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·临床研究·

# 糖尿病骨质疏松的细胞及分子机制研究进展

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**摘要**:糖尿病患者骨质疏松的发生源于骨代谢状态改变,与胰岛素、胰岛素样生长因子-1(IGF-1)的作用有关。此外,高血糖毒性刺激细胞分泌肿瘤坏死因子 α(TNF-α)、巨噬细胞集落刺激因子(MCSF)、核因子 κB 受体活化因子配体(RANKL)、血管内皮生长因子-A(VEGF-A)等破骨源性细胞因子也发挥重要作用。

**关键词**:糖尿病;骨质疏松;机制

## Research progress of cellular and molecular mechanism of osteoporosis in patients with diabetes mellitus

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**Abstract**: Osteoporosis in patients with diabetes mellitus originates from the alteration in bone metabolism, which is regulated by insulin and insulin-like growth factor-1 (IGF-1). In addition, the osteoclastogenic mediators, which are secreted by the stimulation of hyperglycemia toxicity, including TNF-α, macrophage colony stimulating factor (MCSF), receptor activator of nuclear factor-κB ligand (RANKL), and vascular endothelial growth factor A (VEGF-A), also play an important role in the progress of osteoporosis.

**Key words**: Diabetes mellitus; Osteoporosis; Mechanism

骨质疏松症是以骨密度降低和骨组织微结构破坏为特征,导致骨脆性增加和易于骨折的代谢性骨病,是由于骨形成与骨吸收过程出现动态失衡引起。从分子水平看,骨吸收增加、骨质疏松的发生与调节破骨细胞分化和功能的受体活化核因子-κB(RANK)受体(RANKL)和一系列细胞因子生成过多有关。这些因子包括过氧化物酶 Cox-2、前列腺素(PG)E2、肿瘤坏死因子 α(TNF-α)、白介素(IL)-1、IL-6、IL-11 等[1]。

## 1 骨代谢的生理调节

生理状态下,成骨细胞(OB)可分泌介导骨破坏的关键调控因子-RANKL,后者与破骨细胞(OC)前体细胞膜上的受体结合,OB 同时分泌巨噬细胞集落刺激因子(MCSF),刺激 OC 前体增殖、分化为成熟的 OC[2,3]。RANKL 和 MCSF 的上调受各种致破骨性因子如甲状旁腺激素(PTH)、PTH 相关肽及催乳素的影响[4-6]。而 OB 能合成、分泌一种可溶性诱导受体——骨保护素(OPG),阻断 RANK-RANKL 之间的交互作用和骨破坏[7]。骨吸收发生后,OB 介导的骨形成启动,形成新的骨矿结构,填补骨吸收过程中形成的骨缺失。OB 分泌 1 型胶原纤维填充于有机结构中,并在碱性磷酸酶、骨钙素和骨磷素的共同作用下与钙和磷结合完成新生骨的矿物质化,形成羟磷灰石结晶体[$Ca_{10}(PO4)_6(OH)_2$][8]。多种体液因子,如胰岛素样生长因子-1(IGF-1)、胰岛素、骨形态源性蛋白、OPG 等,均能促进骨形成[5,9,10]。此外,胰岛素通过作用于人体成骨细胞样 MG-63 细

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胞,直接发挥促进细胞增殖分化、提高碱性磷酸酶活性、上调 1 型胶原表达、增进骨矿物质化等促成骨作用[11]。

## 2 糖尿病对骨量的影响

糖尿病(DM)不但能够导致各种大、微血管并发症,还能够加重甚至引起骨量减少和骨质疏松[12, 13]。高糖毒性、胰岛 B 细胞功能衰竭、胰岛素抵抗、IGF-1 水平低下、炎症反应以及其他内分泌激素代谢异常和细胞、免疫功能缺陷等都参与了这种病理生理改变[10-12, 14-17]。

