Published online www. wanfangdate. com. cn doi:10. 3969/j. issn. 1006-7108. 2012. 07. 000

·综述·

原发性骨质疏松症的病因学研究进展

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中图分类号：R68 **文献标识码**：A **文章编号**：1006-7108(2012)07-0675-06

摘要：原发性骨质疏松症严重影响老年人的健康和生活质量。近年国内外学者对原发性骨质疏松症展开了大量的研究，发现其发病原因与内分泌因素、营养状况、遗传因素、物理因素、免疫因素以及生活方式等均有相关性，但具体病因还未能明确。本文通过对近 10 年来中外相关文献的查阅，将原发性骨质疏松症的病因学研究现状与进展进行了综述，为原发性骨质疏松症的病因研究与防治提供理论参考。

关键词：骨质疏松症；原发性；病因学；研究进展

Research progress in etiology of primary osteoporosis *WANG Fang, ZHOU Dewei, WU Jigong, et al.*

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Abstract: Primary osteoporosis seriously affects living quality of the elderly. In recent years, national and international scholars have conducted extensive research on primary osteoporosis. It has been found that the etiology of primary osteoporosis is associated to endocrine factors, nutritional status, genetic factors, physical factors, immune factors, and life style. However, the specific cause is not clear. By means of reviewing literatures of the late decade, this paper summarizes the current situation and development of the research in etiology of primary osteoporosis, which can provide theoretical references for etiology research, prevention and treatment of primary osteoporosis.

Key words: Osteoporosis; Primary; Etiology; Research progress

据联合国预测，到 2020 年，中国 65 岁以上老龄人口将达到 1. 67 亿。随着老龄化的加速，因骨质疏松症(osteoporosis, OP)所致的骨折呈显著上升趋势[1]，OP 成为骨科的研究热点。骨质疏松症是一种以单位骨量减少和组织细微结构退变为特征，并导致骨脆性增加、骨强度降低，易于骨折的全身代谢性疾病，其特点是骨矿物质和骨基质呈等比例减少[2]。WHO 根据骨密度(Bone mineral density, BMD)或者骨矿含量(bone mineral content, BMC)值对骨质疏松症进行分级，规定正常健康成年人的 BMD/BMC 值降低 2. 5 标准差(SD)以上为骨质疏松症[3]。

基于目前的认识，骨质疏松症从病因学上可简单地分为原发性、继发性、特发性骨质疏松症三大类。原发性骨质疏松(primary osteoporosis, POP)是随着年龄增长必然发生的一种生理退行性病变，可分为绝经后骨质疏松症(Ⅰ型)和老年性骨质疏松症(Ⅱ型)。绝经后骨质疏松症(Postmenopausal osteoporosis, PMOP)是指妇女绝经后雌激素迅速减少，骨吸收大于形成，骨量丢失加快，形成高转换型的 OP。老年性骨质疏松症(senile osteoporosis, SOP)是指随着年龄增加，人体单位体积骨量低于正常，骨小梁间隙增大，骨基质减少、骨强度降低。OP 的发生与内分泌因素、营养状况、遗传因素、物理因素、免疫因素以及生活方式等因素有关。

1 内分泌因素

内分泌在骨代谢中发挥着重要的作用，骨吸收和形成的过程受多种激素的调节。OP 的发生与女性雌激素缺乏、男性睾酮水平下降以及甲状旁腺激素、降钙素、1,25-(OH)$_2$D$_3$等激素水平的变化有关。

1. 1 雌激素(estrogen)

绝经后妇女卵巢功能衰退、雌激素水平显著下

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降,骨吸收明显增强,骨丢失加快,绝经后妇女最初 3 年内腰椎松质骨的骨量平均每年下降 2.6%[4]。Fitzpatrick 等[5]总结了雌激素缺乏导致骨质丢失的原因:(1)雌激素缺乏使甲状腺 C 细胞对钙离子的敏感性下降,从而减少降钙素的分泌;(2)雌激素缺乏使肾 1,25-$(OH)_2D_3$合成发生障碍,从而使肠钙的吸收减少;(3)雌激素缺乏可直接减少肠钙的吸收;(4)雌激素不足时,破骨细胞对甲状旁腺素(PTM)的敏感性增加,骨吸收增强;(5)雌激素缺乏直接增强骨吸收、抑制骨形成。

