· 综述 ·

肥胖症与骨质疏松症的相关性研究

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摘要: 肥胖症和骨质疏松症都是常见慢性疾病,随着我国人口老龄化进程的加剧,二者的发病率也在逐年上升。骨质疏松症是一种全身性骨骼疾病,导致骨密度降低、骨强度降低和骨微结构恶化,从而增加脆性骨折的易感性。肥胖可以被定义为一种包括异常或过量的身体脂肪堆积的复杂疾病,近年来随着研究的不断深入,发现该病与骨质疏松症的发生密切相关。该文通过总结分析近些年这方面的相关研究报道,就肥胖症与骨质疏松症之间的相关性展开综述,以期有针对性地对这两种疾病进行早期干预,改善患者临床症状,提高患者的生活质量。

关键词: 肥胖症;骨质疏松;相关性

Study on the correlation between obesity and senile osteoporosis

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Abstract: Obesity and osteoporosis are common chronic diseases. With the intensification of the aging process in China, the incidence of the two is increasing year by year. Osteoporosis is a systemic skeletal disease, which leads to the decrease of bone mineral density and bone strength and deterioration of bone microstructure, and increases the susceptibility of brittle fracture. Obesity can be defined as a complex disease including abnormal or excessive body fat accumulation. In recent years, with the deepening of research, it has been found that the disease is closely related to the occurrence of osteoporosis. In this paper, through the summary and analysis of the relevant research reports in recent years, the correlation between obesity and osteoporosis is reviewed. It is expected to target early intervention of the two diseases, to relieve the clinical symptoms of the patients, and to improve the quality of life of the patients.

Key words: obesity; osteoporosis; correlation

骨质疏松症(osteoporosis,OP)是一种全身性骨骼疾病,导致骨密度(bone mineral density,BMD)降低、骨强度降低和骨微结构恶化,从而增加脆性骨折的易感性[1]。随着人口老龄化进程的加剧,骨质疏松症的发病率迅速增加,美国每年约有 150 万例典型的脊柱、髋部和腕部骨质疏松性骨折发生[2]。OP 已经成为当今世界面临的重要公共卫生问题。肥胖被定义为体质量指数(body mass index,BMI)≥30 kg/m^2,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。肥胖的主要特征是脂肪组织的扩张与慢性低度全身炎症,将会导致异位脂肪细胞在骨髓腔中积聚,可能会损害骨再生并导致 OP[3]。本文通过总结分析近些年这方面的相关研究报道,就肥胖症与骨质疏松症之间的相关性展开综述,以期拓展临床防治思路。

1 肥胖与骨质疏松的流行病学关系

骨质的丢失是老年人发生骨折的主要危险因素,据估计全世界 OP 的患病人数超过 2 亿,在美国和欧洲,30%的绝经后妇女受到这种疾病的影响[4]。虽然 OP 发生于两性,但它是女性的一种普遍疾病,通常发生在绝经后。有报道显示截至 2016 年 BMI 超重成人约有 19 亿,其中超过 6.5 亿人肥胖,约占全球人口的 13%[5]。BMI 是一种用于根据体重和身高对个体进行分类的测量方法。婴儿期、儿童期

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和青少年期的 BMI 越高，成人期的骨量就越大[6]。对于 OP 和骨折风险是否随体重的变化还没有达成共识，但已有研究表明，老年人低 BMI（<18.5 kg/m^2）与骨折和 OP 的风险增加密切相关[7]。早期研究表明，与 BMI 正常或低的人相比超重和肥胖的个体骨折风险略有降低。然而，最近的研究表明，高 BMI 与脂肪因子释放和代谢改变有关。

2 肥胖使促炎细胞因子升高进而增加骨吸收

脂肪组织在肥胖中起着重要作用，通过释放大量脂肪因子而调节脂肪质量和营养平衡[8]。肥胖患者脂肪因子的异常生成和某些促炎性信号通路的激活可诱导各种炎症加速发生，有研究证实，在肥胖小鼠脂肪组织中，促炎细胞因子肿瘤坏死因子 α（TNF-α）的表达升高，这一开创性的发现为肥胖和炎症之间的联系提供了有力证据[9]。此后，瘦素（leptin，一种主要由脂肪细胞分泌的小多肽激素）的发现，进一步证明了脂肪不仅仅是一个储能器官，也是一个活跃的内分泌组织[10]。脂肪组织还会产生其他促炎因子，包括白介素 6（IL-6）和 C 反应蛋白（CRP）[11]，已有研究经证实，促炎性细胞因子的增加在肥胖相关健康障碍的发展和进展中发挥了极大的作用。

骨是一个动态器官，持续不断地进行着转换，这个过程称为重塑，涉及破骨细胞对骨的吸收和成骨细胞的骨形成[12]。因此，在任何特定时间的骨量反映了骨形成和吸收之间的平衡。在细胞水平上，随着年龄的增长成骨细胞数量和活性降低，而破骨细胞数量和活性增加[13]。现在已经证实，成骨细胞通过表达受体激活剂来调节破骨细胞的募集和活性。RANKL 表达于成骨细胞表面，并与造血前体细胞表面的 RANK 受体结合，在巨噬细胞集落刺激因子（M-CSF）存在下刺激破骨细胞分化和成熟。骨保护素（OPG）是成骨细胞分泌的一种诱饵受体，与 RANKL 结合以阻止 RANK 的激活，从而阻止破骨细胞的分化和活化[14]。研究表明，绝经后妇女破骨细胞活性的增加和骨吸收的增加与 RANKL 的上调呈正相关[15]。促炎因子包括 TNF-α、IL-1 和 IL-6 是破骨细胞分化和骨吸收过程中的关键介质。有研究表明，上调的促炎性细胞因子是骨质疏松症或骨质疏松症的主要介质。更年期骨丢失加速也与促炎细胞因子（包括 TNF-α、IL-1 和 IL-6）的生成有关[16]，这些促炎细胞因子能够通过调节 RANKL/RANK/OPG 途径刺激破骨细胞活性。

