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·综述·

降糖药物与骨质疏松

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摘要: 糖尿病和骨质疏松之间关系的研究渐成热点,不同的降糖药物对糖尿病患者骨质疏松的发生发展影响不同,故需选择合适的降糖药物,同时良好的血糖控制也可以延缓骨质疏松的进展。

关键词: 糖尿病;骨质疏松;药物;血糖控制

Relationship between glucose-lowering drugs and osteoporosis

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Abstract: The research of the relationship between diabetes and osteoporosis has attracted more attention. Different glucose-lowering drugs have different effects on the development and progression of osteoporosis in patients with diabetes. Thus, it is necessary to select appropriate drugs. Meanwhile, better blood glucose control can postpone the development of osteoporosis.

Key words: Diabetes mellitus; Osteoporosis; Drug; Blood glucose control

随着我国人口老龄化的加速,生活方式的改变以及代谢性疾病的影响,糖尿病(diabetes mellitus, DM)与骨质疏松症(osteoporosis, OP)的患病率逐年增加,影响着我们的健康和生活质量,自从 1948 年 Albright 首次提出 DM 可致骨改变[1]以来,两种疾病之间的联系渐成为医学领域内的关注热点。DM 与 OP 的关系较为复杂,DM 疾病本身及其神经、血管并发症均可能引起骨代谢异常,促进骨质疏松的发展,而一些降糖药也可导致骨量丢失,因此选择合适的降糖药物,早期做到血糖达标,对于延缓或改善骨质疏松的发生发展至关重要。现针对目前国内外有关 DM、降糖药物、血糖控制和 OP 之间的研究作一综述。

1 糖尿病与骨质疏松

1 型糖尿病(type 1 diabetes mellitus, T1DM)可引起骨量减少、骨密度下降,导致骨质疏松,这一认识已达到共识[2-4]。而 2 型糖尿病(type 2 diabetes mellitus, T2DM)与骨量之间的关系一直存在争议,T2DM 通常合并多种慢性并发症,在不同病程阶段骨量变化不同,其骨密度(bone mineral density, BMD)可表现为不同程度的下降,也可以增高[5],或无明显改变[6]。也有研究[7]认为 T2DM 是 OP 的独立保护因素。

DM 对骨代谢的影响主要表现为骨吸收的增加,骨形成的减少,最终导致骨质疏松。然而,DM 引起骨质破坏的确切机制尚不明确[8],可能与低钙血症引起继发性甲旁亢[9],胰岛素分泌不足或敏感性下降导致成骨细胞作用减弱[10],以及 DM 多种慢性并发症如糖尿病肾病、性功能减退[11]有关,对于绝经后的女性 T2DM 患者,其 OP 的风险性进一步增加[8,12]。

目前研究发现多种细胞因子、激素与 OP 的发病机制有关[13]。晚期糖基化终末产物可在骨中蓄积[14],加快成骨细胞凋亡,抑制骨形成[15];氧化应激可抑制成骨细胞分化,诱导成骨细胞凋亡[16];葡萄糖转运蛋白 1 表达的增加与高糖状态下成骨细胞矿化延迟相关,同时 T2DM 患者胰岛素样生长因子Ⅰ水平降低[17,18],可以促进骨吸收和骨形成的耦

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联,加快骨转换,调节成骨细胞和破骨细胞功能的平衡[19]。

2 降糖药物与骨质疏松

2.1 胰岛素

T2DM患者的BMD与胰岛功能相关,胰岛功能明显减退者,其BMD明显下降,易导致骨质疏松[20]。由于胰岛素对成骨细胞有直接刺激作用,胰岛素缺乏或作用缺陷时,成骨细胞生成的骨钙素(Bone Gla protein,BGP)减少,加速骨胶原组织的代谢,使骨吸收大于骨形成从而引起骨量下降。有动物研究[21]证实胰岛素能提高成骨细胞数及骨钙素水平,改善骨矿化。Gopalakrishnan V等[22]的研究显示,胰岛素能够促进骨胶原合成、矿物质沉积,减轻高血糖对成骨细胞的抑制。同时胰岛素还可以促进肾小管对钙、磷重吸收。但也有研究[23]认为胰岛素治疗对DM患者的骨代谢无明显影响,而发病年龄和病程是影响BMD的重要因素。

2.2 二甲双胍

二甲双胍为DM患者的一线降糖药物,和胰岛素一样,也能刺激骨胶原合成、矿物质沉积,促成骨细胞形成[24]。细胞培养实验[25]表明,用二甲双胍对成骨细胞UMR106和MC3T3E1进行干预,可以观察到MC3T3E1成骨细胞碱性磷酸酶的活性增加,培养3周后该细胞矿化骨小节增加明显,二甲双胍通过激活腺苷酸活化蛋白酶,增加BGP、骨成型蛋白-2、内皮细胞型一氧化氮合成酶等基因表达,促进MC3T3E1小鼠胚胎成骨细胞分化和骨矿化。一项119例初发T2DM绝经女性患者随机应用胰岛素、二甲双胍、罗格列酮的研究[26]发现,治疗1年后,胰岛素组、二甲双胍组手指BMD无显著性差异,且均高于罗格列酮组。因此与应用罗格列酮相比,T2DM患者应用胰岛素或者二甲双胍更有益于防治骨质疏松。

