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原发性骨质疏松症病因学研究进展

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摘 要

骨质疏松症是一种以骨量低，骨组织微结构损坏，导致骨脆性增加，易发生脆性骨折为特征的全身性骨病。骨质疏松症包括原发性骨质疏松症和继发性骨质疏松症。原发性骨质疏松包括老年性骨质疏松、绝经后骨质疏松和特发性骨质疏松。近年来，国内外学者研究发现原发性骨质疏松症的发病与遗传因素、细胞衰老、肠道菌群失调、铁代谢失衡、自噬异常、Th17/Treg失衡等有关。本文通过查阅相关文献，对近年来原发性骨质疏松症的病因学研究进展进行阐述。

关键词

骨质疏松症，病因学，肠道菌群，铁，自噬

Research Progress in the Etiology of Primary Osteoporosis

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Abstract

Osteoporosis is a systemic bone disease characterized by low bone mass and microstructural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fragility fractures.

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Osteoporosis includes primary osteoporosis and secondary osteoporosis. Primary osteoporosis encompasses senile osteoporosis, postmenopausal osteoporosis, and idiopathic osteoporosis. In recent years, studies by domestic and international scholars have found that the pathogenesis of primary osteoporosis is associated with genetic factors, cellular senescence, gut microbiota dysbiosis, iron metabolism imbalance, autophagy abnormalities, and Th17/Treg imbalance, among others. This article reviews relevant literature to elaborate on the progress of research in the etiology of primary osteoporosis in recent years.

Keywords

Osteoporosis, Etiology, Gut microbiome, Iron, Autophagy

1. 引言

原发性骨质疏松症(osteoporosis, OP)是自然衰老过程中引起的骨骼系统的退行性改变，是最常见的代谢性骨病。随着人口老龄化的发展，骨质疏松症的发病率逐年增加，骨质疏松症患者常因轻微外力即出现骨折，对患者的生存质量造成严重的影响，但病因仍不明确。因此，充分了解骨质疏松的病因和发病机制，并在此基础上指导骨质疏松症的预防、诊断和治疗策略的制定成为亟待解决的问题。

骨稳态依赖于破骨细胞骨吸收和间充质细胞系成骨细胞骨基质形成之间的精确平衡，涉及一系列复杂且高度调控的步骤，骨质疏松症及其骨折的发生是多种因素交互作用的结果。

2. 遗传因素

原发性骨质疏松有较强的遗传倾向。骨密度(bone mineral density, BMD)的遗传率为60%~80%，也就是说大约60%~80%的BMD来源于父母，较少的一部分来自非遗传因素即环境因素[1]。此外，还有研究表明骨质疏松骨折的遗传率为50%~70%，这也提示对于有骨质疏松家族史的低BMD患者应该及早干预[2] [3]。

3. 内分泌因素

3.1. 雌激素缺乏

雌激素对于男性和女性的骨质均有保护作用，绝经后雌激素的骤然缺乏是导致绝经后骨质疏松的重要原因[4]。雌激素通过破骨细胞上的雌激素受体抑制破骨细胞的分化直接抑制骨吸收，也可通过抑制成骨细胞、T细胞、B细胞核因子-κB配体RANKL的产生间接抑制骨吸收；促进骨髓间充质干细胞成骨分化增加，成脂分化减少，修复衰老的间充质干细胞[5] [6]。雌激素缺乏时一方面对骨吸收的抑制不足；另一方面，对抗氧化应激的作用降低，体内的活性氧(reactive oxygen species, ROS)堆积，造成成骨细胞凋亡增加、成骨细胞分化减少，骨形成不足[7]。雌激素缺乏增加了活化T细胞上表达的共刺激因子CD40L的数量，诱导了基质细胞上M-CSF和RANKL的表达，下调了OPG的产生，最终导致破骨细胞数量显著增加[8]。因而，雌激素缺乏时骨形成与骨吸收之间的平衡被打破，导致净骨丢失，骨密度下降，导致骨质疏松的发生。在过去的几十年，雌激素的替代疗法被应用于治疗骨质疏松症。然而，这一疗法仅仅在绝经后十年内骨折风险升高的女性中雌激素替代疗法的益处高过风险[9]。单独应用雌激素会导致子宫内

