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肥胖与骨质疏松相关机制研究进展

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摘　要

肥胖和骨质疏松症是衰老过程中的常见现象，既往普遍认为肥胖能够增加骨密度，现在研究发现肥胖对骨骼的积极影响并不能降低骨质疏松及骨折发生率。肥胖影响骨代谢的因素包括遗传相关性、骨髓脂肪细胞、脂肪细胞分泌的促炎细胞因子和脂肪因子以及骨源性因子对代谢的影响，不同肥胖种类对骨密度的影响以及抗骨质疏松治疗对代谢的影响。本文通过总结近年来关于肥胖与骨质疏松相关机制研究，为预防和延缓肥胖患者发生骨质疏松提供新的临床诊疗思路。

关键词

肥胖，骨质疏松，机制，相关性

Research Progress on the Correlation Mechanism between Obesity and Osteoporosis

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Abstract

Obesity and osteoporosis are common phenomena in the aging process. It has been widely believed that obesity could increase bone mineral density. Now, studies have found that the positive effects of obesity on bone cannot reduce the incidence of osteoporosis and fracture. The factors of obesity affecting bone metabolism include genetic correlation, bone marrow adipocytes, proinflammatory cytokines and adipocytokines secreted by adipocytes, and the effects of bone derived

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factors on metabolism, the effects of different types of obesity on bone mineral density, and the effects of antiosteoporosis treatment on metabolism. This article summarizes the recent researches on the mechanism of obesity and osteoporosis, and provides a new clinical diagnosis and treatment ideas for preventing and delaying the occurrence of osteoporosis in obese patients.

Keywords

Obesity, Osteoporosis, Mechanism, Correlations

1. 简介

肥胖(Obesity, OB)是一种身体脂肪过多积累到一定程度对健康产生不利影响的状态，体重指数(body mass index, BMI)是世界范围内使用最多的评价肥胖的指标，该指数通过体重(kg)与身高(m)的平方之比计算得出。根据世界卫生组织定义 BMI 值 > 30 kg/m^2 视为肥胖(中国是依据 BMI > 28 kg/m^2)，研究发现肥胖与心血管疾病、2 型糖尿病、癌症、血脂异常等多种疾病密切相关[1]。中国居民营养与慢性病状况报告(2020)数据显示有超过一半的成年居民肥胖(BMI > 28 kg/m^2)或超重(BMI > 24 kg/m^2) [2]。骨质疏松症(Osteoporosis, OP)是一种常见的代谢性骨病，以骨密度和骨强度低为特征，该病可导致骨折风险增加，从而使发病率和死亡率增加[3]。越来越多的研究表明肥胖降低骨密度的同时并增加骨折风险[4] [5]，肥胖对骨骼的积极作用主要是通过体重对骨骼的机械负荷从而增加骨量[6]，然而长期肥胖带来的身体脂肪的增加[7]、骨微结构的破坏[8]等使骨形成和骨转换减少，进而导致骨质疏松及骨折。本文通过对近年来关于肥胖与骨质疏松相关机制进行阐述，为及早干预肥胖人群发生骨质疏松风险提供理论依据。

2. 肥胖与骨质疏松相关性

2.1. 遗传相关性

骨质疏松和肥胖都受到强大的遗传决定因素以及遗传相关性影响[9] [10]。脂肪细胞和成骨细胞来源于共同的骨髓间充质干细胞(Bone esenchymal stem cells, BMSC) [11]，由于共同的生物学途径，两者之间存在遗传相关性，这意味着多效性基因调节这两个过程。既往已经研究了与肥胖和骨质疏松有关的多个多效性基因和候选基因[12]，近来 Martin 等人[13]分析肥胖相关基因的多态性是否可以改变骨质疏松性骨折的易感性分析发现肥胖相关基因 NEGR1 与骨质疏松性骨折有密切相关性；同样 Shi 等人[14]在 390 个中国核心家庭的 1300 名受试者中鉴定出 22 个位于 LGR4 基因及其周围的单核苷酸多态性，表明 LGR4 基因多态性与骨骼和肥胖表型相关。这些研究都证明了这两种疾病在遗传上密切相关，目前也越来越注意到肥胖和骨质疏松遗传相关性的重要性，且发现了更多的基因遗传位点，由此可能提供了一种新的治疗思路。

