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绝经后铁代谢的变化对骨密度的影响

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摘　要

骨质疏松症(OP)由于其在老年人中的高发病率和高致骨折率，长期以来一直受到广泛的关注。随着世界各国人口老龄化的到来及加剧，骨质疏松症的患病率逐年上升，绝经后妇女由于体内雌激素的减少，对破骨细胞的分化和骨吸收的抑制作用降低，加速了骨量的流失，易导致绝经后骨质疏松症。体内铁含量水平及铁代谢与骨代谢有着密切的联系，不管是体内铁增多还是铁缺乏都会影响破骨细胞和成骨细胞的分化和活性，从而促进骨质流失，但对于体内铁代谢是如何影响骨密度及骨代谢，本综述简要阐述了体内铁含量及铁代谢对骨密度及骨代谢影响的有关机制，从而为铁相关性绝经后骨质疏松症的研究、预防及治疗提供新的临床思路。

关键词

绝经后骨质疏松症，雌激素，铁稳态，氧化应激，铁调素

The Effect on Bone Mineral Density of Iron Metabolism Changes in Postmenopausal Women

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Abstract

Osteoporosis (OP) has been widely concerned for a long time because of its high incidence and fracture rate in the elderly. With the arrival and aggravation of the aging of the world's population,

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the prevalence of osteoporosis is increasing year by year. Because of the reduction of estrogen in postmenopausal women, the inhibition of osteoclast differentiation and bone resorption is reduced, which accelerates the loss of bone mass and easily leads to postmenopausal osteoporosis. The level of iron content and iron metabolism in the body are closely related to bone metabolism. Both iron increase and iron deficiency in the body will affect the differentiation and activity of osteoclasts and osteoblasts, thus promoting bone loss. However, how iron metabolism in the body affects bone density and bone metabolism is briefly described in this review, It provides a new clinical idea for the research, prevention and treatment of iron related postmenopausal osteoporosis.

Keywords

Postmenopausal Osteoporosis, Estrogen, Iron Homeostasis, Oxidative Stress, Hepcidin

1. 引言

骨质疏松症是一种由多种因素引起的全身代谢性骨病，其特征为骨微观结构破坏所致的骨量下降，是脆性骨折发生的独立危险因素。在原发性骨质疏松中，绝经后体内雌激素水平的下降是绝经后妇女骨质流失加速的主要危险因素，可诱发及加速绝经后骨质疏松症的发生。近年来的研究发现，绝经后骨质疏松症的发生除了与体内雌激素的减少有关外，还与体内铁含量及铁代谢异常有关，不管是体内铁超载还是铁缺乏，均会导致骨代谢异常，加速骨质流失，易导致骨质疏松症的发生，特别是绝经后体内铁的积累，造成体内铁超载，铁超载在绝经后骨质疏松症中的影响已引起了广泛关注，但铁代谢变化对骨代谢的影响和骨质疏松症发生的机制目前尚未明确。本文将其做简要的阐述。

2. 雌激素对骨代谢的影响机制

雌激素是女性体内重要的激素，具有促进女性生殖器官发育，维持女性第二特征，维持骨代谢平衡等作用，女性绝经期卵巢功能下降使雌激素生成减少，同期卵泡刺激素生成相应升高，两种激素共同作用增加了骨吸收，加速了骨质流失，这是绝经后骨质疏松症发生的重要原因[1]。在绝经初期，雌激素含量的快速下降导致骨重塑增加，其中成骨细胞活性和破骨细胞活性均增加[2]。随着绝经年限的延长，这个过程不再平衡，骨吸收超过骨形成，加速了骨质疏松症的发展[3] [4] [5]。雌激素对骨代谢影响的主要机制为：雌激素缺乏导致雌激素诱导的核因子 kappa-β 配体(Receptor Activator of Nuclear Kappa-β Ligand, RANKL)拮抗剂－骨蛋白(Osteoprotegerin, OPG)的表达减少，使破骨细胞通过 RANKL/OPG 途径增殖和活化[6] [7]，增加了对骨质的破坏和吸收，使骨量减少，骨密度降低。雌激素受体(Estrogen Receptor, ER)在两种骨细胞中高度表达，起着保护骨骼的作用[8]。ER 可与核因子 κB (Nuclear Factor-kappa β, NF-$\kappa\beta$)结合，抑制 NF-$\kappa\beta$ 信号通路的活性和破骨细胞分化[9] [10]，从而抑制了破骨细胞诱导的骨质吸收。此外，雌激素的缺乏会改变雌激素靶基因的表达，雌激素缺乏导致白介素(Interleukin, IL)-7 增加，促进了 T 细胞的活化，T 细胞诱导促炎因子，如 IL-1、IL-6 和肿瘤坏死因子 α，导致破骨细胞活化[10] [11]。在雌激素缺乏期间，骨吸收生化指标增加了 90%，而骨形成指标仅增加了 45% [12]。骨吸收与骨形成平衡失调，骨质流失大于生成，导致骨质疏松，增加骨骼脆性和骨折的风险[12]。因此，雌激素减少不仅与女性绝经