膜癌的风险增加，联合应用孕激素虽然降低了子宫内膜癌的患病风险，但是雌激素可能通过诱导孕激素受体从而放大孕激素信号传导，间接增加乳腺癌风险[10] [11]，这导致雌激素使用量大幅下降。传统雌激素替代疗法的风险使选择性雌激素受体调节剂应运而生。其保留了雌激素对骨的保护作用同时，降低了子宫内膜癌和乳腺癌的发生率。但是，越来越多的证据表明使用选择性雌激素受体调节剂会增加血栓栓塞性疾病、肌肉痉挛和脑卒中的风险[12]。雌激素受体表达十分复杂，尤其是最近的研究推翻了许多用于检测 ERβ 表达的抗体[13]。因此，雌激素受体表达仍需进一步研究，SERMs 用于临床预防和治疗骨质疏松的主要目标是在需要的部位(如骨骼组织)最大化药物的激动活性，同时通过减少其他组织中的雌激素激动活性来避免不良反应。

3.2. 维生素 D 缺乏

维生素 D 在骨代谢、调节钙通道功能、促进肠道对钙磷的吸收和骨钙化中起着核心作用，成人维生素 D 的缺乏是骨质疏松的重要原因[14]，维生素 D 和钙的结合补充能提高骨密度降低髋部和非锥体骨折的发生率[15]。然而，越来越多的证据表明，补充维生素 D 的益处仅见于维生素 D 缺乏的患者[16]。甚至还有证据表明，间歇性大剂量服用维生素 D 可能有害，增加跌倒或骨折的风险[17]。因此，老年人是否应该常规补充维生素 D 以预防骨质疏松的发生仍有待商榷。

3.3. 维生素 C 缺乏

维生素 C 不仅具有清除 ROS 的抗氧化作用，而且在骨代谢、基因表达调控和免疫系统激活等方面具有重要的介导作用。维生素 C 大量缺乏时会导致包括骨骼在内的结缔组织的大量破坏[18]。维生素 C 缺乏时骨小梁减少在靠近生长板的地方最为突出，表明在维生素 C 缺乏状态下骨生成障碍[19]。去卵巢小鼠服用维生素 C 后可以防止骨流失和成骨细胞耗竭，维生素 C 能增加成骨分化基因的表达，减少 RANKL 的生成[18]。此外，维生素 C 可以减少炎症条件下的骨吸收[20]。这些研究表明维生素 C 对于雌激素减少所致的绝经后骨质疏松症和慢性炎症所致的骨质流失均有抑制作用。

3.4. 铁代谢异常

铁是生物体内重要的元素，参与多种生化反应，对氧气的运输和储存、呼吸链复合体和 DNA 复制等生物功能至关重要[21]。

3.4.1. 铁过载

铁过载时过量的铁通过芬顿反应生成大量的 ROS，而 ROS 会影响成骨细胞和破骨细胞的生理活性，有利于破骨细胞并抑制成骨细胞的功能，最终破坏骨平衡，ROS 的过度积累是骨质疏松症发展的重要致病因素[22] [23]。ROS 能激活 MAPKs 信号通路诱导成骨细胞凋亡，ROS 还能上调 RANKL 的表达、下调 OPG 的表达使 RANKL/OPG 的比值增大促进破骨细胞的分化[24]。铁过载时除 ROS 外，血清 TNFα、IL-6 的水平也升高，这表明氧化应激和炎症途径均参与铁过载时的骨质流失[25]。Wnt 激动剂被证实显著减少铁过载导致的成骨细胞凋亡[26]，有望成为治疗铁过载相关骨质疏松症的治疗靶点。

3.4.2. 铁缺乏

铁缺乏是世界上主要的疾病负担之一，常见于儿童、绝经前妇女和中低收入国家的个体；它是许多疾病的病因[27]。研究表明骨质疏松症的风险随着膳食铁摄入量的适度增加而降低[28]，铁缺乏时会使生成 I 型胶原和维生素 D 活化的相关酶的活性降低进而影响骨代谢，使骨的转换率下降[29]。此外，铁缺乏时会导致缺铁性贫血，诱导产生 iFGF23，生理条件下 iFGF23 会直接裂解，但经静脉补铁会影响 iFGF23 的裂解出现高水平 iFGF23，增加磷酸盐排泄，导致低磷血症并增加骨吸收[23]。

