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· 综述 ·

绝经后骨质疏松症发病机制研究进展

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摘要: 绝经后骨质疏松症(postmenopausal osteoporosis,PMOP)是指女性绝经后卵巢内分泌功能失调衰退,导致雌激素水平下降,从而导致破骨细胞的骨吸收大于成骨细胞的骨形成的一种代谢性疾病。骨质疏松症没有特异性的临床表现,直到轻微的创伤诱发骨折时才会引起重视,所以预防骨质疏松症是临床工作的重中之重。目前有很多研究报道了骨质疏松症发生发展的机制,在机体内雌激素的缺乏引起炎症因子与 MicroRNA 激活,从而引起 RANKL-RANK-OPG 轴的紊乱,引起骨质流失。同时雌激素充当抗氧化剂来保护骨,抵抗氧化应激。本文就绝经后骨质疏松症的发生机制做一综述。

关键词: 绝经后骨质疏松症;雌激素;RANKL-RANK-OPG 轴;氧化应激

Advances in research on the mechanism of postmenopausal osteoporosis

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Abstract: Postmenopausal osteoporosis (PMOP) is a metabolic disease that leads to the decrease of estrogen level in women, Resultsing in the osteoclastic bone resorption over osteoblastic bone formation. There are no specific clinical symptoms of osteoporosis, until a slight stress-induced fracture occurs when people may pay attention. Therefore, prevention of osteoporosis is the priority of the clinical work. Numerous studies have reported the mechanism of development of osteoporosis. The lack of estrogen in the body causes inflammation and microRNA activation, causing disorder of RANKL-RANK-OPG axis, then result ing in bone loss. Estrogen acts as an antioxidant to protect the bone loss and against oxidative stress. This article aims to summarize the mechanism of postmenopausal osteoporosis.

Key words: postmenopausal osteoporosis; estrogen; RANKL-RANK-OPG shaft; oxidative stress

骨质疏松症(osteoporosis)是由于多种原因导致的骨密度下降,骨微结构破坏,造成骨脆性增加,从而易于发生骨折的全身性骨病。骨质疏松症分为原发性和继发性两大类,原发性骨质疏松症又分为绝经后骨质疏松症、老年性骨质疏松症和特发性骨质疏松症(包括青少年型)3 种。绝经后骨质疏松症一般发生在女性绝经后 5 ~ 10 年内;老年性骨质疏松症一般指 70 岁后发生的骨质疏松;而特发性骨质疏松主要发生在青少年,病因尚不明确[1]。

绝经后骨质疏松症(postmenopausal osteoporosis,PMOP)是指女性绝经后卵巢内分泌功能失调衰退,导致雌激素水平下降,从而导致破骨细胞的骨吸收大于成骨细胞的骨形成的一种代谢性疾病[2-4],其特征为进行性全身性骨密度(bone mineral density, BMD)降低和骨组织微结构发生改变[5]。骨质疏松症是老年人脊柱、髋部、桡骨远端骨折的最常见的原因[6]。通常,骨质疏松症没有特异性的临床表现,直到轻微的应激诱发骨折时才会引起重视[6]。在发达国家的女性中绝经后骨质疏松症的发生率为 38%,根据临床诊断标准,目前全世界有

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800 万 50 岁以上的女性被诊断为骨质疏松症,3 400 万女性有明显的骨质减少症状[7]。绝经后骨质疏松性骨折对绝经后女性的生活质量产生了很大的影响[8]。绝经后骨质疏松症的病因是多因素的,现有的研究认为雌激素水平降低导致的骨吸收、骨形成平衡破坏是主要因素,除此之外,钙和其他环境因素对骨质流失也有影响[9]。目前研究骨质疏松发生机制及其相关信号通路是科研工作的重中之重。

1 绝经后骨质疏松症的致病因子

1.1 炎症因子

白介素(interleukin, IL)是一种具有多功能的细胞因子,由 T 细胞、B 细胞、单核巨噬细胞、纤维母细胞及某些肿瘤细胞、基质细胞和成骨细胞激活后分泌。在体内水平甚微,以自分泌和旁分泌作用于局部,发挥多种生物学活性,能够促进骨吸收,并能促进造血干细胞的生长[10]。肿瘤坏死因子(tumor necrosis factor, TNF)主要由单核巨噬细胞产生,活化的 T 细胞、自然杀伤细胞、肥大细胞、软骨细胞也能分泌这种因子。TNF 与受体结合后,信号传入细胞内,通过 NF-κB 或活化蛋白(AP)-1 转录因子来实现其功能[11]。