雌激素对骨代谢的调节机制有两条途径:(1)细胞途径:成骨和破骨细胞上均发现了雌激素受体(ER),雌激素作用于 ER 引起破骨细胞前体细胞及破骨细胞凋亡,而对成骨细胞主要呈现抗凋亡作用。Hayashi 等[6]对 62 例绝经后老人随机分组对照研究,发现使用雌激素替代治疗组比对照组的 BMD 明显提高。(2)细胞因子途径:Inada 等[7]发现雌激素能上调胰岛素生长因子(IGF)、骨形成蛋白(BMP)、转化生长因子(TGF),下调白细胞介素(IL-1、IL-6)、肿瘤坏死因子(TNF),从而抑制成骨细胞凋亡,发挥抗骨质疏松作用,绝经后雌激素缺乏则加快骨髓基质细胞向破骨细胞的诱导分化,骨吸收因子(IL-1、IL-6 等)分泌增多,促进破骨细胞骨吸收功能,使骨转换率增加,导致骨质疏松。

1.2 雄激素(androgen)

雄激素是由睾丸和肾上腺分泌的 C-19 类固醇,主要为睾酮(T),在 20~30 岁达到最高峰。随着年龄增长,男性体内睾酮分泌水平逐渐下降,80 岁以上男性中约 30% 存在雄激素缺乏,雄激素不足会导致骨吸收大于骨形成,出现 OP[8]。Allan 等[9]发现雄激素主要通过直接和间接两种方式发挥作用:直接作用于雄激素受体;或者在芳香化酶作用下转化为雌激素,间接作用于雌激素受体(ER)。雄激素作用于骨细胞内的雄激素受体可以增加 TGF-β、IGF-I 和 IL-6 分泌量来发挥抗骨吸收作用[10],老年男性中 BMD 的下降常伴随着睾酮和 IGF-I 血浓度的下降[11]。王颖等[12]对 192 例老年男性研究有同样的发现:血清雌二醇(E_2)、游离睾酮(FT)水平与老年男性 BMD 呈正相关。

1.3 甲状旁腺素(Parathyroid hormone, PTH)

PTH 是维持体内血钙浓度正常的最重要的激素,它对血钙浓度的敏感性高于 1,25-$(OH)_2D_3$和降钙素。Amizuka 等[13]指出 PTH 小剂量可刺激成骨细胞形成新骨,大剂量则抑制成骨细胞,并且使大单核细胞转化为破骨细胞,从而增加骨质的吸收。Sigurdsson 等[14]研究发现 PTH 水平与全身 BMD 呈负相关($R = 2.2\%$, $p = 0.04$)。多种因素可以引起 PTH 分泌增多:(1)雌激素缺乏可导致 1,25-$(OH)_2D_3$合成障碍,肠钙吸收减少,继发甲状旁腺功能亢进,PTH 分泌增加,骨吸收作用增强[15]。(2)老年人存在肾功能生理性减退,表现为 1,25-$(OH)_2D_3$生成减少,血钙降低,进而刺激 PTH 分泌。Mazzaglia 等[16]报道血中 PTH 浓度常随年龄增加而增加,增加幅度可达 30% 甚至更高。

1.4 降钙素(calcitonin, CT)

