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· 综述 ·

芳香化酶抑制剂相关关节痛研究进展

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摘要

雌激素缺乏、炎症反应、代谢紊乱等被认为是导致乳腺癌患者发生芳香化酶抑制剂(AIs)相关关节痛的可能机制。运动和其他手段(维生素D、Omega-3 脂肪酸、针灸等)对改善 AIs 相关关节痛均有积极效果。运动可能通过直接或间接效应影响其相关发病机制而发挥作用, 但结果尚存在一定争议。

关键词 乳腺癌; 芳香化酶抑制剂; 关节痛; 运动; 综述

Advance in Aromatase Inhibitor Related Arthralgias (review)

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Abstract

Estrogen deficiency, inflammatory reactions, metabolic disorders, etc., are considered to be possible mechanisms leading to arthralgias (or joint pain) associated with aromatase inhibitors (AIs) in breast cancer patients. The use of exercise and other non-pharmacological means (such as vitamin D, Omega-3 fatty acids, acupuncture, etc.) may relieve AIs-related arthralgia, and exercise may play a direct or indirect role to deal with the related pathogenesis. But the results of the studies are still controversial.

Key words: breast cancer; aromatase inhibitors; arthralgia; exercise; review

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第三代芳香化酶抑制剂(aromatase inhibitors, AIs), 如 anastrozole、letrozole、exemestane 等, 相对于他莫昔芬能够提高无病生存时间, 是临床绝经后雌激素受体阳性乳腺癌患者内分泌治疗的金标准^[1-2], 但这种辅助治疗带来的关节痛却是降低患者生活质量的重要因素, 也是患者中断治疗的最主要原因^[3-4]。关节痛不仅使患者关节活动受限^[5], 而且增加患者恐惧复发的心理负担^[6]。在现有医疗条件下, 要根治乳腺癌, 可能需要患者

连续治疗 5~10 年^[7], 对患者治疗的依从性提出更高要求。研究者一直在寻找能够提高患者治疗依从性的可行方式, 如药物、营养补充、针灸、放松、生活方式改变等。运动对癌症患者的生存率和生活质量有积极效果, 作为一种非药物的安全干预方式被广泛关注。

1 流行病学及定义

乳腺癌患者 AIs 相关关节痛以肘、腕/手、膝、踝/足为

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多^[5,8-9]。美国2007年调查显示^[10], 47%经AIs治疗的乳腺癌患者经历关节痛。最近的Meta分析也表明^[11], 乳腺癌患者AIs治疗相关关节痛合计发生率为46%。Lombard等^[12]报道AIs相关关节痛发生率高达82%。

众多研究采用简明疼痛量表(Brief Pain Inventory, BPI)、视觉模拟评分(Visual Analogue Scale, VAS)或西安大略和麦克马斯特大学骨性关节炎指数(Western Ontario and McMaster Universities Arthritis Index, WOMAC)等评估疼痛程度^[13-15], 缺乏针对乳腺癌患者AIs相关关节痛的疼痛量表或评价体系。疼痛作为一种主观感觉, 患者在被问及是否有关节痛时, 可能只回答有或无; 个人对疼痛的敏感性或认知差异、情绪的变化都可能给研究结果带来影响。Castel等^[16]设计一种用于AIs相关骨骼肌肉症状(AI-associated musculoskeletal symptoms, AIMSS)和乳腺癌关节痛的患者报告关节痛量表(Patient Report Arthralgia Inventory, PRAI), 研究显示内部一致性很高(Cronbach $\alpha = 0.9$), 重测信度高, 或许可用于AIMSS测验的可靠工具。

引起关节疼痛的原因复杂多样, 乳腺癌患者AIs治疗相关关节痛的定义尚不统一。众多研究采用AIMSS^[17]或关节痛, 描述为关节僵硬和关节终末端疼痛, 伴关节灵活性和稳定性降低^[18], 缺乏明确诊断的客观指标。部分研究将纳入标准设定为乳腺癌术后进行AIs治疗后出现这种关节症状^[19-20]。Niravath^[3]提出AIs相关关节痛的评判标准, 认为必须满足3个主要条件和至少3个次要条件。主要条件: ①目前正在服用AIs; ②开始服用AIs后出现关节痛或关节痛加剧; ③停用AIs后关节症状改善或消失; ④重新服用AIs关节痛又出现。次要条件为: ①非对称性关节痛; ②疼痛在手和/或腕关节; ③腕管综合征; ④握力下降; ⑤晨僵; ⑥活动后关节不适症状改善。这些标准仍有很大主观性, 没有得到公认。明确乳腺癌AIs相关关节痛的定义、设计合理的关节痛评价指标, 将有益于流行病学调查和临床诊治。

