·综述·

双膦酸盐治疗股骨非典型性骨折的研究进展

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【摘要】 骨质疏松症为一种有较高发病率和死亡率的病症，会导致患者骨折风险增加。双膦酸盐已在许多大型临床试验中被证明可降低骨质疏松性骨折的风险，特别是阿仑膦酸钠已广泛成功地用于骨质疏松症的治疗。双膦酸盐可抑制骨吸收（抑制破骨细胞活性），同时也可引起骨小梁微损伤的积累或胶原纤维的老化。长期使用双膦酸盐会导致股骨非典型性骨折（AFF）风险增高。本文综述了与双膦酸盐相关AFF的发病机制和管理相关的6个主题，包括双膦酸盐作用机理、双膦酸盐相关AFF的发病机制、AFF的危险因素、双膦酸盐相关AFF的预防、双膦酸盐相关AFF的手术治疗、双膦酸盐相关AFF的医疗管理。

【关键词】 骨质疏松症； 双膦酸盐； 股骨骨折

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【Abstract】 Osteoporosis is a condition associated with significant morbidity and mortality, resulting increased risk of fractures. Bisphosphonates have been shown to reduce the risk of osteoporotic fracture in numerous large clinical trials, particularly alendronate sodium have been extensively and successfully used for the treatment of osteoporosis. As a result of inhibition of bone resorption (through the inhibition of osteoclasts activity), bisphosphonates may cause accumulation of trabecular microdamage or perhaps contribute to the aging of collagen fibers. Long-term use of bisphosphonates causes an increased risk of atypical femoral fractures (AFF). Six broad themes related to the pathogenesis and management of bisphosphonate-related AFFs are presented in this article and including mechanism of bisphosphonates action, pathogenesis of bisphosphonate-related AFF, risk factors for AFF, preventing bisphosphonate-related AFF, surgical management of bisphosphonate-related AFF and medical management of bisphosphonaterelated AFF.

【Key words】 Osteoporosis; Bisphosphonates; Femur fractures

骨质疏松症（osteoporosis，OP）是一种具有较高发病率和死亡率的病症，可导致患者骨折风险增加。双膦酸盐是一类用于减轻这种风险的药物。大约有50%的50岁以上妇女会患有骨质疏松性骨折或脆性骨折，并且骨折后12个月内有1/5的患者死亡[1-4]。双膦酸盐已在许多大型临床试验中被证明可降低骨质疏松性骨折的风险[5-6]，特别是阿仑膦酸钠已广泛成功地用于治疗骨质疏松症[7-9]。临床试验已证明阿仑膦酸盐、利塞膦酸盐和唑来膦酸可有效降低脊柱和非脊柱骨折的发生率，而伊班膦酸钠可减少非脊柱骨折，并可降低医疗相关成本[7,10-18]。双膦酸盐作为一线治疗药物，用于一级和二级预防妇女脆性骨折，以及预防和治疗类固醇诱导的骨质疏松症[19-22]。双膦酸盐抑制骨吸收（抑制破骨细胞活性），同时也会引起骨小梁微损伤的积累或胶原纤维的老化[23-26]，导致骨折和骨愈合延迟[23,25-29]。长期使用双膦酸盐会使股骨非典型性骨折（atypical femur fractures，AFF）的风险增高，这是继发于双膦酸盐相关的骨重建抑制[18]。双膦酸盐相关的股骨非典型骨折不同于其他一般骨折的临床表现和放射学特征[30]。本文就目前关于使用双膦酸盐的AFF发病机制和治疗作一综述。

Porrino等[31]于2005年报道了首例AFF，另有9名患者在3～8年的阿仑膦酸钠治疗后发生了AFF和其他非椎体骨折。最近大量研究表明，长期应用阿仑膦酸治疗的患者，低能转子间骨折和股骨干骨折的发病率增加，造成“股骨非典型骨折”[32-35,18]。为探究双膦酸盐和AFF之间的关联，2009年美国骨矿研究协会（American association for the study of bone mineral，ASBMR）成立了一个专家组进行研究[18]。多学科专家组分析了已发表的AFF文献，以及其发病机理的临床研究。该专家组确定了完全和不完全AFF的主要和次要特征，并于2013年进行了更新[36]。专家组建议，为了将股骨骨折确定为非典型性，必须至少符合五个主要特征中的四个。