CT 也是一种重要的钙调节激素,它可以维持骨代谢的稳定性并能预防过度骨吸收。Kallio 等[17]报道 CT 可以使破骨细胞绒毛的减少、缩短、变性,可以看出其对破骨细胞有直接的抑制作用。CT 对成骨细胞亦有直接影响,它可增加大鼠和兔子皮质骨的生长,促进体外培养成骨细胞增殖,使成骨细胞数量上升[18]。张宣东等[19]研究绝经后女性激素水平,发现女性 CT 的基础分泌即低于男性,绝经后雌激素迅速减少,甲状腺 C 细胞合成 CT 的活性下降,对钙的反应性也降低,导致骨量丢失。

1.5 维生素 D(vitamin D)

vitamin D 在体内的生物作用形式为 1,25-$(OH)_2D_3$,有 3 个主要作用:(1)促进小肠对食物中钙磷的吸收,使血钙浓度维持正常,为骨骼形成提供原料;(2)促进骨骼中钙盐的形成,让血钙转移到骨骼中,为新骨的形成提供条件;(3)促进肾对钙磷的重吸收,减少钙磷从尿中排出。老年人存在肾功能生理性减退,绝经后妇女雌激素缺乏影响 1a 羟化酶的活性,两者均表现为 1,25-$(OH)_2D_3$生成减少,钙吸收和骨形成减少[20]。朱国英等[21]对上海市 723 例绝经后妇女调查发现:血清 1,25-$(OH)_2D_3$含量与腰椎 BMD 值呈高度正相关($r = 0.693$, $P < 0.01$),绝经后妇女的血清 1,25-$(OH)_2D_3$和 25-$(OH)D_3$含量均明显低于非绝经妇女,表现为高骨转换型 OP。

2 营养状况

矿物盐的摄取对骨量的积累和维持有重要的影响,其中保证钙、磷的摄人尤为重要。血钙主要受甲状旁腺素(PTH)、降钙素(CT)和 1,25-$(OH)_2D_3$的调节,PTH 分泌增加可促进钙从骨中游离入血,使血钙升高。而 CT 则抑制破骨细胞的活性,减少骨钙的释放,使血钙下降。如果饮食中钙摄入量不足、肠钙吸收减少,将导致 PTH 分泌增多、骨钙释放增

加、骨量丢失[22]。Key 等[23]对 26749 例女性进行钙和骨折 5 年前瞻性研究发现,女性低钙饮食(< 525 mg/日)增加了骨折风险(相对风险度 RR = 1.75)。中老年人每天钙的摄入量应维持在 1000 ~ 1500 mg[24],当然,在补钙的同时也应补充一定量的磷,因为磷也是构成骨骼不可缺少的元素,Ito 等[25]对 441 例女性研究发现:钙磷摄入比例对桡骨远端骨密度有明显影响,当血磷过低时骨吸收活跃,骨密度下降。

vitamin D 能促进钙、磷的吸收和骨骼的钙化,维持骨骼和牙齿的正常生长。中老年人日光照射减少,皮肤对前体物质活化能力、肾和肝脏羟基化 vitamin D 的能力、饮食量及吸收能力等均下降而导致 vitamin D 水平降低。Jackson 等[26]对 36282 例 50 岁以上的绝经后妇女长达 7 年的研究表明,每天额外补充 25-(OH)D_3 400 IU 同时补钙 1000 mg/d 能有效提高 BMD,降低骨折风险。Cranney 等[27]也发现老年人每天额外补充 25-(OH)D_3 ≥ 700 IU 并同时补钙(500 ~ 1200 mg/d)能有效防止腰椎和股骨颈的骨量丢失。

蛋白质、氨基酸是提供骨骼有机基质合成的重要原料,如摄人不足会影响骨基质的合成[28]。然而,Surdykowski 等[29]研究中发现蛋白质摄入过高时尿酸排泄增加,使钙的储存减少,对钙平衡起负面作用,特别是在低钙摄入时,肠钙吸收的增加不足以弥补其所致的强制性钙丢失量,从而增加 OP 的发生率,Surdykowski 建议保持适量的蛋白质摄人(每天 0.8 g/kg)。此外,日常生活饮食中其它一些元素如镁、氟及锌等摄入不足亦会对骨量的维持产生不良的影响。