## 3 糖尿病骨质疏松的发病机制

### 3.1 高血糖毒性作用

**3.1.1** 高血糖对 OB 功能的影响:最近一项体外研究[18]表明,高血糖一方面能够显著抑制成骨细胞样 MG-63 细胞的生长、骨矿化及表达多种 OB 相关标记物,如 runt-相关的转录因子-2(RunX-2)、1 型胶原蛋白、骨钙蛋白及骨粘连蛋白,降低 MG-63 对 PTH 和 1,25-(OH)-维生素 D3 的反应性;另一方面可以刺激脂源性因子的表达,如过氧化物酶增殖物活化受体-γ(PPAR-γ)、脂肪细胞脂肪酸结合蛋白(aP2)、抵抗素、脂肪酶等[19],造成骨髓由 OB 优势性到脂肪细胞优势性的转化,使体内分化成熟的 OB 数量减少,影响骨形成。最近一项动物实验表明,在 STZ-诱导的 1 型糖尿病小鼠模型中,活化的血浆纤溶酶原激活物抑制剂-1(PAI-1)也能抑制 OB 活性和骨矿化,提示 PAI-1 也参与了 1 型糖尿病骨质疏松的发病机制[20]。

**3.1.2** 高血糖对 OC 的影响:STZ-诱导的糖尿病大鼠体内 OC 数量以及破骨趋向性调节因子的表达均显著升高,例如 TNF-α[21]、巨噬细胞集落刺激因子(MCSF)、RANKL[22]、血管内皮生长因子-A(VEGF-A)[23]。PPAR-γ、aP2、抵抗素 mRNA 表达上调导致骨髓脂肪细胞数量增多,诱导骨髓脂肪聚集[24, 25]。

**3.1.3** 糖基化终末产物(AGEs)对骨代谢的影响:1 型和 2 型糖尿病小鼠的体内实验已证实 AGEs 增加与骨密度和骨强度呈负相关[26, 27]。AGEs 使骨胶原糖基化,阻碍生长因子对骨原始细胞的促分化作用,成骨作用受损;AGEs 与 OC 表面的非酶糖化终产物受体结合,产生过多的 IL-1、IL-6、TNF-α 等细胞因子,刺激 OC,使骨吸收陷窝的面积扩大和数目显著增多,破骨作用增强。

**3.1.4** 高血糖对血管内皮祖细胞(EPCs)的影响:STZ-诱导的糖尿病大鼠循环血液中骨髓源性 EPCs 数量较非糖尿病大鼠显著减少,高糖呈量效和时效地减少外周血 EPCs 数量并降低其增殖、迁移、黏附能力,延迟骨折部位的血管再生和修复[28]。

### 3.2 胰岛素作用不足

**3.2.1** 胰岛素对 OB 的影响:胰岛素与 OB 表面受体结合,促进 OB 合成核酸,分泌骨基质和合成骨钙素(BGP)。有学者观察 62 例 T1DM 患者发现,7 年胰岛素强化治疗使所有部位的骨密度(BMD)保持稳定,推测内源性胰岛素缺乏可能是 BMD 降低的原因。此外,胰岛素作用不足可使Ⅰ型胶原合成减少,OB 数目减少和作用减弱,BGP 合成减少,致骨基质成熟和转换下降,骨基质分解,骨矿物质丢失。研究显示人成骨样细胞Ⅰ型胶原 COL1mRNA 数量随胰岛素浓度的升高呈增加趋势。

**3.2.2** 胰岛素对维生素 D、肠道钙、磷代谢的影响:胰岛素可兴奋 25-羟化酶,协同 PTH 调节 1-α 羟化酶活性,刺激肾近曲小管合成 1,25-(OH)-$D_3$。胰岛素不足时会引起 1,25-(OH)-$D_3$ 减少,肠钙、磷吸收减少,尿钙排出增加,骨钙动员,骨量下降。