AFF的主要特征：（1）骨折一般由低能量创伤引起或无

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创伤，如从站立高度或更低处摔伤；(2)骨折线起源于外侧皮质，且方向基本上是横向的，且可能在跨越股骨时倾斜；(3)完全骨折通过两个皮质延伸，不完全骨折仅涉及外侧皮质；(4)骨折是非粉碎性的或粉碎较轻微；(5)骨折处存在局部骨膜或外侧皮质内膜增厚。AFF的次要特征：(1)股骨骨干皮质厚度广泛增加；(2)单侧或双侧前驱症状，如腹股沟或大腿的钝痛或酸痛；(3)双侧不完全或完全的股骨干骨折；(4)延迟骨折愈合；(5)合并症（如维生素D缺乏症、类风湿关节炎、低磷血症）；(6)药物的使用（例如双膦酸盐、糖皮质激素、质子泵抑制剂）。

一、双膦酸盐作用机理

Fleisch等[37]在1969年提出初步理论，即双膦酸盐通过减少羟基磷灰石溶解来实现骨吸收的抑制。然而随后的结构-活性关系研究显示，羟磷灰石结合水平与骨吸收抑制之间没有密切关系，这一发现促进了双膦酸盐直接作用于骨细胞的理论发展[38]。其作用机制包括：(1)成熟破骨细胞的细胞毒性或代谢损伤[39-40]；(2)抑制破骨细胞附着于骨骼[41]；(3)抑制破骨细胞分化或招募[42-46]；(4)干扰破骨细胞结构（细胞骨架），这是骨吸收所必需的。Hughes等[44]的研究结果表明阿仑膦酸盐结合吸收表面，并在随后的破骨细胞酸化期间局部释放，防止骨吸收而不破坏破骨细胞。Masarachia等[47]指出，阿仑膦酸盐与成骨细胞以8∶1的比例结合，优于与破骨细胞结合的比例。该研究还证明，在矿化基质深处存在阿仑膦酸盐，但处于休眠状态，仅在破骨细胞酸化期间被活化以预防再吸收。

双膦酸盐的两个亚类包括含氮（Nitrogen-containing bisphosphonates，NBP）和非含氮（Non-nitrogen containing bisphosphonates，NNBP）双膦酸盐。NNBP亚类（依替膦酸、替鲁膦酸）会形成诱导破骨细胞凋亡的毒性ATP类似物，从而影响骨吸收。NBP亚类（阿仑膦酸盐、伊班膦酸盐、帕米膦酸盐、利塞膦酸盐和唑来膦酸盐）抑制甲羟戊酸途径，在破骨细胞形成和发挥功能的过程中起重要作用[48，27，49-56]。

二、双膦酸盐相关AFF的发病机制

尽管骨转换抑制对骨强度的提升有益，但研究认为双膦酸盐对骨转换的严重抑制在AFF的发展中起主要作用。目前在瑞典，AFF每年的发病人数约为2 000人，其中78%的AFF与双膦酸盐的使用有关[57]。双膦酸盐在高成骨活性部位（如微裂缝修复区域）的累积可导致局部扩增其作用，导致骨矿化，胶原交联及矿物质和有机基质的潜在致病性变化。以下是Shane等[18]提出的AFF可能的致病机制：(1)微损害积累；(2)骨矿化的变化，包括矿化增加和矿化异质性降低；(3)胶原蛋白交联的正常模式的改变，这是由于通过酶促反应或晚期糖基化终产物积累形成的交联成熟度的变化；(4)骨转换率的变化；(5)血管分布减少；(6)抗血管生成作用。

（一）双膦酸盐对微量损伤积累的影响

在正常骨骼中，循环负荷造成的微量损伤是引发骨重建的天然生理事件。它在骨转换减少的状态下积累，通常在高龄时发现[58]。相关研究表明，双膦酸盐会加速骨转换减少，并且随时间呈指数级累积微量损伤[59-60]。双膦酸盐损害破骨细胞活性，从而减少骨重塑和抑制微裂缝的修复，导致微损伤累积，特别是在高机械应力的区域[61]。值得注意的是，相对程度较小的骨转换的减少即可引发微量损伤的指数级增长，一项利塞膦酸盐的研究显示转换量减少40%，微量损伤量增加三倍[62-63]。