绝经后骨质疏松症的特征是雌激素水平降低,有研究报道,雌激素缺乏一方面能够产生促炎因子如 IL-2、IL-6、TNF-α、TNF-β1;另一方面能够减少分泌细胞的凋亡,增强破骨细胞形成,从而影响骨吸收与骨形成的平衡[12]。Ozmen 等[13]的研究表明绝经后女性服用选择性雌激素受体调节剂雷洛昔芬盐酸盐 12 周后,相较于服用安慰剂的女性相比,其骨密度有明显的提升,血清骨钙素和维生素 D 都趋于正常水平。治疗组的患者血中 IL-6 和 TGF-β1 的水平相较于对照组均有明显的降低。Tural 等[14]调查了绝经前人群和绝经后人群的白细胞介素 10(IL-10)和转化生长因子 beta 1(TGF-beta 1)水平,其结果显示 IL-10 在两组中的水平差异有明显的统计学意义,这表明了 IL-10 的表达差异是绝经后骨质疏松的原因之一。Molnar 等[15]分析了绝经前后女性的 IL-17 A 和 OPG 水平与骨密度之间的关系,其结果也显示 IL-17 A 和 OPG 水平在两组中差异具有明显的统计学意义。综上所述,绝经后的女性血清中白介素及肿瘤坏死因子的水平明显升高,从而导致破骨细胞生成增加,骨质流失。

1.2 MicroRNA

MiRNA 是内源性非编码 RNA(长度为 18 ~ 25 个核苷酸),通过不完全碱基配对靶 mRNA 的 3'非翻译区来负调节基因表达[16]。越来越多的证据表明 MiRNA 在调节不同的病理生理过程中发挥着重要的作用,如发育时间、器官发生、细胞凋亡、细胞增殖和分化等[17]。目前已有多个研究报道 MiRNA 在骨形成中发挥积极作用,如 MiR-20a、MiR-26、MiR-27、MiR-29、MiR-30、MiR15 和 MiR-206 等[18-19]。有研究报道,绝经后骨质疏松症患者的血清中许多 MiRNA 的表达都比正常人群低,差异有显著的统计学意义[20]。有文献报道 MiR-27 在脂肪形成和成骨分化中起着重要的作用[21]。Wang 等[22]报道 MiR-27 通过激活 Wnt 信号通路传导促进成骨细胞分化,且 MiR-27 水平在骨质疏松症的发展过程中逐渐降低。Pan 等[23]报道 MiR-27a 通过 JNK/p38 信号通路促进骨肉瘤的生成。Liu 等[24]研究证明 MiR-214-3P 与 TRAF3 结合,在绝经后骨质疏松症的发展过程中发挥作用。Li 等[25]报道 MiR-27a 在绝经后骨质疏松症患者血清中水平显著降低。综上所述,MiRNA 在正常人体的成骨方面起着重要的作用,而在绝经后的女性中,其体内 MiRNA 水平会下降,从而导致了骨吸收与骨生成平衡被打破,从而造成骨质流失。

2 绝经后骨质疏松症的通路

目前认为肿瘤坏死因子(TNF)家族的 NF-κB 受体激活子(RANKL),其受体(RANK)和骨保护素(osteoprotegerin, OPG)组成的 RANKL-RANK-OPG 轴参与调节骨吸收与骨生成平衡[26]。RANKL 是一种 II 型跨膜蛋白,是目前发现的唯一具有诱导破骨细胞分化,发育和发挥功能的因子。RANKL 通过与 RANK 结合不仅促进破骨细胞的分化,而且呈剂量依赖性地激活成熟的破骨细胞,提高骨吸收的能力[27]。OPG 是一种分泌型糖蛋白,具有抑制骨吸收的功能。在间充质干细胞的培养过程中,加入 RANKL 可形成功能完善的破骨细胞,加入 OPG 则完全抑制破骨细胞功能。进一步研究发现,OPG 抑制骨吸收功能通过与 RANKL 竞争性结合 RANK 来实现的。RANKL、RANK 和 OPG 之间的平衡决定了破骨细胞的分化和活化的调节,影响骨组织代谢,RANKL-RANK-OPG 轴直接参与破骨细胞的增殖和凋亡。