2 发病机制

目前, 乳腺癌患者由AIs治疗引起关节痛的机制尚不清楚, 主流观点有以下几种。

2.1 雌激素缺乏

AIs通过抑制雌激素合成步骤中的关键酶——芳香化酶, 抑制雌激素合成, 从而抑制雌激素依赖性乳腺癌细胞生长, 但同时也抑制了雌激素对其他组织(如骨骼)的保护效应^[21]。雌激素可通过多种通路防止骨成分丢失, 调节成骨细胞和破骨细胞的生存。①通过抑制核因子 κ B受体活化剂配体(receptor activator of nuclear factor κ B ligand, RANKL)诱导的酸性磷酸酶-1(acid phosphatase-1, AP-1)活化, 下调破骨细胞转录因子c-Jun的表达, 抑制破骨细胞的形成^[22]。②通过鸡肉瘤病毒基因(sarcoma gene, Src)/鸡肉瘤病毒基因同源和胶原蛋白(sarcoma gene homolog and collagen, Shc)/细胞外信号调节激酶(extracellular signaling regulates kinase, ERK)介导抗成骨细胞凋亡^[23]。③通过激活雌激素受体 β (estrogen receptor β , ER β)直接诱发破骨细胞凋

亡, 从而抑制骨吸收^[24]。反之, 雌激素缺乏则会增加成骨细胞凋亡, 减少破骨细胞凋亡, 从而增加骨吸收^[25]。这与骨性关节炎(osteoarthritis, OA)的病因类似。绝经后女性发生OA与其体内雌激素分泌减少有关^[26]。Hernandez等^[27]发现, 芳香化酶在正常骨组织呈高表达; 而从髌OA或OA致髌关节骨折患者股骨颈取样的骨小梁样本和成骨细胞体外培养, 发现芳香化酶表达明显下降, 证实芳香化酶减少可能在骨质疏松和软骨退行性变中扮演重要角色。AIs治疗后患者最明显的特征是骨质丢失加剧^[28-29], 如何防止骨质丢失一直是临床进行性激素敏感的内分泌治疗时要考虑的重要因素^[30]; 而且OA最明显的症状就是关节疼痛^[31]。AIs治疗后关节痛患者有关节积液的影像学改变^[32-33]。很多研究者认为^[34-35], 乳腺癌患者AIs相关关节痛可能与雌激素剥夺效应有关。也有人认为^[31], OA是关节整体的疾病, 软骨不受神经支配, 其退行性变不太可能是中到重度疼痛的直接来源, 可能是骨赘脱落物刺激关节周围骨膜、韧带和滑膜, 产生炎症反应。所以, OA关节疼痛机制与AIs治疗相关关节痛之间的确切关系还有待进一步验证。

2.2 炎性反应

长期炎性反应是疼痛来源的直接因素之一, 也是乳腺癌发生发展的一个关键因素^[36-37], 临床应用抗炎药能有效缓解AIs相关关节痛。Bauml等^[38]发现, 乳腺癌患者AIs相关关节痛程度与C反应蛋白(C-reaction protein, CRP)、嗜酸性粒细胞趋化因子(eosinophil chemokines, ECK)、单核细胞趋化蛋白-1(monocyte chemotactic protein-1, MCP-1)、维生素D结合蛋白(vitamin D binding protein, VDBP)的升高有关。目前关于乳腺癌AIs相关关节痛与疼痛特异性相关的白介素6(interleukin 6, IL-6)、肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)等促炎因子表达之间关系的直接报道还很少见。

