

青春期骨密度变化研究进展

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摘要: 骨密度是反映骨营养状况的重要指标。儿童骨密度随年龄逐渐增加, 青春期骨密度累积大幅度提速, 是影响峰值骨量最敏感的时期。性激素促进骨形成与骨密度获得, 生长激素和胰岛素样生长因子-1 分泌峰值提升骨密度累积。性早熟儿童青春期发育提前, 青春期时长多有缩短, 带来骨量累积的改变, 促性腺激素释放激素类似物(GnRHa)治疗性早熟的同时影响骨代谢。儿童 25-(OH)D₃ 水平随年龄变化呈“U 形曲线”, 且青春期最低。青春期骨量等体成分改变对骨健康、乃至成年体质产生长远影响。

关键词: 青春期; 骨密度; 性早熟

中图分类号: R725 **文献标识码:** A **文章编号:** 1008-6579(2024)01-0049-05 **doi:** 10.11852/zgetbjzz2023-0084

Research advance in the changes of bone mineral density during puberty

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Abstract: Bone mineral density is an important indicator of bone nutrition. The bone mineral density of children gradually increases with age, and the accumulation of bone mineral density in adolescence increases significantly, which is the most sensitive period to affect the peak bone mass. Sex hormone promotes bone formation and bone mineral density acquisition, and the peak secretion of growth hormone and insulin-like growth factor-1 increases bone mineral density accumulation. Children with precocious puberty develop earlier, and the length of puberty is shortened, resulting in changes in bone mass accumulation. GnRHa (gonadotrophin releasing hormone analogue) treatment of precocious puberty also affects bone metabolism. The level of 25-(OH)D₃ in children varies with age in a U-shaped curve, which is the lowest in adolescence. Changes in body composition such as bone mass in adolescence have a long-term impact on bone health and even adult physique.

Keywords: puberty; bone mineral density; precocious puberty

骨密度(bone mineral density, BMD)是指单位体积内骨矿物质的含量, 敏感特异地反映骨营养状况, 是评估骨发育状态的重要指标。青春期 BMD 获得对成年骨强度维持、减少骨质疏松症发生风险至关重要^[1]。本文就青春期儿童骨密度变化特点、骨密度影响因素进行综述。

1 青春期骨密度变化的特点

儿童期骨量累积与身高增长趋势一致。儿童身高呈线性生长, 青春期前身高增长 5~7cm/年; 青春期线性生长加速, 出现第二生长高峰, 可达 7~12cm/年, 整个青春期女性身高增加 20~25cm, 男性增加 25~30cm, 至青春期末期, 身高达到成年终身高的 95%左右^[2]。儿童青春前期骨量稳定增长, 累积约 30%的峰值骨量。青春期身高增长加速同

时, 骨量累积大幅度提速, 累积约 50%的峰值骨量, 至青春期末, 骨量累积达峰值骨量的 90%^[3]。我国一项覆盖 7 地区纳入 10 818 名 3~18 岁儿童的 BMD 调查显示, 3 岁男/女童 BMD 为 0.385~0.395g/cm², 3 岁至青春期前 BMD 无性别差异; 女性在 9 岁、男性在 11 岁性腺轴开始启动, 青春期 BMD 累积提速, 11~13 岁女性 BMD 高于男性, 14 岁后女性 BMD 低于男性, 18 岁时女性 BMD 达 0.850g/cm²、男性则达到 0.949g/cm²^[4], 青春期女性 BMD 累积提速早于男性, 但男性 BMD 青春期末高于女性。儿童 BMD 累积增速与青春期启动及进程密切相关。

2 青春期生理变化对骨密度的影响

2.1 青春期内分泌升高促进骨形成与骨密度获得

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青春期性激素升高,性激素对长骨生长、峰值骨量获得和 BMD 维持起重要作用。性激素受体广泛存在于骨组织,青春期升高的性激素与受体结合,促进骨形成、抑制骨吸收,并加速 BMD 累积,在骨骼生长、峰值骨量的获得和骨量维持中起重要作用。雌激素和雄激素作用其受体,直接调控骨基质蛋白、骨钙素、骨碱性磷酸酶等表达,促进成骨细胞增值与分化;间接调控 Wnt/ β -catenin、PI3K/Akt 及 ERK-MAPK、RANKL/OPG、Fas/FasL 等多个信号通路,抑制成骨细胞凋亡和破骨细胞的增殖与活性^[5-8]。青春期早期,较低浓度性激素通过增加生长激素/胰岛素样生长因子-1(growth hormone/insulin-like growth factor-1, GH/IGF-1)水平来刺激骨骼生长;青春期后期,女性较高的雌激素浓度刺激骨骺生长板闭合从而阻止长骨生长^[9]。雌激素主要促进骨内膜骨形成,与骨内膜周长呈负相关。雄激素增加小梁骨厚度和骨膜宽度,增加皮质骨大小和厚度,雄激素也可通过促进肌肉重量间接对骨骼更好的支持和刺激,最终男性比女性长骨更长、骨宽更大、强度更高^[10]。雄激素增加体内骨形成的作用更强。骨量丢失和骨密度降低与雌激素的关系更密切,雌激素不足则骨吸收增强。在骨形成和骨量的维持上雌激素和雄激素均有重要作用,而在骨骺闭合和骨吸收的调控上雌激素可能占优势。