### 3.3 胰岛素抵抗(IR)

2 型糖尿病(T2DM)以 IR 或其受体缺陷为主要表现,导致 BMD 下降的可能机制是 IR 使肾脏对钙、磷、PTH 等分泌异常影响骨代谢。但多数 T2DM 患者既存在 IR,同时也合并 INS 分泌缺陷。病情早期以 IR 为主,而 OB 对 INS 敏感性无改变,故高 INS 血症促使成骨速度大于破骨速度,导致 BMD 升高[29]。Dennison 等对 909 名无糖尿病史的研究对象(59-71 岁)行糖耐量试验后发现,新诊断的 T2DM 患者前臂及股骨颈 BMD 增高,且 BMD 增高与 IR 呈正相关[30]。随着病情发展,INS 分泌缺陷加重,骨吸收速度大于骨形成速度,最终致 BMD 降低[31]。

### 3.4 胰岛素样生长因子(IGF)

IGF-1 是长骨生长的必需因子,它在骨的干骺端刺激软骨细胞增殖和分化,在皮质骨及松质骨形成过程中发挥作用,增加碱性磷酸酶活性以及 BGP 的产生。IGF-1 作用于 OB 的 IGF-1 受体,可如刺激细胞摄取氨基酸及合成胶原从而促进骨形成。IGF-1 作用于骨原细胞,刺激 DNA 合成,增加 OB 数目。IGF-1 缺乏上调葡萄糖转运载体-1(GLUT1)表达,导致高糖条件下 OB 矿化延迟[32]。IGF-1 也可调节骨吸收,通过抑制转录过程,减少间质中胶原酶 3m-RNA 表达,减少骨胶原降解[33]。因此,IGF-1 功能或受体缺陷可能与骨量减少及骨质疏松有密切关

系[5, 34, 35]。

### 3.5 其他内分泌激素

**3.5.1** 瘦素：DM 患者血清瘦素水平增高，瘦素可抑制胰岛素分泌，后者缺乏可致骨质疏松。其次，瘦素可与骨髓间充质细胞 hMS2-12 表达的瘦素受体结合，使其向骨细胞分化，同时抑制向脂肪细胞分化[36]。此外，由于瘦素-性激素-骨密度之间的负反馈机制，高瘦素可抑制绝经后女性类固醇（E2、T）的合成，雌激素水平降低，与 OB 结合及刺激产生 IGF-1 能力下降，对 IL-6 及 TNF 等骨吸收因子的抑制作用减弱。在老年男性骨质疏松组瘦素水平升高而雄激素及 BMD 明显下降，提示高瘦素水平可减弱人成骨样细胞增殖，PTH、IL-1 及 IL-6 等生成增加，BMD 降低[37]。

**3.5.2** 胰淀素：胰淀素亦称胰岛淀粉多样肽（IAPP），可激活蛋白激酶 C（PKC），而 PKC 的活化对于 OB 增殖有重要作用。IAPP 也可抑制 OC 在脊髓内的培养，阻止 OC 前体细胞融合为成熟的多核巨细胞，从而抑制骨吸收[38]。糖尿病患者 IAPP 水平下降对骨质疏松的发生具有促进作用[39]。

**3.5.3** 骨形成抑制糖蛋白（sclerostin）：Sclerostin 是成熟性骨细胞分泌的一种抑制骨形成的糖蛋白，在 2 型糖尿病患者中水平显著升高[40]。通过对绝经期女性 2 型糖尿病患者研究发现，sclerostin 可通过 WntWnt/β-catenin 信号传导途径抑制成骨作用[41]。

### 3.6 细胞因子

糖尿病骨质疏松患者血清 IL-6、EGF、TNF-α 水平升高[42]。IL-6 刺激 OC 前体细胞分裂增殖，形成骨吸收陷窝，增加胶原酶释放而加强骨基质降解[43]；TNF-α 可增加 OC 形成，增强 OC 活性，并刺激 IL-6、金属基质蛋白酶-1、2 的产生，抑制骨形成。细胞因子诱导 NO 浓度升高，增加 OC 活性，抑制 OB 生成及其功能，NO 还可通过环氧酶 C 旁路抑制 OB 碱性磷酸酶活性，并阻断前列腺素对 OB 作用，从而抑制 BGP 生成，使骨矿化受阻。表皮生长因子 EGF 能激活 OC，促进骨吸收，并能抑制 OB 功能。糖尿病患者转化生长因子（TGF-β）、IL-10 水平减低，而 TGF-β 可促进 OB 复原和增殖，抑制 OC 的破骨作用；IL-10 则能抑制 TNF-α、IL-1、IL-4 和 IL-6 等的生成，促进骨质疏松发生[44]。