3 遗传学因素

OP 发生与性别、地域、种族和家族因素等相关。近年来对 OP 易感基因的关联分析主要在以下方面:(1)调节钙平衡的激素及其受体;(2)细胞因子、生长因子及其受体;(3)骨基质;(4)性激素及其受体;(5)其他方面。其中最受瞩目的是维生素 D 受体(VDR)基因、雌激素受体(ER)基因以及 I 型胶原蛋白(CoLlA1)基因等。

3.1 VDR 基因

VDR 基因是 OP 重要的候选基因。VDR 基因编码 VDR 蛋白,该基因位于 12q13.14 染色体,包含 11 个外显子,现已发现 VDR 基因有 4 个多态位点,即 Bsml、Tagl、Apal 和 Fokl[30]。维生素 D 与维生素 D 受体结合,进而调节钙转运、维持钙稳态和调节骨吸收。Morrison 等[31]对澳大利亚孪生子进行研究,发现同卵双胎(MZ)比异卵双胎(DZ)的 BMD 值更接近,Morrison 认为决定 BMD 的遗传因素中,VDR 基因中的等位基因占 75% 左右,可通过 VDR 基因多态性预测 BMD。Zambrano-Morales 等[32]对土耳其 144 例绝经后女性进行研究,发现 BsmI, TaqI and ApaI 三个位点的多态性与骨质疏松有相关性(RR = 5.6),但对此还有争议,Uitterlinden 等[33]对 26242 例进行 meta 分析,结果发现 Bsml、Tagl、Apal 和 Fokl 与 BMD 及骨折的发生率没有相关性。

3.2 ER 基因

绝经后妇女罹患 OP 的主要原因是雌激素的缺乏,但个体之间 BMD 降低程度不同,这种不同反应与 ER 基因多态性有关。Nam 等[34]研究位于 ER 基因起始内含子区的 PVull、Xbal 多态性与绝经后妇女 BMD 之间的关系发现:Pp 基因型者股骨颈、Ward 三角 BMD 值均明显高于 pp 型,pp 型基因者比其他型更容易骨折(P = 0.05)。同样,Gómez 等[35]对墨西哥 670 例绝经后女性研究,发现 ER 基因标记物 G2014A 与 OP 有明显关联。

3.3 I 型胶原蛋白(CoLlA)基因

在成骨生长与骨骼发育中,作为骨胶原构成主要成分的 CoLIA 发挥重要的作用。I 型胶原由 2 条 a1 链和 1 条 a2 链组成,a1 和 a2 分别由 CoLIA1 和 CoLIA2 基因编码,现已证实 CoLIA1 基因突变可致低骨量、骨脆性增加。Grant 等[36]发现位于 CoLIA1 基因 Spl 结合部位的 G-T 多态性与 BMD 变化相关,该多态性是 G→T 突变所致,具 G/G 基因型妇女腰椎 BMD 值明显高于 G/T 及 T/T 基因型。携带 T 等位基因者发生骨折相对危险度为 2.97,显著高于 G/G 基因者。Yazdanpanah 等[37]对 6280 例白种人对比研究有相似的发现,纯合子 TT 基因者股骨颈 BMD 比正常人群低 3.8%(P = 0.03),椎体骨折风险增加 2.3 倍。然而,Hu 等[38]对 1252 例绝经后女性进行 SNP-单核苷酸多态性分析得出不同的结论,即 COL1A1 和 COL1A2 基因多态性与骨折发生率没有关联。

4 物理因素

骨骼发育程度及骨量的大小与运动密切相关,运动负荷可以使松质骨骨量增加,如果运动负荷停止则增加的骨量可以再度丢失。宇航员由于长期失重 MBD 减低,说明了骨量大小与其所受到的机械负