2.2 青春期体成分改变对骨密度的影响 人体成分包括骨骼、肌肉、脂肪,随着年龄增长,人体成分发生改变,青春期变化显著,性别差异显现。青春期早期女性肌肉百分比约为 80%,成熟期下降到 75%;男性青春期早期肌肉百分比 80%~85%,成熟期增加到 90%^[11]。肌肉通过重力增加骨的承载负荷,骨骼肌收缩增加骨的机械负荷,刺激骨强度增大和 BMD 累积^[12]。女性脂肪比例从青春期早期的 13%增加到成熟期的 23%,男性则由早期的 11%下降至成熟期的 9%^[13]。脂肪对 BMD 的影响目前结论不一致。Rokoff 等^[14-15]调查表明脂肪通过重力增加骨的承载负荷,对 BMD 有积极作用。然而 Liu 等^[16-17]调查排除体重混杂因素,发现脂肪和 BMD 之间可能负相关或无相关。过量脂肪引起瘦素水平升高,抑制下丘脑 5-羟色胺合成,调节交感神经系统抑制成骨细胞分化、促进破骨细胞增值^[18]。过多的脂肪组织分泌白细胞介素(interleukin, IL)-1、IL-6、重组人转化生长因子(transforming growth factor- α , TGF- α)等炎症因子,通过调节 RANKL/RANK/OPG 通路,刺激破骨细胞活化,增加骨吸收,影响骨代谢^[19]。关于脂肪分布,Pollock 等^[20-21]认为中心

性肥胖损害 BMD,而有研究认为臀部脂肪是一个保护因素。青春期脂肪比例与分布改变对骨密度的影响鲜有报道。近年来,儿童肥胖率大幅度增长^[22],青春期体成分改变对骨健康、乃至成年体质产生的深远影响,需要重视。

2.3 青春期生长激素/胰岛素样生长因子-1 分泌峰值促进骨密度累积 GH 和 IGF-1 在骨骼生长中扮演重要角色。GH/IGF-1 参与骨形成和骨重建,增加成骨细胞的分化,支持矿化和骨形成,主要影响长骨,保护骨小梁的完整,维持 BMD^[23]。历时 10 年的前瞻性研究表明 GH 替代疗法对生长激素缺乏患者的 BMD 有持续积极的影响^[24]。过度表达 IGF-1 的转基因小鼠骨量增加,而 IGF-1 缺失的小鼠表现出骨形成减少、矿化减少和皮质骨减少。Yuan 等^[25]研究发现较高 IGF-1 水平可以减缓 BMD 丢失,降低骨折风险。IGF-1 高峰促进身高增长第二高峰出现。幼儿期 IGF-1 水平约 40ng/mL,逐步增长,女性 13~15 岁达高峰约 536ng/mL,男性 14~16 岁达峰值约 682ng/mL,青春期后随年龄下降,70 岁约 80~100ng/mL^[26-27]。青春期 GH 分泌峰值大幅提升、峰值持续时间延长、IGF-1 浓度升高与性激素激增密不可分。动物研究表明,雌激素和雄激素均能上调小鼠 IGF-1 通路基因水平表达,双氢睾酮和睾酮可以增加细胞生长和 IGF-1 表达^[28]。男性青春期 GH 峰值、IGF-1 水平高于女性。青春期 GH/IGF-1 水平升高与性激素水平增高相契合,对青春期儿童长骨快速生长和 BMD 累积产生积极作用。

2.4 青春期维生素 D 水平与骨密度 维生素 D 是一组具有生物活性的脂溶性类固醇激素,1,25-(OH)₂D₃ 是活性钙调节激素,较低浓度 1,25-(OH)₂D₃ 刺激成骨细胞,促进骨样组织成熟和钙盐沉积,高浓度 1,25-(OH)₂D₃ 增加成骨细胞的骨钙素合成,促进骨重吸收,释放旧骨钙盐入血^[29]。Zhang 等^[30]调查 0~6 岁儿童 25-(OH)D₃ 平均水平约为 65.4nmol/L。我国 6~18 岁儿童青少年的调查显示,25-(OH)D₃ 水平随年龄变化,6 岁约 51.6nmol/L,14 岁约 35.2nmol/L,后逐渐上升,18 岁约 44.3nmol/L,成年后逐渐达到稳态约 60nmol/L^[31]。德国和丹麦的调查也显示儿童 25-(OH)D₃ 水平随年龄变化呈“U 形曲线”,且青春期最低^[32]。根据中华儿科学会定义儿童血清 25-(OH)D₃ < 50nmol/L 为不足/缺乏的标准,Li 等^[33]调查显示我国儿童维生素 D 不足/缺乏率为 78.14%,青春期则高达 88.4%。青春期较低浓度维生素 D,与青春期骨快速生长与骨量累积增速相契合,因此青春期维生素 D 补充需注重“U