后骨质疏松症的发生关系密切，而且很大程度上增加了骨质疏松症患者发生骨折的风险。

3. 雌激素与铁代谢的关系

体内雌激素水平对铁代谢有一定的影响，研究发现，雌激素特别是雌二醇可通过减少铁调素合成和维持转铁蛋白的完整性来影响体内铁稳态[13]。雌激素浓度升高与铁需求和释放到体循环中的铁量呈正相关，并且与铁调素浓度呈负相关，但雌激素对铁代谢影响的确切机制目前仍未明确[14]。禄林等的动物模型实验发现，随着去势小鼠体内雌激素水平的下降，其体内铁吸收也相应减少，循环铁量减少，而肝脏储铁增加，这种变化可能与雌激素下降影响了铁代谢通道蛋白表达变化有关[15]。费等在对雌激素和铁积累与骨代谢异常的研究中发现，雌激素可能影响着铁对骨吸收的吸收水平，在雌激素水平正常时，单纯的铁蓄积对绝经后骨质疏松的影响较小，当雌激素缺乏时，铁蓄积能显著增强破骨细胞的作用，使骨量下降，其可能与雌激素与铁的拮抗作用影响了破骨细胞的活性有关[16]。综上，雌激素与铁代谢之间存在联系，雌激素可能通过影响铁代谢进而对骨代谢产生影响，两者共同作用加速了骨质疏松症的发展。

4. 绝经后体内铁代谢变化

绝经后的女性体内除雌激素外，铁代谢也发生着一定的变化，研究表明，女性每年经经期排出的铁约 36 mg [17]。女性绝经后经期失铁停止，使女性绝经前后铁含量变化较大，在更年期过渡期间，尽管雌激素减少了 90%，但铁水平在同期会发生相反的变化。例如，血清铁蛋白水平从绝经前到绝经后增加了两到三倍[18]。据估计，妇女 45 岁到 60 岁之间，体内铁储存量可由 4.8 mg/kg 增加到 12 mg/kg [19]，证明了绝经后女性容易出现铁积累。纽约大学的一项研究显示，与绝经前相比，绝经后女性的平均血清铁蛋白浓度增加了 2 倍以上[20]。有研究将绝经后股骨颈骨折行髋关节置换的绝经后女性(年龄均 > 50 岁)按每 10 岁年龄段分组，共 5 组，测定了受试者股骨头骨铁含量和血清铁蛋白，结果发现骨铁和血清铁蛋白随年龄增加而升高，其铁超负荷率达到 64.1% [21]。金等研究发现，人体内血清铁蛋白与骨量丢失呈正相关，且体内铁储存可能存在性别上的差异，绝经后女性更容易发生轻度铁超负荷，相比中年男性，绝经后女性体内铁储存对骨质的影响更加突出[22]。因此，除了雌激素减少外，绝经期相关的铁积累也可能是影响绝经后女性健康的危险因素[23]。

5. 铁对成骨细胞及破骨细胞代谢的影响

铁是人体内重要的微量元素，研究发现铁含量及铁代谢影响着骨代谢，其主要通过影响成骨细胞及破骨细胞的活性对骨代谢产生影响。多铁与少铁均与骨量减少有关，这表明平衡的骨稳态需要适宜的铁水平。越来越多的证据表明，铁超载和铁缺乏都会影响破骨细胞和成骨细胞的分化和活性，从而促进骨质流失、使骨密度减少，加速了骨质疏松症的发展。由于破骨细胞与成骨细胞的生理机制不同，体内铁对两种细胞的影响机制也有所差异。