荷有关,Lang 等[39]报道,在 4 ~ 6 月的空间飞行中,脊柱骨 BMD 以每月 0.9% 的速度减少。因为机械应力对成骨细胞的活性是一种重要的刺激,废用时成骨细胞活性减弱,破骨细胞活性则相对增强。Englund 等[40]对 48 例 66 ~ 87 岁的女性在进行每周 2 次,每次 50 min 的负重、有氧、协调性的综合锻炼 1 年后,训练组 Ward 三角区的 BMD 比对照组有明显的提高(8.4%, $P < 0.01$)。Prior 和 Borer 等[41-42]提倡中等程度的运动强度,在最大运动限度 70% ~ 80% 能对 BMD 起保持作用,每周 2 ~ 3 次,每次 15 ~ 60 min 足够强度的运动足以对 BMD 产生影响,而强度比较低的运动方式(如散步)、过量的运动(如长跑)和不连续的运动不利于骨量维持。

5 免疫因素

免疫系统与骨骼代谢密切相关,目前认为其主要机制是通过有关的体液因子如白细胞介素(IL)、干扰素(IFN)、C-反应蛋白(CRP)等影响破骨和成骨细胞的数量和活性发挥作用。Wei 等[43]研究发现 T 细胞产生的细胞因子 TNF、IL-1 可通过促进骨髓基质细胞 NF-KB 配体的受体或激活因子(RANKL)的形成促进破骨细胞的分化增殖,抑制破骨细胞的凋亡。Ganesan 等[44]研究发现 65 岁以上的老年女性 BMD 降低与高 CRP 水平相关($P < 0.001$)。关于体液因子在上述内分泌因素中大量谈到,此处不再赘述。

6 其他因素

生活方式和习惯比如吸烟、饮酒、节食、美白等也与 OP 有相关性。Gao 等[45]研究发现小鼠被动吸烟 4 个月后骨碱性磷酸酶(ALP)显著性下降、抗酒石酸酸性磷酸酶 5b(TRACP 5b)显著性升高、腰椎和股骨 BMD 显著性下降,说明吸烟抑制骨形成、促进骨吸收。Tamaki 等[46]对 1576 例老年男性的调查研究也表明,吸烟男性的腰椎骨量丢失比非吸烟者大($P < 0.05$),随着吸烟年限增加,腰椎及髋部 BMD 呈下降趋势。摄入酒精量与骨质疏松和高骨折风险之间也有明显关联。Ganry 等[47]通过对 7598 例非卧床老年女性研究发现:每天摄入酒精 11 ~ 29 g 的饮酒者股骨大转子 BMD 比不饮酒者显著增高;每天摄入酒精 > 30 g 者全身骨 BMD 较不饮酒者显著降低;每天摄入酒精 < 10 g 者股骨大转子 BMD 无明显变化。同样,Tucker 等[48]也证实适量饮酒可减少骨量的丢失,而过量饮酒增加骨量的丢失。雌激素一部分是由脂肪组织中的激素-雄甾烯二酮合成,过于节食的女性雌激素水平的相对不足,骨质疏松也就在不知不觉中产生。此外,如果为了美白而减少日照,也使得通过阳光照射合成的维生素 D3 减少,最终使骨形成减少。

7 总结

综上所述,原发性骨质疏松症(POP)是多种病因综合作用的结果,其中遗传因素是先天因素,随着年龄增大,体内内分泌及免疫状况发生的不良改变,运动减少、不良的饮食和生活方式是后天因素,两者都与 POP 的发生相关。虽然先天因素难以改变,但是后天因素的作用不容低估,所以推广健康的生活方式、适当的体育锻炼和合理的膳食习惯就显得非常重要。总之,POP 的病因还未明确,对于 POP 病因的研究将有利于促进新药的研发和临床疗效的提高。

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(收稿日期:2011-11-08)

原发性骨质疏松症的病因学研究进展

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刊名： 中国骨质疏松杂志 ISTIC
英文刊名： CHINESE JOURNAL OF OSTEOPOROSIS
年，卷(期)： 2012,18(7)

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