Brennan等[64]使用羊骨质疏松模型来检验双膦酸盐对骨细胞凋亡和微量损伤累积的影响，研究表明在骨骼成熟的母羊中，经过双膦酸盐治疗的母羊骨骼微裂纹数量增加。尽管如此，骨折风险也没有相应的增加。事实上，双膦酸盐相关微量损伤累积与股骨非典型性骨折之间的直接联系尚未在人体中建立。此外，关于接受双膦酸盐治疗的人体中是否存在微量损伤累积，Stepan等[65]研究显示，双膦酸盐治疗与髂嵴微量损伤累积之间无相关性。这些研究都没有评估股骨皮质的样本，并且由于微损伤的累积有位点特异性，所以目前尚不清楚微损伤对股骨干的影响。

（二）双膦酸盐对骨矿化的影响

骨转换的抑制改变骨矿物质和基质的特性。双膦酸盐可延长现有骨重塑单位的寿命，并减少新的骨重塑单位形成。这种延长使更多的骨重塑单位变得老化和完全矿化，导致矿化同质性的增加。虽然增加的矿化导致骨骼的强度和刚度的增加，但也导致骨的脆性增加，因此更容易发生骨折[66]。Boskey等[67]使用红外光谱成像来研究从7名接受阿仑膦酸盐治疗的妇女和10名年龄匹配的对照组中获取的髂嵴活组织的性质，结果显示，阿仑膦酸盐增加骨量的同时可减少组织异质性，这可能损害骨组织力学性能。

健康的异质骨不同区域的顺应性和刚度不同，可以阻止微裂纹的传播。在经过双膦酸盐治疗的骨骼中，增加了有机基质的均匀性，同时增加了矿化的均匀性，可能进一步增加微裂纹，诱发更高的骨折风险。

（三）双膦酸盐对胶原蛋白的影响

构成骨的90%有机骨架的胶原，是通过酶促反应和非酶促反应相交联。酶促反应由赖氨酰羟化酶和脯氨酰羟化酶介导，导致三价胶原交联。这些交联可产生更稳定的胶原蛋白基质，与骨骼的刚度和强度呈正相关[68-69]。Saito等[70]使用犬模型显示酶促交联的总数不受3年双膦酸盐治疗的影响。

另一方面，当还原糖与胶原中的游离氨基相互作用时，会发生非酶促交联，导致晚期糖基化终产物（advanced glycation end products，AGEs）。骨中AGEs浓度的增加显著增加了骨骼的脆性[68]。多项犬模型研究表明，使用双膦酸盐处理1～3年可导致骨骼中AGEs浓度的升高[69-70]。目前尚无关于长期双膦酸盐治疗患者AGEs积累的数据，因此在人体中的积累程度尚不清楚。

三、AFF的危险因素

2013年Franceschetti等[71]的研究表明，代谢性特征可能在骨折发展中起关键作用。该研究认为甲状旁腺激素（parathyroid hormone，PTH）对低钙血症的反应不足是AFF患者的主要危险因素，并表明肥胖、早期绝经和年龄较小（＜70岁）

为其他潜在危险因素。Taormina等[72]分析了53位服用双膦酸盐并发AFF患者骨折前的放射照片，发现颈干角与中心角之间的联系与AFF的发展有关。虽然目前没有指导原则，但长期接受双膦酸盐治疗的患者如存在以上危险因素时，应该及时考虑AFF并监测其发展。

四、预防双膦酸盐相关AFF

在双膦酸盐治疗的最佳持续时间方面存在相当大的争议。由于AFF以及下颌骨骨坏死促使美国食物和药物管理局重新评估三年至五年持续双膦酸盐治疗患者的治疗效果[73]。他们的审查重点是三项长期延伸性试验：Fosamax骨折长期干预延伸性试验（the fosamax fracture intervention trial long-term extension，FLEX）、骨折延伸性试验后，使用唑来膦酸所恢复的健康结果和骨折降低发生率（the reclast health outcomes and reduced incidence with zoledronic acid once yearly – pivotal fracture trial extension，HORIZONPFT）以及利塞膦酸盐的功效 - 多国延伸性试验（the actonel vertebral efficacy with risedronate therapy – multinational trial extension，VERT-MN），其治疗持续时间为6至10年。FLEX试验随机观察了1 099名绝经后妇女，她们之前平均接受了5年的阿仑膦酸钠治疗，现继续进行阿仑膦酸钠或安慰剂治疗5年[74]。HORIZONPFT试验使用类似设计，治疗时间较短（治疗3年，随后3年安慰剂或有效延长）[75]。这两项研究都将骨密度变化作为主要观察点，并将被报道的骨折作为探索性观察点。两项研究均显示继续双膦酸盐治疗的椎骨骨折风险显著降低。