4. 衰老

衰老导致细胞、器官衰老使骨重建失衡，随着年龄增长骨髓间充质干细胞数量减少，成骨分化减弱，成脂分化增强，成骨细胞减少，骨细胞在衰老机体内也会出现凋亡增加，数量减少的现象[30] [31]。衰老细胞在胚胎发育的早期阶段产生，并随着年龄的增长而积累(5)。然而，衰老细胞通过分泌过多的炎症性细胞因子、趋化因子、氧化应激相关蛋白、生长因子和蛋白酶，对组织产生有害的影响，这被称为衰老相关分泌表型(senescence-associated secretory phenotype, SASP)。积累的衰老细胞是衰老的标志，并导致与年龄相关的 OP 在内的多种骨骼疾病[32]。SASP 因子是衰老的关键调节因子，因此驱动系统性慢性炎症，其特征是即使在没有急性感染或显性临床疾病的情况下，也能维持低级别持续的炎症反应[33]。与 SASP 相关的细胞因子，包括 IL-6、IL-8、单核细胞趋化蛋白 1 (MCP-1)和肿瘤坏死因子 α (TNF-α)，在老龄小鼠的骨细胞中显著上调[34]。IL-6 可能是年龄相关骨丢失中相关炎症因素的主要炎症因子。在肥胖模型中，IL-6 通过 IL-6/STAT3 信号通路加速骨髓间充质干细胞的衰老，IL-6 敲除可防止骨髓间充质干细胞衰老，并减轻肥胖诱导的骨丢失[35]。此外，IL-6 可能通过 Akt 通路抑制 Setd7 的表达，并损害 MSC 的成骨作用[36]。虽然 SASP 与衰老相关骨疾病之间的关系受到了广泛的关注，但还需要更多的研究来确定 SASP 在骨稳态调节中的分子机制，这将为骨骼疾病的治疗干预提供潜在的靶点。

5. 肠道菌群失调

Sjogren 等人首次描述了微生物和骨骼代谢之间的关系，他们通过动物实验发现与对照组相比，无菌饲养的小鼠骨小梁量增加，经传统饲养的小鼠体内肠道菌群定植后这一现象又发生逆转，这说明肠道微生物可以使净骨量下降[37]。肠道菌群失调会影响维生素 D、叶酸在肠道的吸收。菌群失调引起的维生素 D 吸收障碍会导致骨重建失衡，进而诱发骨质疏松；叶酸参与同型半胱氨酸的代谢，叶酸吸收障碍会导致高同型半胱氨酸血症会导致细胞外骨基质降解，使骨密度降低[38]。肠道菌群的失调还可通过提高 5-HT 合成的限速酶 5-HT-色氨酸羟化酶-1(TPH-1)的活性降低肠源性 5-HT 的合成，进而使骨形成减少[38]。近来研究表明肠道益生菌能促进肠道碳水化合物的消化并产生短链脂肪酸(包括乙酸、丙酸、丁酸等) [39]，而丁酸盐被证明在肠道菌群诱导的骨形成有重要影响。在无菌小鼠中添加鼠李糖乳酪杆菌可以调节增加肠道和全身的丁酸盐浓度、股骨小梁体积分数和骨形成标志骨钙素的水平[40]。肠道菌群对铁代谢也有重要作用，乳酸杆菌能感知肠道中铁水平并增加宿主矿物质元素(如铁、镁和锌)的吸收[41]。此外，肠道微生物群凭借其强大的生物合成能力，在调节炎症方面发挥着关键作用，无菌动物的研究表明，缺乏肠道微生物群会导致显著的免疫系统缺陷[42]。梭菌属 vadinBB60 群与健康小鼠的 Treg 细胞计数呈正相关群与健康小鼠 Treg 细胞计数呈正相关，鼠李糖乳酪杆菌可通过调节肠道微生物组和肠道屏障以及刺激肠道和骨骼中的 Th17/Treg 平衡来改善雌激素缺乏诱导的骨质疏松症[43] [44]。改善肠道微生态平衡可能是治疗和预防骨质疏松症的新方法。