### 3.7 免疫细胞

研究表明，未活化 T 淋巴细胞能通过产生粒-巨噬细胞生长因子和干扰素 γ 抑制 OC 生成[45]。DM 是一种慢性炎症状态，导致 T 淋巴细胞活化，分泌更多的 OC 分化因子，产生 TNF-α、IL-6 等细胞因子，通过细胞核因子 κB 受体活化因子配基/细胞核因子 κB 受体活化因子/护骨素细胞因子系统增加 OC 的生成和活性[46]。

### 3.8 神经与脂肪细胞的交互作用

糖尿病患者自主神经功能异常和瘦素功能缺陷也会间接导致骨量减少甚至骨质疏松。这可能与交感神经系统和瘦素通过交互作用调节骨重塑有关[47]。交感激活的最终结果依赖于成骨细胞中活化的肾上腺受体亚型的构成比[48]。β2 肾上腺素受体和瘦素受体基因同时敲除的大鼠较对照组大鼠骨量增加，提示 β2 肾上腺素受体激动剂和瘦素能够激活骨吸收。成骨细胞样 UMR106 细胞表达 RANKL 和 OPG 会因 β3 肾上腺素受体兴奋而降低，提示 β3 肾上腺素受体活化对骨吸收具有抑制作用[48]。

### 3.9 激肽功能失调

许多证据表明，糖尿病引起的骨量减少在一定程度上与调节血液循环、炎症和疼痛的因子—激肽有关。激肽功能失调与糖尿病心肌病、视网膜病变等多种并发症有关[49]。在 insulin-2 基因突变的糖尿病 Akita 大鼠中，敲除缓激肽受体-1（B1R）和 B2R 可导致大量蛋白尿、肾小球硬化、神经传导速度下降、骨量显著减少等多种并发症[50]。这说明 B1R/B2R 及其相关的激肽信号传导异常可能促发糖尿病性骨质疏松。

## 4 临床提示与展望

针对糖尿病性骨质疏松的发病机制，合理使用降糖药能够促进骨形成，抑制骨吸收，联合使用胰岛素治疗能够通过位于成骨细胞上的受体发挥积极作用[51]。在一项体外研究中，高糖状态下培养的骨髓间充质干细胞经胰岛素处理后碱性磷酸酶活性显著提高，提示成骨细胞分化活跃[52]。另一项体外实验发现，胰岛素联合 17β-雌二醇能够促进 1 型胶原生成和骨矿物质化[53]。

此外，某些降糖药物可以直接作用于 OB 或骨髓间充质干细胞、减少细胞调亡，发挥抗骨质疏松作用。二甲双胍能够促进 STZ 诱导的糖尿病小鼠成骨细胞分化，上调 Runx2 和骨钙素蛋白水平表达，提高碱性磷酸酶活性，促进 1 型胶原蛋白合成和骨钙沉积。在另一项体外实验中，格列美脲也能够刺激初级成骨细胞的增殖和分化。除了人工合成的药物，某些中草药制剂如桂皮提取物能够升高血浆脂

联素水平、上调 PPAR-α 和 PPAR-γ mRNA 表达,从而增加胰岛素分泌,可能具有减少骨髓脂肪堆积、间接促进骨形成的作用。与此相反,噻唑烷二酮类降糖药如罗格列酮在绝经期后妇女中应用应谨慎。因为该药能降低碱性磷酸酶、骨钙素合成,可能引起骨丢失和骨折[54, 55]。但具体的细胞和分子机制还需要进一步研究。某些血管扩张药物如己酮可可碱(pentoxifylline),也具有提高成骨细胞活性的作用,在治疗骨质疏松方面具有一定的发展前景[56]。

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# 糖尿病骨质疏松的细胞及分子机制研究进展



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