接受双膦酸盐治疗6年以上（2 496例）患者的三项延伸性试验的汇总数据显示，椎体和非椎体骨质疏松性骨折率为9.3%～10.6%。相比之下，延长期转为安慰剂患者（阿仑膦酸钠为4年，利塞膦酸和唑来膦酸盐为3年）的骨折率较低，为8.0%～8.8%[73]。但持续的双膦酸盐治疗是否能超过3～5年，研究显示，当阿仑膦酸盐和唑来膦酸盐作为治疗剂时，停止双膦酸盐治疗时的骨丢失适度，而在停用利塞膦酸盐时则会发生更大的骨丢失，伊班膦酸盐治疗停止后无数据资料[76]。

总体而言，关于这种持续3～5年的双膦酸盐治疗增加骨折风险的证据仍然有限，随机对照试验的数据表明椎体骨折的风险总体仍然降低。然而，现仍缺乏一致的证据证明延长双膦酸盐治疗与非椎骨骨折的显著减少有关。

Black等[76]在2012年提出了几个建议。首先，他们建议在3～5年治疗后，股骨颈骨密度低的患者（T值低于–2.5）是椎体骨折的最高风险人群，因此似乎最适合继续使用双膦酸盐。其次，现有骨质疏松性椎体骨折患者骨密度稍高（但T评分不高于–2.0），也可受益于继续治疗。最后，股骨颈T评分高于–2.0的患者椎体骨折风险较低，不太可能受益于继续治疗。但是大部分患者骨折之前无症状，目前的文献未能为长期双膦酸盐治疗的患者建立明确的监测指南。可以使用股静脉造影监测识别早期应激反应/骨折，尽管如此，也得依靠经验丰富的放射科医师[72]。目前还需进一步研究长期双膦酸盐治疗的优势和风险，以及停止双膦酸盐后骨折风险的监测，以优化患者的疗效。

五、双膦酸盐相关AFF的手术治疗

ASBMR工作组未对AFF的外科治疗策略进行对照研究[36]。因此，他们的治疗建议是以相关观点为基础，结合骨科医师的共识。他们开发了一种依据骨折是否完全的层次化治疗方法。Egol等[77]报道了完全或不完全股骨非典型骨折的患者经过手术固定治疗后，其疗效普遍较好但骨折延迟愈合。

（一）双膦酸盐治疗的患者存在大腿或腹股沟疼痛的病史

必须排除这些存在大腿或腹股沟疼痛病史患者发生股骨骨折的可能性，需行骨盆正位、股骨正侧位及股骨全长X线片。如果X线片显示无异常，但临床怀疑度仍然很高时，应该行骨扫描或股骨MRI。如骨髓水肿表现为活动应激性骨折，应以部分负重，停止双膦酸盐治疗，补充钙和维生素D，并开始注射重组人PTH（1-34）来保守治疗[36]。需要密切跟踪MRI以监测骨髓水肿，防止进展到完全骨折[36,56]。

（二）完全的股骨转子间骨折/股骨干骨折

虽然尚未有研究对比股骨非典型骨折不同手术选择的疗效，但髓内钉优于其他固定装置，因其具备生物学和生物力学优势。生物学上，经髓内钉治疗的骨折为通过软骨内骨化愈合[78]。尽管双膦酸盐不损害骨折愈合的初始阶段或增生愈合组织的发育，但它们确实抑制破骨细胞重塑。这会导致重塑期延长，并延迟钙化软骨愈合组织向成熟骨组织的转化。然而，使用金属板的手术方式需要膜内骨愈合，膜内骨愈合被双膦酸盐抑制。从生物力学的角度来看，由于金属板侧向的位置和它们的非负载共享特性，疗效不如髓内钉。因此不推荐使用金属板-螺钉构造[22]。应使用全长髓内钉，并且应扩张髓内管，以便插入重建钉并防止剩余的股骨轴断裂。无论症状如何，必须通过X线片评估对侧股骨是否存在骨折[79]。

