌激素改善骨折愈合，增加骨痂组织密度和小梁宽度，产生与健康骨相当的骨内膜及骨膜愈合过程。雷洛昔芬在非骨质疏松动物模型中同样显著增加骨矿物质含量和骨密度，增强生物力学特性，改善骨

折愈合，加速骨桥接[70,72]。在去卵巢大鼠模型中，雷洛昔芬或雌激素均轻度抑制骨痂重塑，但不影响骨折修复[73]。尽管两种药物均增加骨小梁密度，增强骨痂生物力学性能，但作用方式不同，雷洛昔芬增加骨痂总形成量，而雌激素则促进骨内膜骨形成。与对照组相比，雷洛昔芬组和雌激素组产生具有更大软骨细胞面积的骨痂，并增加骨痂矿化度、小梁和新皮质厚度，缩短骨折愈合时间[70,74]。在术后骨折愈合方面，雷洛昔芬组与安慰组大鼠相比在组织学结果以及骨-植入物方面得到改善[75]。另外，也有研究未发现雷洛昔芬对骨痂组织形成或生物力学特性的影响[76]，这可能是由于卵巢切除术刺激骨转换率增加或者骨痂组织通过形态适应补偿了卵巢切除术或治疗的负面影响。

目前关于雷洛昔芬治疗患者骨折的临床研究十分匮乏，雷洛昔芬在临床中对骨折愈合是否有积极作用，仍需更多证据证明，但雷洛昔芬增加脊柱和股骨颈骨密度，降低脊椎骨折风险的作用已被证实[77]。

3 兼具两种作用的药物

3.1 骨硬化蛋白抑制剂

罗莫珠单抗（Romosozumab）是针对骨硬化蛋白的单克隆抗体，用于治疗有骨质疏松性骨折史、伴多个骨折危险因素或经其他药物治疗失败的绝经后骨质疏松症。硬化蛋白是由 SOST（Sclerostin）基因编码的分泌型糖蛋白，在骨细胞特异性表达，通过 Wnt/β-catenin 通路抑制成骨细胞的分化和增殖，强有力地抑制骨形成[78]。硬化蛋白还促进破骨细胞肿瘤坏死因子受体配体的表达，通过增加肿瘤坏死因子受体配体与调节骨保护素结合的比例促进骨吸收。敲除 SOST 基因的小鼠表现为进行性骨量增多，骨强度增强，而 SOST 基因过表达小鼠的骨量下降。因此，罗莫珠单抗是目前唯一兼具双重作用的抗骨质疏松药物。

Farhang 等[79]通过给大鼠应用硬化蛋白中和抗体（Sclerostin neutralizing antibody，Scl-Ab）并评估其骨愈合情况后，得出硬化蛋白中和抗体可促进新骨形成，增强骨修复，但不足以对骨缺损产生持续治愈作用的结论。此外，该团队观察到硬化蛋白中和抗体促进缺损部位近端、远端及对侧股骨的骨形成，这可能提示当未发生骨缺损时，或发生脆性骨折和假体周围骨折时，硬化蛋白中和抗体作为辅助治疗药物的潜力。Ominsky 等[80]在大鼠模型中研究了硬化蛋白中和抗体和甲状旁腺激素类药对松质骨和皮质骨的影响，发现硬化素免疫中和作用对增加不同骨骼部位的骨形成、骨量和生物力学稳定性具有一致的作用。Bandeira 等[81]也通过用硬化蛋白中和抗体干预大鼠，发现在健康雄性和骨质减少的雌性大鼠中骨量均明显增加，皮质和小梁结构改善，骨钙素增加，骨强度改善。组织形态计量学分析显示，骨小梁和皮质骨的骨形成和矿化程度增加，破骨细胞减少或不变，这提示随着骨吸收的减少或维持，骨形成受到刺激。研究表明罗莫珠单抗增加腰椎。全髋关节和股骨颈部位的骨密度，改善骨皮质和小梁的骨微结构，降低临床骨折风险[82-84]。尽管目前缺乏使用罗莫珠单抗进行临床组织形态计量学分析的数据，但骨转换标志物中形成标志物的瞬时增加和吸收标志物的减少明确其对骨重塑有双重影响[81]。值得注意的是，罗莫珠单抗的合成代谢作用仅限于接受治疗后的数月，超过 12 个月后骨形成作用将会减弱[85]。

4 总结与展望

在大量动物实验中，骨质疏松被认为是骨折发生的危险因素，对骨折愈合有负面影响，涉及细胞过程、骨痂形成、矿化程度和生物力学强度等方面。在临床试验中，虽能观察到骨质疏松对骨折愈合有负面影响的趋势，但并没有明确的证据证明。在非骨质疏松和骨质疏松动物模型中，抗骨质疏松药物治疗均改善或不影响骨折愈合。大量研究表明，抗吸收药物或合成代谢药物都不干扰骨折愈合，甚至可能增强机械性能，缩短愈合时间，改善关节功能。

目前，抗骨质疏松药物对骨折愈合的研究仍有局限性。动物模型中通过卵巢切除等方法诱导的骨质疏松与人类骨质疏松病程进展过程存在差异，可能对研究结果产生影响。临床研究往往选择不同而便于观察的骨折部位进行，目前仍缺乏从一处骨折部位或骨折类型推广到整体骨修复作用的统一标准。另外，骨折的治疗常有手术介入，故手术方式和时机对服用抗骨质疏松药物患者的骨折愈合影响也是相关研究应该深入的方向。

抗骨质疏松药物总体而言对骨折愈合和骨修复可以预见到正向的干预趋势，对骨质疏松性骨折治疗产生良好影响，加快骨折愈合并改善骨折愈合质量，但这仍需要大量随机对照试验证据来证明。

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位，或正其斜，或完其阙，则骨之截断、碎断、斜断，筋之弛、纵、卷、挛、翻、转、离、合……”，可见作者对筋骨同治的重视。从外治手法来看，《正骨心法要旨》总结了“摸、接、端、提、推、拿、按、摩”八法，尤其是接法和提法，是“完其阙”的具体操作，正是有了该八法，给了我国现代骨科大家们启迪，进而总结出了“手摸心会、拔伸牵引、旋转回旋、屈伸收展、成角折顶、端挤提按、挟挤分骨、摇摆触碰、对扣捏合、按摩推拿”等骨伤疾病治疗十法[8]。这些理论和手法在临床广泛应用，体现了中国中西医结合治疗骨伤疾病的特色，贡献了骨科疾病研究的中国智慧。

4 小结

《医宗金鉴·正骨心法要旨》作为一部论述正骨手法及内外用药治疗骨伤科疾病的专著，其“完其阙”所阐述的手法要求和操作方法虽然受成书年代科学水平的限制而不够精确，但其总的原则和一些具体的手法对骨科临床和基础研究有着极为重要而现实的指导意义，其学术思想尚有待进一步的探究和挖掘。

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