RANKL-RANK-OPG 轴的紊乱主要是由绝经后雌激素减少引起的。研究认为雌激素可作用于成骨细胞上具有转录活性的雌激素受体,引起细胞表达

骨保护素，雌激素缺乏可引起骨髓干细胞和成骨细胞上 OPG 表达降低，RANKL 表达升高[28]。RANKL 与 RANK 结合后诱导破骨细胞分化，抑制破骨细胞凋亡[29]。OPG 是 RANKL-RANK-OPG 轴的第三个因素，OPG 一方面促进破骨细胞凋亡；另一方面与 RANKL 竞争性结合 RANK，抑制破骨细胞生成、成熟、终止骨吸收，并通过临近接触的成骨细胞促进骨形成[30]。此外，有研究报道编码 RANKL-RANK-OPG 轴的基因密切参与骨质疏松症的发展[29-31]。综上所述，RANKL-RANK-OPG 轴是体内调节骨吸收与骨生成平衡的重要通路，在绝经后的女性中，其体内由于雌激素的缺乏导致 OPG 表达降低，RANKL 表达升高，造成了 RANKL-RANK-OPG 轴的紊乱，破骨细胞增加，成骨细胞减少，从而导致了骨质流失。

3 绝经后骨质疏松症的机制

氧化应激（oxidative stress，OS）是指体内氧化与抗氧化作用失衡，倾向于氧化，导致中性粒细胞炎性浸润，蛋白酶分泌增加，产生大量氧化中间产物。氧化应激是由自由基在体内产生的一种负面作用，并被认为是导致衰老和疾病的一个重要因素[32]。

日前有研究认为，雌激素通过充当抗氧化剂来保护骨，抵抗氧化应激[33]。此外，也有研究提出了从“以雌激素为中心”的发病机制转变为氧化应激也参与骨质疏松症发生的机制[34]。这进一步强调了氧化应激在绝经后骨质疏松症的发生和发展中的重要作用。当女性进入绝经期后，一方面，体内的氧化物质生成增加，如丙二醛（malonaldehyde，MDA），蛋白质羰基化合物，3-硝基酪氨酸，8-羟基鸟苷（8-OHG）等；另一方面，抗氧化物质（如维生素 E、C、A 和 B6 和叶酸）和抗氧化酶活性显著降低。因此，氧化物质的产生增加和抗氧化系统的受损导致细胞氧化还原平衡被打破并导致活性氧（reactive oxygen species，ROS）过量产生[35]。过量的 ROS 对脂质、蛋白质和 DNA 产生氧化损伤[36]，从而促进破骨细胞骨吸收，抑制成骨细胞介导的骨形成，同时成骨细胞和骨细胞的凋亡增多，骨重建失衡，骨密度降低和骨微结构破坏，骨折风险增加[37-38]。

Spilmont 等[39]使用石榴提取物及其衍生物干预去卵巢小鼠，发现干预组与对照组在骨小梁数目、骨体积、骨密度、骨小梁分离等方面差异都有显著的统计学意义，并且炎症标志物 CCL2 的表达量在干预组中的水平明显减少，同时 IL1-R2 和 IL1-Rn（两种抗炎介质）的水平显著提高，表明了石榴提取物通过减少绝经后骨质疏松症的动物模型中的炎症和氧化应激来改善骨骼健康。综上所述，绝经后女性由于其体内雌激素的减少，抗氧化作用降低，从而导致 ROS 生成增加，ROS 促进破骨细胞生成，抑制成骨细胞的成骨作用，造成了骨质流失。

4 总结与展望

绝经后骨质疏松症在骨质疏松症中占有比例最大，是目前全球公共卫生亟待解决的重要问题。目前，在临床上对绝经后骨质疏松症的治疗主要有激素替代疗法，钙剂，维生素 D，双膦酸盐，选择性雌激素受体调节剂和甲状旁腺素等。但是其治疗效果均不太理想。找到绝经后骨质疏松发生机制是科研工作人员首要解决的问题，从而能够针对其机制，找到能够预防甚至治疗绝经后骨质疏松的药物。现有研究认为绝经后骨质疏松症的发生主要是由于 RANKL-RANK-OPG 轴的紊乱，体内免疫系统的紊乱，氧化应激作用以及 microRNA 的下降所造成的，但是这些并不是研究的终点，相信随着科研工作的进展，未来会探明更多的绝经后骨质疏松发生的机制，从而对其进行多方面的预防以及治疗，能够真正意义上的解决这一世界性难题，造福人类。

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