完全的AFF治疗结果通常较差，一些研究显示53%需要在最初髓内钉治疗后进行返修[23]。Schilcher等[57]提出可以考虑采用先天性自体骨髓移植术，但目前还没有相关研究检验其在AFF中的疗效。

（三）不完全的股骨转子间/股骨干骨折

不完全非典型骨折的治疗取决于几个因素，包括症状、X线片和MRI。对于伴有疼痛的不完全骨折，建议使用预防性髓内钉固定[57,75-76,80-81]。应检查有皮质增厚和应激反应的股骨X线片，如存在穿过外侧皮质的骨折线，则是一种不良预后指标，要求用预防性髓内钉固定[82]。对于不完全骨折和无疼痛的患者，建议保持适当的体重及避免剧烈活动，直到MRI显示无骨髓水肿。

六、双膦酸盐相关AFF的医疗管理

（一）停止双膦酸盐

来自加利福尼亚健康维护组织的一项大型观察性研究发现，继续或停止使用双膦酸盐治疗的患者存在股骨非典型性骨折后，又出现了对侧AFF[83]。Dell等[84]研究表明，存在AFF指数后，持续3年以上双膦酸盐治疗患者的双侧AFF发生率为41%，而停药患者为19%。另有研究[85-86]同样证实，股骨非典型骨折的风险随着双膦酸盐使用时间的延长而稳步

增加，出现股骨非典型骨折后，停止双膦酸盐治疗，对侧股骨发展为非典型骨折的相对危险度可降低70%，但由于双膦酸盐的骨骼积聚，骨折的风险在停药后可继续存在多年。因此，最近国际骨质疏松基金会骨折工作组建议在AFF之后停止双膦酸盐治疗[87]。

（二）补充钙和维生素D

应评估膳食中的钙和维生素D，如有必要，应给予足够的补充，因为这可将各类骨折的风险降低12%～26%[88-90]。最佳治疗建议应包括每日摄入1 000 mg至1 200 mg的钙和至少1 000 IU至2 000 IU的维生素D3，以及定期监测血清25-羟基维生素D和PTH水平[91-92]。

（三）重组人PTH（1-34）

相关研究显示双膦酸盐相关性骨折的患者骨愈合延迟。例如，Molvik等[93]发现桡骨远端骨折愈合时间显著延长。在AFF患者中应考虑使用重组人甲状旁腺激素（parathyroid hormone，PTH）（1-34）[56]。它可以改善患者长期阿仑膦酸钠治疗所形成的骨转换和微结构，通过增加愈合组织形成和机械强度来增强骨折愈合[94-99]。两项临床试验显示重组人PTH（1-34）可缩短骨质疏松性骨折患者的愈合时间[100]。上述研究为其在这些患者中的应用提供了有力论据。

总之，股骨非典型骨折是长期使用双膦酸盐的公认并发症，但比较罕见。服用双膦酸盐的股骨非典型骨折的绝对风险约为每3.2～50/100 000人/年。但长期使用双膦酸盐患者的风险可能会更高，高达100/100 000人/年[101]。这些股骨非典型骨折的特征在于独特的临床特征（前驱性疼痛 和双侧性）和独特的放射学特征（横向或短斜方向、不存在粉碎、皮质增厚、应力断裂或应激反应及延迟愈合）。双膦酸盐是防治常见骨质疏松性骨折的重要药物，而股骨非典型性骨折较为少见。双膦酸盐治疗5年后是否终止应用仍然存在争议，尽管骨折风险低的患者不太可能受益于此后的治疗。

一旦出现非典型性骨折，必须停止双膦酸盐的应用，患者应每日补充钙和维生素D。手术固定应该是选择髓内钉进行固定，术后使用重组人PTH（1-34）来加快愈合。医患双方均应了解AFF发生的可能性和双侧性。未来的研究应着眼于加强监测，以确定AFF的真实发生率和危险因素。

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