2.2. 骨髓脂肪细胞

如上述脂肪细胞和成骨细胞来源于共同的 BMSC，Wnt 信号同时激活 Runt 相关转录因子 2 (Runx2)和抑制过氧化物酶体增殖物激活受体 γ (PPARγ)的表达，它们分别指导成骨和脂肪生成，在早期 BMSC

分化过程中起关键作用[15]。在肥胖人群中，PPARγ 可通过 Runx2 减少抑制成骨细胞分化，导致骨质减少和骨质疏松[16]。研究发现从 BMSC 分化的脂肪细胞和成骨细胞之间的平衡还受到肥胖相关蛋白(obesity-associated protein, FTO)的调节[17]，在骨质疏松发病过程中，FTO 表达的上调促进 BMSC 向脂肪细胞的转移并抑制成骨细胞的活性。虽然在 BMSC 分化过程中，脂肪生成和成骨之间存在竞争关系，但脂肪生成和成骨信号通路可以改变，以利于成骨细胞生成并预防骨质疏松症[18]。因此，有必要阐明脂肪形成和成骨分化之间的关系，并开发新的药物来防止 BMSC 分化为脂肪细胞。

2.3. 脂肪细胞的分泌

研究证明脂肪不止是一个储能器官，也是一个活跃的内分泌组织，能够表达和分泌多种活性物质，如促炎细胞因子、芳香化酶、瘦素、脂联素、抵抗素等，在骨代谢中发挥重要作用。

2.3.1. 细胞因子

肥胖的主要特征是脂肪组织的扩张和慢性低度全身炎症。在肥胖患者中，脂肪组织被大量巨噬细胞浸润，巨噬细胞是炎症细胞因子的主要来源；肥胖患者脂肪组织表达更高的肿瘤坏死因子-α (TNF-α)、白介素6 (IL-6)和C反应蛋白(CRP)等，高水平的促炎因子通过激活核因子(NF)-κB 受体活化因子配体(RANKL)与骨丢失相关[19] [20] [RANKL/RANK (NF-κB 受体)/OPG (骨保护素)途径是骨代谢中的关键途径，OPG 可阻断 RANKL/RANK 结合抑制破骨细胞形成] [21]。最近对 IL-6 基因敲除小鼠的研究发现 IL-6 基因敲除可能会抑制 BMSC 的衰老使骨质流失减轻[22]。由于肥胖是一种促进生化和免疫变化的多因素代谢紊乱，因此肥胖的预防和治疗变得很重要。

2.3.2. 脂肪因子

脂肪细胞产生的芳香化酶促进雌激素含量增加。研究发现涉及瘦素和雌激素的肥胖相关代谢因素对骨密度具有保护作用，瘦素可通过增加骨保护素水平在外周发挥作用，与 RANKL 结合从而抑制破骨细胞生成，雌激素通过减弱炎症性骨微环境减少骨吸收并促进骨形成[23] [24]。脂联素被发现是一种抗炎细胞因子，肥胖患者的慢性炎症状态可能部分与脂联素缺乏有关，脂联素的浓度与许多炎症细胞因子的浓度成反比。另一方面脂联素通过增加碱性磷酸酶、骨钙素及I型胶原蛋白来刺激成骨细胞增殖和分化促进骨形成[25]，内脂素则在 BMSC 分化过程中通过诱导促炎因子损害骨重塑[26]。Glogowska 等人[27]对绝经后肥胖的骨质疏松患者研究发现，瘦素可以是绝经后妇女的骨组织保护因子，没有发现肥胖对绝经后骨质疏松症妇女脂联素或抵抗素分泌的影响。目前关于抵抗素对骨骼作用尚有争议，且相关研究较少，仍需更多的研究来证明抵抗素对骨代谢的影响。有研究发现肥胖小鼠的血清中趋化素(一种由脂肪细胞分泌的蛋白)水平增加而在骨髓中减少[28]，且骨髓中的趋化素能够通过 Akt/Gsk3β/β-catenin 轴促进 BMSC 的成骨分化和骨形成，而且 Akt 抑制剂能够消除趋化素对成骨的分化作用；由此可见，趋化素可能成为预防和治疗骨质疏松症的新潜在靶点。