形曲线”年龄特点与骨快速增长的需求,过度或不恰当补充,不利于身高增长与骨代谢。

骨骼肌在储存、维持维生素 D 稳态中发挥重要作用^[34]。25-(OH)D₃与维生素 D 结合蛋白结合储存于肌肉细胞中,Abboud 等^[35]报道骨骼肌吸收 25-(OH)D₃的速度是成骨细胞的 2~3 倍,释放 25-(OH)D₃的速度是成骨细胞的 1/2。程虹等^[36]调查表明维生素 D 充足的儿童后期可能获得更高的肌肉量。脂肪同样是维生素 D 的储存场所。脂肪组织表达多种合成维生素 D 的酶,大量的脂肪抑制 25 羟化酶和 1 α 羟化酶的表达,限制维生素 D 羟化过程及发挥生物活性,过多的脂肪会蓄积维生素 D 导致血清 25-(OH)D₃水平降低,Abbas^[37]的研究证实全身脂肪指数和全身脂肪百分比与 25-(OH)D₃水平呈负相关。儿童内脏脂肪水平越高,维生素 D 水平越低,腹型肥胖儿童和体脂肪过多的儿童维生素 D 缺乏率高^[38]。儿童 25-(OH)D₃水平随年龄呈“U 形曲线”改变,青春期平均水平最低<50nmol/L,这可能是青春期骨建模和重塑增强,以及青春期脂肪和肌肉含量与分布变化,所产生的一种相对性不足、适应性改变。维生素 D 缺乏是否依据年龄有所区分值得思考。

3 中枢性性早熟儿童骨密度变化

中枢性性早熟(central precocious puberty, CPP)是下丘脑-垂体-性腺轴提前启动,青春期发育提前。CPP 儿童青春期前期时间缩短,青春期进程加速和时程变短,骨骼线性生长时间减少,骨量沉积周期和峰值骨量沉积时间不足,成年期 BMD 可能受到影响。CPP 儿童 BMD 的研究结果并不统一,4 项小样本研究表明 CPP 女童腰椎 BMD 高于正常儿童,但 van der Sluis 等^[39]研究提示 CPP 女童全身 BMD 与正常儿童无差异,Alessandri 等^[40]调查发现 CPP 儿童桡骨远端 1/3 处 BMD 高于正常同龄儿童。Elhakeem 等^[41]调查青春期发育延迟的女童(青春期前期时间延长、青春期进程与正常儿童一致),成年后 BMD 低于青春期发育正常儿童。目前尚无关于 CPP 女童成年后 BMD 报道。

促性腺激素释放激素类似物(gonadotropin releasing hormone analogue, GnRHa)是目前治疗 CPP 的主要药物,抑制促性腺激素的脉冲分泌,性激素水平下降,直接抑制骨成熟,导致骨矿物质沉积受限。Saggese 等^[42]发现 CPP 儿童经 GnRHa 治疗 12 个月 BMD 较治疗基线下降 8%。Boot 等^[40]观察到 CPP 儿童在诊断时腰椎 BMD 高出正常儿童 0.5s,

GnRHa 治疗 2 年逐渐下降至 0.11s。van der Sluis 等^[39]研究得出相同的结论,而按骨龄计算 BMD s 逐年追赶但仍低于平均值。由此可见 GnRHa 对 BMD 可产生负面影响。一些研究表明,虽然 BMD 在 GnRHa 治疗期间有所降低,但可以通过补钙来预防,并且停止 GnRHa 治疗 2 年后,骨密度基本恢复正常水平^[43-44]。

综上所述,青春期快速生长,骨骼建模和重塑增强。儿童性激素的升高,肌肉和脂肪含量与分布、IGF-1 水平、维生素 D 水平的改变,共同促进 BMD 的快速累积,对成年峰值骨量产生重要的积极影响。青春期提前、CPP 儿童 BMD 改变以及成年后骨健康均需多中心、大样本、前瞻性研究。

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- 收稿日期:2023-01-30 修回日期:2023-05-19 本文编辑:李少闻

(上接第 48 页)

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- 收稿日期:2023-04-16 修回日期:2023-08-15 本文编辑:李少闻