2.3 代谢激素

高胰岛素血症、高胰岛素样生长因子-1 (insulin-like growth factor, IGF-1)水平和低胰岛素样生长因子结合蛋白(insulin-like growth factor binding protein, IGFBP)水平增加乳腺癌的发生、复发和死亡风险^[39-40]。胰岛素作为糖代谢的一个重要激素, 被认为至少有3种机制(胰岛素本身、IGF和改变内源性性激素调节)与乳腺癌相关^[36]: 胰岛素通过刺激芳香化酶的活化提高循环中雌激素水平^[41], IGF-1则可抑制肝脏分泌性激素结合蛋白(sex hormone-binding globulin, SHBG), 导致循环中游离雌激素增加^[39-41], 从而提高乳腺癌发生风险。Lintermans等^[42]研究显示, AIs治疗6个月后, 患者血清IGF-1水平较他莫昔芬治疗患者显著升高; 12个月时, IGFBP-3则呈下降趋势, AIs治疗患者IGF-1/IGFBP-3比值呈升高趋势, 提示关节痛可能与生长激素/IGF-1轴的改变有关。

肥胖是乳腺癌患者关节痛的危险因素, 体质指数(body mass index, BMI) $> 30 \text{ kg/m}^2$ 的肥胖患者关节痛发病率相对较高^[10,43]。但Crew等^[10]研究显示, BMI $25 \sim 30 \text{ kg/m}^2$ 的患者, 关节痛发生率较BMI $> 30 \text{ kg/m}^2$ 或 $< 25 \text{ kg/m}^2$ 小。可能肥胖患者外周

(如脂肪)分泌的雌激素水平较高,而体内较高的代谢激素水平也增加雌激素水平,从而在一定程度上减少关节痛产生;而过于肥胖者下肢关节和软骨承受过大应力,引发机械性疼痛。

2.4 其他

Mao 等^[8,44]发现,绝经后时间(<5 年的女性比 >10 年的女性报告更多关节痛)和 CYP19A1 多态性,与 AIs 相关关节痛有关,提示激素环境可能促进关节痛发生。RANKL 单核苷酸多态性(single nucleotide polymorphisms, SNP) *rs7984870cc* 和骨保护素(osteoprotegerin, OPG) SNP *rs2073618cc* 基因型携带者,发生乳腺癌 AIMSS 事件的可能性高^[45]。

维生素 D 缺乏也被认为是 AIs 诱发关节痛的因素^[46-47]。还有研究者认为^[48],疼痛是一种中枢感觉,长期的炎症反应使脊髓神经元超兴奋性,降低关节疼痛阈值,导致患者疼痛敏感性增加。AIs 的长期使用使雌激素对中枢超兴奋性的抑制作用减弱或消失,引起关节疼痛敏感性增加^[49]。但目前还没有直接研究证实。

3 干预

目前对乳腺癌 AIs 相关关节痛的临床处理,除更换 AIs 药物、应用非甾体类抗炎药外,营养补充、针灸及运动^[50-52]也常被用来缓解患者的关节痛等症状。

3.1 维生素 D

接受 AIs 治疗的乳腺癌术后患者,体内 25-羟基维生素 D (25-hydroxy vitamin D, 25OHD)普遍不足或缺乏^[53],推测乳腺癌患者术后关节痛可能与 AIs 治疗引起的骨成分快速丢失有关。Rastelli 等^[46]的随机对照试验(randomized controlled trial, RCT)结果表明,补充维生素 D 可改善患者纤维肌痛症影响问卷(Fibromyalgia Impact Questionnaire, FIQ)结果和 BPI 评分。另一项前瞻性队列研究结果显示^[47],25OHD 浓度 <30 ng/ml 的患者补充维生素 D,使浓度 >40 ng/ml,关节痛发生的风险明显减少。Khan 等^[54]对乳腺癌 AIs 治疗早期女性补充维生素 D 5000 IU/周,共 12 周,发现患者 25OHD 水平明显上升,关节痛改善不明显,但关节功能受损明显减少;疼痛改善不明显可能与干预时间短有关,有待进一步的研究。

3.2 Omega-3 脂肪酸

补充 Omega-3 脂肪酸能改善风湿性关节炎和背痛等炎症性疼痛^[55],可能对 AIs 相关关节痛有效。Hershman 等^[56]发现,补充 Omega-3 脂肪酸 24 周可降低患者 BPI 评分,同时降低患者甘油三酯水平,但安慰剂组 BPI 评分也改善,且与实验组之间无显著性差异^[57]。Shen 等^[58]的研究显示, Omega-3 脂肪酸降低 BMI >30 kg/m² 乳腺癌患者的疼痛评分和血脂水平。补充 Omega-3 脂肪酸可防止患者生活质量下降,并降低 IL-6 水平^[59]。补充 Omega-3 脂肪酸可一定程度减轻接受 AIs 治疗乳腺癌患者体内的血脂或炎症介质水平,提高抗氧化应激水平^[60],从而间接减轻患者关节痛症状。