3 脂肪组织和骨髓脂肪在骨代谢中的作用

肥胖通常与内脏脂肪的增加有关，同时也会增加骨髓脂肪[17]。有研究表明，脂肪组织可能对骨骼产生有益的影响，而另一些研究则表明，过多的脂肪团可能无法保护骨质疏松症，从而导致骨折[18]。成骨细胞和脂肪细胞具有相同的干细胞前体，而脂肪细胞的增加将以成骨细胞数量为代价。与 Runt 相关的转录因子（Runx2）被认为是成骨细胞分化的关键，Runx2 的过度表达抑制成骨细胞的成熟，导致骨质减少和多发性骨折[19]。此外，过氧化物酶体增殖物激活受体（PPARg2）是脂肪细胞分化的重要因素，它可以通过 Runx2 还原抑制成骨细胞分化[20]。

骨髓脂肪和骨组织表现出一种尚未完全理解的复杂关系。研究表明，这些脂肪细胞可能在骨质疏松症的发病机制中发挥作用[21]，骨髓脂肪的数量与 BMD 呈反比。值得注意的是，另一个与肥胖和 OP 相关的机制是干扰骨骼发育的脂肪因子分泌。其中，脂联素被描述为抗炎药，对肥胖患者的胰岛素敏感性有好处[22]。在一些研究中发现，这种脂肪因子与人类的骨密度呈反比[23]。

4 肥胖对骨代谢的影响

机械负荷通过 Wnt/b-catenin 信号通路减少凋亡和增加成骨细胞和骨细胞的增殖和分化来刺激骨形成[24]。因此，由体重引起的机械负荷是一个假设的一部分，这使得人们普遍相信肥胖可以防止骨质疏松和骨质疏松[25]。

但有报道显示，过多的脂肪量可能不会保护人类免受骨质疏松症的侵袭，相反，脂肪量的过度增加与低总骨密度和总骨矿物质含量有关[26]。在一项对 60 名 10～19 岁女性的横断面研究中发现，体脂百分比与未达到最佳峰值骨量有关[27]。肥胖增加也可能与骨折风险增加有关。例如，在一项对 100 例骨折患者和 100 名年龄 3～19 岁的无骨折对照受试者的病例对照研究中，高肥胖与前臂远端骨折的风险增加相关[28]。在瘦素缺乏（ob/ob）小鼠肥胖模型中，小鼠体重是瘦鼠的两倍，但股骨骨密度、皮质厚度和骨小梁体积较低[29]。显然，增加体重的机械负荷的积极作用不能克服瘦素缺乏（或可能是肥胖）对这些小鼠骨骼的不利影响。虽然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，但对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，一般来说，包括过量摄入其他营养物质，如蛋白质和矿物质，已知会影响骨代谢[30]。肥胖对人体骨骼健康影响的研究结果是基于统计相关性或建模而不是对照试验。因此，用肥胖动物模型进行对照研究将有助于剖析过量脂肪积累对骨代谢的影响机制。

使用饮食诱导的肥胖小鼠模型，有实验证明给小鼠喂高脂肪饮食（45%的能量作为脂肪）14周后，尽管在培养的BMSC中体重和骨形成标志物显著增加，但仍降低了胫骨近端的小梁骨体积和骨小梁数量[31]。有报道表明饮食诱导肥胖小鼠骨髓源性巨噬细胞增加破骨细胞活性和降低IL-10（一种抗炎细胞因子）的表达[32]。高脂诱导的肥胖动物表现出骨髓脂肪增加，同时不同骨骼部位的骨密度降低，过氧化物酶体增殖物激活受体g、组织蛋白酶k、IL-6和TNF-α上调[33]。

有文献表明肥胖可能减少骨形成（成骨细胞生成），同时增加脂肪生成，因为脂肪细胞和成骨细胞来源于一个共同的多潜能间充质干细胞[34]。肥胖可直接或间接通过脂肪细胞衍生的细胞因子如瘦素和脂联素影响骨代谢。脂肪细胞分泌瘦素的增加［和（或）脂联素的减少］也可能通过模拟巨噬细胞向脂肪组织的转运和促进巨噬细胞与内皮细胞的粘附来促进巨噬细胞的聚集[35]。以往人们普遍认为体重或BMI与骨密度或骨量呈正相关，低体重或BMI是人类低骨量和骨丢失增加的危险因素[36]。然而，在肥胖动物模型中已证实体重的积极影响不能完全抵消肥胖对骨骼的有害影响。

综上所述，肥胖患者的骨量减少可能是由于以成骨细胞生成为代价的骨髓脂肪生成增加，或由于促炎性细胞因子的分泌上调，或瘦素分泌过多，或脂联素生成减少，或与高脂肪相关的钙吸收而增加破骨细胞生成摄入。了解肥胖与骨代谢之间的相关性可有助于识别新的分子靶点，这些分子靶点可以增加成骨细胞的生成，同时抑制脂肪生成和减少破骨细胞生成。最终这些相关性知识将有助于开发新的治疗干预措施来预防肥胖对骨质疏松症的影响。

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