铁在破骨细胞中的影响：破骨细胞是由 RANKL 的受体激活剂的诱导形式融合单核巨噬细胞系或骨髓间充质干细胞融合而成的大型多核细胞，铁离子可以通过产生活性氧(Reactive Oxygen Species, ROS)来促进破骨细胞分化和骨吸收[24]。在体外研究发现应用铁螯合剂可抑制破骨细胞的形成[25]，减缓骨质的丢失。铁减少对破骨细胞也产生影响，一项对破骨细胞分化过程的研究发现，在细胞实验中发现在正常缺铁情况下，铁饥饿反应(转铁蛋白受体 1 增加，铁蛋白减少)后的 RANKL 刺激证实了铁减少对骨质的影响，在 RANKL 刺激下，骨髓来源的巨噬细胞中的丙二醛和前列腺素内过氧化物合酶 2 基因表达增加，使培养基中的谷胱甘肽和铁水平降低，线粒体中观察到铁积累[26]，细胞易发生铁死亡。

铁在成骨细胞中的影响：成骨细胞在骨质的合成、分泌和矿化中起主导作用[27]。研究表明，铁对间

充质干细胞的成骨分化有抑制作用，过量的铁以浓度依赖性方式抑制成骨细胞活性。相比之下，低铁浓度对成骨细胞产生不同影响：轻度低铁促进成骨细胞活性，但严重的低铁抑制成骨细胞活性[28]。去铁胺能降低了成骨细胞生成和碱性磷酸酶的表达，同时降低了细胞内铁离子的浓度[29]，该途径涉及细胞内外铁离子的交换以及细胞中铁离子的代谢。成骨细胞在分化过程中可以通过该途径维持细胞内铁稳态。小鼠铁超负荷与致密骨源细胞中铁蛋白增加和 RUNX 相关转录因子 2 (Runt-related transcription factor 2, RUNX2)水平降低有关[30]。二价金属离子转运体 1 (Divalent metal transporter 1, DMT1)是人体内铁离子的主要调控物质，研究发现，DMT1 可影响成骨细胞凋亡和自噬，DMT1 在骨质疏松症中增加并诱发铁超负荷，铁超负荷可诱导氧化应激并增加 ROS，ROS 可诱导细胞凋亡和自噬[31]。DMT1 可通过此途径影响成骨细胞自噬和凋亡，从而影响骨质疏松症的病理过程。综上，铁对成骨细胞及破骨细胞的影响会抑制骨形成，促进骨吸收，导致骨质流失。

6. 铁稳态系统对骨代谢的影响

铁稳态环境对维持体内多种组织及器官的正常生理活动至关重要，铁稳态的系统性调控依赖于铁调素与铁转运蛋白之间的相互作用。转铁蛋白是一种对 Fe^{3+}具有高亲和力结合位点的糖蛋白，两者结合维持血浆中铁的可溶性形式，并通过转铁蛋白受体将其输送到细胞中，从而减少血浆中有毒自由基的生成[32]。铁从十二指肠肠细胞和巨噬细胞释放到循环中，衰老的红细胞中铁经肝脏，脾脏和骨髓中的巨噬细胞回收，参与体内铁循环[33]。铁调素与铁转运蛋白结合后，减少了巨噬细胞和肠道吸收细胞的铁输出，减少了血清铁水平，使血浆中的铁处于稳态状态[34]。铁通过上述途径维持着铁含量及铁代谢的稳态。

铁代谢的细胞调控是通过铁调节蛋白和铁响应元件的作用以转录后的方式进行的[32]。对小鼠长期给予葡聚糖铁会导致不同器官的组织铁超负荷和骨质疏松症[32]。铁超负荷模型中观察到骨质流失与 ROS 产量升高有关，而抑制 ROS 形成可在一定程度上预防骨质流失[35]。同时高铁应激会诱发斑马鱼幼虫和成虫的快速骨质疏松症[36]。对血色病动物模型(即铁调素缺乏的小鼠和铁调素缺乏的斑马鱼)进行的研究也支持铁过载对骨骼健康的有害影响[37] [38] [39] [40] [41]。

乳铁蛋白是一种内源性铁结合糖蛋白，乳铁蛋白可促进成骨细胞的分化，同时减少成骨细胞50%~70%的凋亡，也可刺激软骨母细胞的增殖[42]。研究发现乳铁蛋白可抑制单核细胞的破骨细胞分化，降低 RANKL 的表达，并通过降低 RANKL/OPG 比值降低了破骨细胞对骨质的破坏和吸收[43] [44]，铁螯合剂去铁胺可抑制破骨细胞分化，使破骨细胞形成减弱并抑制破骨细胞特异性基因表达[45] [46]。以上研究均进一步证实了铁稳态环境及铁代谢对骨代谢的影响。