2.3 噻唑烷二酮类药物

噻唑烷二酮类药物是T2DM患者常用的胰岛素增敏剂,目前关于其对骨代谢的影响成为研究热点。噻唑烷二酮为PPARγ激动剂,有研究报道PPARγ被配体激活后能够作用于骨髓,促干细胞向脂肪细胞转化,从而抑制成骨细胞的形成,导致骨量减少,造成骨质疏松[27,28]。一项对666例服用噻唑烷二酮的T2DM患者长达4年的随访[29]发现,老年女性患者各部位BMD均下降明显,而老年男性患者BMD变化不明显。ADOPT研究[30]也发现,应用罗格列酮的女性患者骨折发生率明显高于应用二甲双胍或格列本脲的患者,且骨折部位常见于上臂肱骨、手或足部。这些部位与绝经后骨质疏松症引发的骨折部位(髋部、腰椎)不同。Lazarenko OP等[31]用噻唑烷二酮类药物对不同年龄的非糖尿病雄性C57BL/6鼠进行干预,结果显示,罗格列酮明显增加成年和老龄鼠的PPARγ2表达,导致成骨细胞数目减少,破骨细胞和脂肪细胞数目增加。罗格列酮可能促进干细胞向脂肪细胞转变,而抑制成骨细胞的形成[32],同时也可影响性激素水平,导致骨量减少,BMD下降[33]。与二甲双胍相比,噻唑烷二酮类更易增加骨折风险[34]。文达敏为马来酸罗格列酮类与二甲双胍的复方制剂,一项随机双盲对照研究[35]表明T2DM患者使用文达敏80周后,与单用二甲双胍相比,腰椎和髋部的BMD显著降低,但桡骨远端1/3、股骨颈、全身的BMD无显著差异。

2.4 GLP-1

肠促胰素主要包括胰高血糖素样肽-1(glucagon-like peptide-1,GLP-1)和糖依赖性胰岛素释放肽(glucose-dependent insulinotropic peptide,GIP),其中GLP-1在T2DM的发生发展中起着更为重要的作用。GLP-1由胰高血糖素原基因表达,以葡萄糖浓度依赖性方式促进胰岛β细胞分泌胰岛素,并减少胰岛α细胞分泌胰高血糖素,从而降低血糖。依泽那太是GLP-1类似物,通过模拟GLP-1的效应而发挥作用。Bunck MC等[36]发现T2DM患者每日注射依泽那太两次,连续应用44周,仅会降低其体重,对BMD、血钙及碱性磷酸酶水平无明显影响。

2.5 DPP-4抑制剂

二肽基肽酶IV(dipeptidyl peptidase IV,DPP-4)抑制剂可抑制DPP-4对肠促胰素的水解作用,提高GLP-1与GIP的浓度,提高活性肠泌素的浓度。一项比较吡格列酮和DPP-4抑制剂sitagliptin对高脂饲养(high fat diet,HFD)的野生型大鼠骨量的影响的试验[37]显示吡格列酮可显著降低卵巢切除(ovariectomized,OVX)雌性大鼠的脊椎骨力度,降低雄性大鼠的脊椎BMD,影响骨小梁结构及骨矿化;Sitagliptin可以显著增加HFD野生型雌性大鼠的脊椎BMD,但对于OVX雌性大鼠无此改变。而遗传灭活的DPP-4对雄性和雌性大鼠骨骼无影响,但是对于OVX大鼠,可显著引起股骨的形态和力学减退。但DPP-4抑制剂对DM患者的骨量改变是否存在影响,目前暂无相关文献报道。

2.6 其它类降糖药

其它类降糖药物，如磺脲类药物可以引起骨量丢失，通过增加环磷酸腺苷来干扰磷酸酯酶催化剂的降解，同时降低竞争性抑制酶的活性，增加骨钙盐的丢失，从而导致骨质疏松[38]，但对髋部的骨折发生率影响较小[39]；格列奈类可以促进胰岛 β 细胞分泌胰岛素，促进骨形成。目前国内外暂无 α 糖苷酶抑制剂与骨质疏松的关系的相关报道。

3 血糖控制与骨质疏松

DM 患者 BMD 低于正常人，血糖控制不佳者更为显著[40]。DM 患者不管是应用口服降糖药，还是胰岛素治疗，其 BMD 较同年龄段正常人明显降低，OP 患病率上升[41]。血糖控制水平与骨代谢之间存在何种关联，大部分的研究观点认为良好的血糖控制可以减缓 OP 的发生和发展。秦健的研究[42]显示，高血糖状态下骨形成指标 BGP 水平降低，骨吸收指标尿 1 型胶原氨基末端肽（N-terminal telopeptide of type I collagen，NTX）水平升高，在血糖控制稳定后 BGP 水平升高，NTX 水平下降，故此研究认为血糖的良好控制可提高 T2DM 患者的 BMD，提高 BGP、IGF-1 水平，降低 NTX 水平。肖丽平等[43]研究认为 T2DM 患者治疗后血骨特异性碱性磷酸酶、尿脱氧吡啶酚降低，且骨特异性碱性磷酸酶和尿脱氧吡啶酚变化水平与糖化血红蛋白、尿糖和尿钙、磷变化水平呈正相关。因此控制血糖能使 T2DM 患者骨转换降低。Okazaki 等[44]研究证实，无论是口服降糖药或胰岛素，还是联合用药，其对骨代谢的影响无明显差异，因此，骨代谢指标的水平与胰岛素水平、IGF-1 等水平不一定相关，与血糖的控制水平相关。

4 小结

综上所述，胰岛素、二甲双胍等降糖药均能促骨形成，有助于防治骨质疏松，噻唑烷二酮类易增加骨折风险，GLP-1 和 DPP-4 抑制剂对 DM 患者的骨质影响暂无定论。因此，DM 患者不仅需要加强血糖控制，保持血糖水平的稳定，而且要选择合适的降糖药物，预防和减缓 OP 的发生，降低骨折发生风险率，已发生骨折的 DM 患者尤其需要注意，避免选择可能引起骨量减少的降糖药物。

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