2.4. 骨源性因子

除了脂肪组织的分泌对骨代谢的影响，骨组织通过分泌一些骨源性因子，如骨钙素、骨桥蛋白和成纤维细胞生长因子(Fibroblast growth factor, FGF)等能够在内分泌水平上调节全身能量代谢[29]。既往针对高加索老年人群的研究表明，血清 FGF23 水平与 BMI、腰围、腰臀比、血脂和脂肪质量呈正相关[30]，由于慢性炎症是肥胖的原因之一，FGF23 与炎症因子的关系可能是肥胖和脂代谢的潜在机制。最近研究发现 FGF19 可能促进成骨分化并减轻肥胖引起的骨质流失[31]，肥胖症、骨质疏松症和肌少症(与年龄相关的肌肉质量损失和身体机能障碍)通常在老年人中同时出现，FGF19 可以保护骨骼肌免受肥胖或衰老引

起的肌肉萎缩，这在肌肉相关疾病中具有潜在的治疗作用。

3. 不同类型肥胖

BMI 是一个容易获得的总体肥胖指数，但它有局限性，相对无法区分瘦体重和脂肪量，更重要的是，无法区分整体肥胖和腹部肥胖。现有证据表明，与整体肥胖相比，中心性肥胖与慢性代谢危险因素的相关性更强[32]; 中心性肥胖以腹部肥胖为主要特征，评价该肥胖类型的指标包括腰围(waist circumference，WC，腰围被认为是流行病学调查中最可靠的中心性肥胖替代品)、臀围(hip circumference, HC)、腰高比(腰围与身高之比，waist-to-Height Ratio，WHtR)、腰臀比(Waist-to-Hip Ratio，WHR，腰围和臀围之比)等。Hasani 等人[33]进行的一项横断面研究发现 BMI 增加与骨密度增加直接相关，而 WHR 与全髋骨密度呈负相关。同样 Du 等人[34]采用双样本孟德尔随机化分析中心性肥胖对骨密度的研究发现臀围调整的体重指数与骨密度成负相关而腰臀比与骨密度成正相关，表明评价中心性肥胖的不同指标对骨密度的影响存在差异。因此有必要研究中心性肥胖指数以促进其作为 BMI 的替代或补充的适当使用。

4. 抗骨质疏松治疗对代谢的影响

在老年人群中，除了肥胖，骨质疏松症可能与其他代谢疾病共存，包括糖尿病、血脂异常、心血管疾病等。由于这些疾病的高患病率以及与骨质疏松症之间可能存在共同的发病机制，抗骨质疏松药物可能会影响其中一些代谢疾病的发病机制以及一些当前或新出现的代谢疾病药物会对骨代谢产生不利影响[35]。关于骨质疏松症的治疗，在一项观察性研究中，即使在肥胖受试者中，双膦酸盐也可将 2 型糖尿病风险降低 50% [36]。没有关于特立帕肽对肥胖绝经后妇女影响的报道，但最近在去卵巢大鼠中进行的一项研究表明，特立帕肽增加了骨骼肌质量的百分比，并降低了脂肪质量的百分比和骨髓脂肪体积[37]。此外用于肥胖治疗的胰高血糖素样肽-1(GLP-1)受体激动剂利拉鲁肽显示出减肥后骨量的保存以及抗骨折功效[38]。因此针对肥胖合并骨质疏松的患者应选择合适的抗骨质疏松药物，而且也需要更多的研究来明确两者之间的机制，以期获得一种可能同时对两种疾病均有益的新兴药物。

5. 总结

虽然对肥胖动物模型的研究已经确定了肥胖对骨代谢的负面影响，但在人类受试者的研究仍然存在争议。人类肥胖是一个复杂的问题，通常涉及过度消耗其他营养素，如蛋白质和矿物质，已知会影响骨代谢。肥胖对人类骨骼健康影响的发现是基于统计相关性或建模，而不是对照实验，因此，对肥胖动物模型的对照研究有助于剖析过度脂肪积累影响骨代谢的机制。也有研究发现骨质疏松症风险最小的最佳 BMI 为 23~24.9 kg/m^2，因此将体重保持在适当范围对骨骼有更好的保护。未来需要更多的研究来阐明肥胖与骨质疏松的相关性，从而为肥胖合并骨质疏松及骨质疏松治疗对代谢的影响提供更准确的依据。

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