6. 细胞自噬异常

细胞自噬是细胞内蛋白质和细胞器降解和循环的一个基本的进化上保守的过程，是调节细胞和器官稳态的重要基本过程[45]。包括成骨细胞、破骨细胞、骨细胞和 BMSCs 在内的多种细胞的自噬参与了骨重塑，在维持骨稳态和 OP 的发病机制中起着重要作用。在 BMSCs 中，自噬抑制剂 3-MA 可减少 BMSCs 成骨分化，而自噬激活剂雷帕霉素增加成骨分化[46]。自噬可以拮抗 ROS 所致的细胞损伤，延缓 BMSCs 衰老，促进成骨分化并为成骨分化提供能量[47]。自噬相关基因 ATG5、ATG7、Beclin-1 缺失会使 BMSCs 成骨分化降低、成骨细胞矿化能力降低，使骨稳态失衡[48] [49]。在骨细胞中，自噬的失调会导致骨组织的衰老[50]。在 RANKL 诱导的破骨细胞分化过程中细胞自噬上调以促进单核巨噬细胞分化为破骨细胞

[51]。自噬有助于成骨细胞前分化、成骨细胞－骨细胞转化以及破骨细胞的分化和功能[52]。近来在自噬相关研究中出现了矛盾的情况，PAX8-AS1 是一种长的非编码 RNA，在 OVX 诱导的 OP 大鼠胫骨近端区域的表达上调，而 PAX8-AS1 沉默已被证明通过抑制自噬来减少骨质流失[53]。这表明细胞自噬途径十分复杂，相关机制仍需进一步研究，以阐明细胞自噬和 OP 之间的关系。

7. Th17/Treg 失衡

骨髓中富含造血干细胞，为这些细胞的生长提供了必要的微环境，并可分化为免疫细胞，发挥免疫功能，免疫系统与骨骼系统因骨髓这一共同的微环境而紧密相连。在 OVX 小鼠中，Th17 亚群在免疫细胞中的百分比和 Th17/Treg 比值均增加，而 Treg 亚群的百分比和 Th17/Treg 的比值均显著降低[54]。T 辅助细胞 17 (Th17)和调节性 T 细胞(Treg)是两种可以相互作用，通过 OPG/RANK/RANKL 通路调节破骨细胞分化和形成的 T 细胞[55] [56]。在体内和体外的研究表明，Treg 细胞抑制破骨细胞的分化，而 Th17 细胞促进破骨细胞的分化[54]。Th17 细胞对骨代谢的影响主要体现在其分泌的 IL-17 能上调 RANK 在巨噬细胞的表达促进 RANKL-RANK 的结合并且 Th17 本身也可以分泌 RANKL 使 OPG/RANKL 比值降低促进破骨细胞分化[57]。Treg 分泌的 IL-10 可通过上调骨保护素 OPG 的分泌，下调 RANKL 和 M-CSF 的表达，抑制破骨分化，减少骨吸收[58]。然而，免疫系统是一个复杂的网络，骨免疫领域的药物研发面临着如何在抑制 T 细胞致病性激活的同时维持其正常的免疫应答功能等问题。

8. 小结

骨质疏松症是多病因共同作用的结果，骨质疏松症的预防和治疗仍面临着困难和挑战。在过去的几十年内，开发了多种不同机制的药物。现有的药物具有较好的疗效，但长期应用存在一定的安全性问题。长期使用阿仑膦酸钠和地诺单抗会导致颌骨坏死和不典型股骨骨折；在动物实验中发现，长期高剂量使用特立帕肽骨肉瘤的患病率明显增加等[59]。近年来的研究发现肠道菌群、自噬、铁代谢、细胞衰老、Th17/Treg 平衡失调等均与骨稳态相关。未来对于骨质疏松发病机制的研究应更多地向临床治疗转化，寻找更加精准的靶点，达到更佳药效的同时尽量减少药物的副作用。

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