3.3 针灸

针灸对于乳腺癌患者关节痛的治疗效果尚存在争议。Chen

等^[61]的 Meta 分析显示,6~8 周针灸治疗可明显降低关节痛程度评分。Hershman 等^[62]的研究显示,针灸可改善早期乳腺癌患者 AIs 相关关节痛。Chien 等^[63]的 Meta 分析则显示,针灸对乳腺癌患者关节痛与假针灸相比较并无显著性差异。这可能与不同研究者采用的治疗方法有关。如采用标准针灸穴位^[64]或阿是穴^[65],或采用电针^[65-66]。

3.4 运动

体力活动不足是乳腺癌患者全因死亡率的高风险因素^[67-68]。运动被誉为“抗肿瘤良药”。众多研究显示^[69-74],运动或体力活动对乳腺癌患者的身体成分、胰岛素敏感性、骨代谢、心肺功能、疲劳、免疫、睡眠和生活质量方面有积极影响,能降低乳腺癌致死率和全因死亡率^[75]。2016 年美国癌症协会的乳腺癌临床治疗指南明确指出^[76],患者诊断后应尽早开始正常生活活动,至少保证每周 150 min 中等强度或每周 75 min 大强度有氧运动,以及每周 2 次力量训练,特别强调在进行化疗和内分泌治疗时要进行力量锻炼。Arem 等^[77]的研究表明,参加锻炼计划的乳腺癌患者, AIs 相关关节痛得到有临床意义的改善;12 个月有氧训练结合力量训练可以降低乳腺癌患者 BPI 评分和疼痛的频率^[19]。Fields 等^[78]的研究显示,每周 120 min、持续 6 周的北欧步行训练可以减轻乳腺癌患者关节痛。每周 150 min 以上、持续 6 周的家庭锻炼可减轻乳腺癌患者关节痛,且干预后 6 周仍有积极效应。对乳腺癌患者进行早期干预的效果更好^[79]。

瑜伽和太极拳也能对乳腺癌患者 AIs 相关关节痛产生积极影响。瑜伽能显著减轻服用 AIs 或其他莫昔芬乳腺癌患者的骨骼肌症状,包括关节痛、肌肉疼痛和酸痛等^[80]。Galantino 等^[81]和 Jacobsen 等^[82]的研究也表明瑜伽对于减轻患者的关节痛有积极效应。每次 1 h、每周 2 次、持续 8 周的太极拳运动能够改善患者情绪和压力,一定程度缓解疼痛^[13]。瑜伽运动多为静力性动作,太极拳则要求动作稳定和柔和^[83],这两种方式都需要结合呼吸和冥想等放松方法,因此,瑜伽和太极拳对乳腺癌患者 AIs 相关关节痛的影响除了运动效应外,对心理因素的影响也值得进一步研究。

3.5 其他

对乳腺癌患者关节痛的干预措施还包括泼尼松龙^[84]、药物补充方案^[85]、硫酸盐葡萄糖胺+硫酸软骨素^[86]、免疫疗法^[87]、中医药^[17,88]、耳穴按压^[89]、顺势疗法^[90]、局部 Emu 油按摩^[91]等。虽然这些干预被认为可减轻乳腺癌患者 AIs 相关关节痛,但大多属非临床随机对照,或临床开展较少、干预时间短、缺乏长时间随访,且研究样本量都较小,有的还只是个案报道,缺乏重复性研究证实,目前尚不足以肯定其有效性,但可为临床治疗提供思路。

4 运动改善乳腺癌患者 AIs 相关关节痛的可能机制

运动改善 AIs 相关关节痛的机制可能涉及性激素、代谢激素、脂肪因子、免疫系统因素和氧化应激等方面。Volaklis^[69]和 de Boer 等^[36]报道,运动可降低雌激素水平,增加 SHBG 水平;降低胰岛素水平,改善胰岛素抵抗;提高脂联素水平,降低瘦

素和促炎性单核细胞如CRP、IL-6、TNF- α 水平,活化T_{reg}细胞和自然杀伤(nature killer, NK)细胞;降低氧化应激水平,增加身体抵抗氧化应激能力等。