7. 铁超载通过氧化应激机制促进骨吸收

铁超载可通过产生活性氧对骨代谢产生影响，其可能的机制包括以下几方面：铁过载可以通过 Fenton 和 Haber-Weiss 反应产生 ROS 来诱导骨质疏松症[47] [48]，铁超负荷介导 ROS 产生，ROS 阻断了磷脂酰肌醇 3-激酶(Phosphatidyl inositol 3-kinase, PI3K)/蛋白激酶 B (protein kinase B, AKT)和酪氨酸蛋白激酶(Janus Kinasa, JAK)/信号传导与转录激活因子 3 (Signal transducer and activator of transcription, STAT3)信号通路，激活了 p38/丝裂原活化蛋白激酶(Mitogen activated Protein Kinasa, MAPK)，并在成骨 MC3T3-E1 细胞中诱导 G1 停滞和自噬，抑制成骨细胞生成[49]，ROS 可与过氧化物酶体增殖物激活受体 γ 共激活因子(Peroxisome proliferator-activated receptor γ coactivator, PGC)-1β 结合以增加线粒体的数量并激活破骨细胞分化。铁调素可限制破骨细胞对铁的使用，下调了 ROS 和 PGC-1β，减少线粒体诱导的破骨细胞的骨吸收功能，从而显著改善了骨量。Zhang 等观察到小鼠骨质流失的趋势在过度表达铁调素基因的卵巢切除小鼠中被抑制[50]。Tian 等利用动物模型实验证明了铁超负荷诱导体外成骨细胞的凋亡及坏死，部分

通过受体相互作用蛋白 1 (Receptor-interacting protein 1, RIPK1)/受体相互作用蛋白 3 (Receptor-interacting protein 3, RIPK3)/混合系数区域样蛋白(Mixed lineage kinase domain-like protein, MLKL)途径介导。此外，还发现 ROS 通过涉及 RIPK1/RIPK3 的正反馈回路介导铁过载诱导的成骨细胞的凋亡与坏死[51]。王啸等观察到铁蓄积可使氧化应激水平升高，通过激活 NF-KB 通路，使破骨细胞分化能力增强，促进骨吸收，进而导致骨重建失衡，骨量丢失[52]。铁蓄积可能骨通过刺激 NF-KB 信号通路使破骨细胞分化能力增强，骨吸收增加[53]。

8. 铁调素对代谢的影响机制

铁调素是由肝细胞合成的一种肽类激素，是铁代谢和体内铁稳态的主要调节剂。在血液中铁调素与靶细胞，巨噬细胞和肠细胞中的铁转运蛋白结合，从而促进铁转运蛋白的内化和降解，抑制铁从肠细胞膜与巨噬细胞中释放出来，导致从食物中吸收的铁减少，使巨噬细胞中储存的铁增加[54]。铁调素的表达受铁含量、炎症(如 IL-6)和红细胞生成的调节。在成熟的成骨细胞中，铁通过抑制骨形态发生蛋白 2 和 Wnt 信号通路来抑制成骨细胞骨重塑[55] [56]。铁调素是铁的负性调节剂，铁调素可通过降低骨组织中的铁水平，延缓由铁超载所导致骨质疏松的发展，此外，还发现铁调速还可与 PGC-1β 结合，减少 ROS 的产生和线粒体的数量，从而抑制破骨细胞分化和骨吸收[25] [57]，抑制了骨质吸收及骨密度的降低，延缓了骨质疏松症的发生、发展。随着铁调素的降低，骨密度呈明显下降趋势。铁调素的过表达可能对绝经后骨质疏松症有保护作用。在铁调素较高的绝经后女性人群中，骨质量也升高，铁调素水平与骨矿物质密度之间存在正相关关系[51]。铁调素敲除后的小鼠存在慢性铁蓄积和显著骨质流失[37]。相反，补充铁调素和减少铁蛋白可防止这些小鼠股骨骨质流失[58]。在动物模型中，铁调素的过表达显著保护了由去卵巢大鼠引起的骨量丢失和骨密度下降。这表明铁调素过表达可以预防由雌激素缺乏引起的骨质疏松症，可为绝经后骨质疏松症的临床治疗提供新的靶点。

9. 结论

综上所述，人体内铁含量及铁代谢通过多种途径影响体内骨代谢，体内铁缺乏及铁超载均会诱发及加速骨质疏松的发展，特别是绝经后妇女体内，由于雌激素的减少及经期铁丢失的减少，更易发生体内铁积累，铁负荷的增加可通过上述一系列途径，诱发及加速骨质流失，使骨密度减少，诱发及加速了绝经后骨质疏松症的发生。

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