4.1 雌激素

运动可降低雌激素水平已在众多研究中得到证实。Verkasalo等^[92]发现,绝经前女性随着体力活动增加,雌激素水平降低,伴SHBG升高。Emaus等^[93]也发现,绝经前女性中,体力活动水平高者雌激素水平低。绝经后女性体力活动的增加也能明显降低雌激素水平,提高SHBG水平^[94],降低乳腺癌的发生风险。运动降低乳腺癌患者的体脂率,减少脂肪分泌的雌激素水平,从而降低乳腺癌复发风险^[36]。

值得注意的是,如果雌激素缺乏是AIs相关关节痛的原因,那么运动降低雌激素的效应并不能缓解疼痛,而是加重疼痛。但最近有研究表明^[95],运动与绝经后女性前体雌激素呈负相关,而与雌激素代谢产物无关,这可能表明运动对乳腺癌AIs相关关节痛的改善效果可能独立于雌激素途径。

4.2 炎症反应

运动能降低机体炎症因子水平^[96],被认为是减少乳腺癌发生风险的重要机制^[36]。Idorn等^[97]发现,运动对癌细胞的抑制效应与运动诱导NK细胞在肿瘤实质中的浸润和活化,以及介导IL-6等促炎因子的表达有关。动物研究表明^[98],运动增加NK细胞在肿瘤组织中的聚集程度;肾上腺素可能诱导IL-6敏感NK细胞的选择性动员,因为IL-6阻断会钝化运动诱导的肿瘤抑制、髓内NK细胞浸润和NK细胞活化;运动的抗肿瘤效应可能与肾上腺素信号通路活性增加有关。Jones等^[99]发现,6个月中等强度有氧运动虽能减轻关节痛,但对乳腺癌患者体内炎症标记物未产生明显影响,可能的原因是干预时间较短,运动强度不达标。未来研究可能需要更多考虑运动处方的选择。

4.3 代谢激素

肥胖患者体内炎症因子高表达,而长期炎症反应会导致患者胰岛素抵抗^[100],体内胰岛素水平代偿性升高。运动既可以减少患者体脂,减少雌激素产生,还能改善胰岛素抵抗^[101]。Fahey等^[102]发现,运动可降低乳腺癌患者血清IGF-1水平,增高IGFBP-3水平。虽然没有涉及关节痛问题,但结合Lintermans等^[42]的研究,可以推测运动对预防或减轻乳腺癌患者关节痛的机制也可能与运动改善生长激素/IGF-1轴有关。

4.4 OPG/RANKL/RANK

运动,特别是抗阻运动对骨关节的机械应力刺激可能影响骨重塑^[103]。机械应力刺激成骨细胞OPG的分泌,从而促进骨形成^[104]。OPG通路与AIs相关关节痛之间存在关联^[45,105]。OPG由骨间充质细胞和成骨细胞分泌,能竞争性抑制RANKL与RANK结合,从而抑制破骨细胞分化和成熟^[106]。West等^[107]的研究显示,运动能增加OPG表达,增加骨密度。炎症因子通过调节OPG/RANKL/RANK信号通路,调节破骨细胞的分化和激活,从而对骨代谢产生负面影响^[108]。

5 小结

乳腺癌患者AIs相关关节痛是一个复杂的病理过程,诊断标准尚未统一,缺乏客观检测指标。现有的研究显示,其发病机制可能与治疗后雌激素缺乏导致骨代谢失衡、炎症反应、代谢激素失衡等有关。非药物治疗手段改善AIs相关关节痛是当前的研究热点,针灸、营养补充等都能不同程度改善疼痛,但普遍存在研究设计方面的不足,临床指导价值有限。

运动是一种安全、低成本的非药物干预方法,可以多方面提高乳腺癌患者生活质量,对AIs相关关节痛也有积极效果,但同样存在研究设计方面的不足,且运动处方存在较大差异,还存在受试者中途退出的情况,表明患者的依从性不足或运动处方与患者能力不匹配。

运动等非药物手段对改善乳腺癌患者AIs相关关节痛有益。需开发更加客观的测验工具,扩大研究样本量,设计更多科学严谨的研究探讨相关机制。对于运动而言,研究者应尽量考虑乳腺癌患者的功能状态,制定个性化运动处方,而不是简单套用指南推荐的处方。

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