·综述·

糖尿病患者骨代谢的变化及运动对其影响的研究进展

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摘要: 糖尿病主要是以胰岛素分泌缺陷或胰岛素作用障碍导致的以高血糖为主的代谢性疾病。大量的临床研究及动物研究证实,糖尿病患者骨代谢易紊乱,多发骨质疏松等疾病。胰岛素分泌对骨代谢具有十分重要的作用。本文分别从高血糖环境、胰岛素及高血脂环境对糖尿病患者骨代谢的影响进行详细综述,探讨其影响骨代谢、造成骨质疏松的相关机制。此外,通过分析运动改善糖尿病患者骨代谢,为体育锻炼防治糖尿病患者骨质疏松等疾病提供基础理论参考。

关键词: 糖尿病;骨质疏松;高血糖;胰岛素;瘦素;脂联素;运动

Research progress in bone metabolism and the effect of exercise on it in diabetic patients

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Abstract: Diabetes mellitus is a metabolic disease that is mainly due to the secretion defect and function obstacle of insulin, resulting in hyperglycemia. Most clinical research and animal experiments find that diabetes mellitus can easily cause disturbance of bone metabolism, resulting in osteoporosis. The secretion of insulin plays an important role in bone metabolism. This article summaries the reasons resulting in diabetic osteoporosis from the aspects of hyperglycemia environment, insulin, and high fat, and explores the mechanism of the effect on bone metabolism and osteoporosis. Moreover, by analyzing how sports improve bone metabolism in diabetic patients, we provide theoretical basis and reference for the prevention and treatment of diabetic osteoporosis.

Key words: Diabetes mellitus; Osteoporosis; Hyperglycemia; Insulin; Leptin; Adiponectin; Exercise

研究糖尿病患者的骨质疏松问题,都从高血糖环境、糖基化终末期产物(AGEs)、胰岛素、微量元素等角度入手进行防治[1];对于肥胖型糖尿病患者骨质疏松问题,同时也关注其瘦素及脂联素。研究发现,胰岛素可改善糖尿病患者的骨代谢,瘦素、脂联素会影响糖尿病患者的骨骼代谢[2,3]。目前关于糖尿病患者胰岛素、瘦素和脂联素之间的关系,三者之间的相互作用,对骨代谢的影响研究的较少。

本文将从糖尿病对骨代谢影响的角度,重点分析高血糖环境、胰岛素、高血脂环境下机体骨代谢的变化,和胰岛素、瘦素和脂联素之间的交互作用,以及对骨代谢的影响,且分析运动对糖尿病患者骨代谢的作用。

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1 高血糖环境对骨代谢的影响

高血糖环境对骨代谢通过不同的机制产生不利影响,使骨代谢指标及参数出现异常,导致骨密度降低及骨量流失等问题。

高血糖会促进骨髓间充质干细胞(BMSCs)向脂肪细胞分化,抑制成骨细胞的分化,而成骨细胞和脂肪细胞均来源于共同的细胞前体BMSCs[4]。骨质疏松症中,骨代谢的异常往往是伴随着骨髓脂肪成分的增加[5]。Botolin等[6]动物实验中发现,糖浓度增加,细胞内的cAMP/PKA/ERK信号被激活,脂肪细胞的特异性标记物LPL、P2、PPARγmRNA也随之增加,脂肪细胞的分化率提高,骨髓中含致密脂质的脂肪细胞增多。高血糖环境下,葡萄糖转运蛋白1的表达增加,导致成骨细胞的基因表达受限,包括骨钙素(BGP)、基质金属蛋白酶13、血管内皮生长

因子(VEGF)和甘油醛 3 磷酸脱氢酶等的表达减少,使成骨细胞最后阶段的成熟和分化被抑制[7,8]。

高血糖环境对某些骨代谢信号也会产生影响。Wnt/β-catenin 和 RANKL/RANK/OPG 信号通路在骨形成和骨代谢中具有十分关键的调控作用,高血糖会使其信号通路失调,并参与了糖尿病患者骨质疏松的发生发展[9]。Holmen 等[10]的动物实验研究中发现,糖尿病大鼠中 Wnt/β-catenin 表达量的减少将可能引起 OPG 表达量的降低,从而使 RANK 与 RANKL 的结合作用增强,促使破骨细胞的分化,导致骨量下降。但邓艳华等[11]动物实验研究发现,在急性高血糖环境下,MAPK 信号通路可促进成骨细胞的分化增殖。

糖基化终末期产物(AGEs),可破坏骨的矿化特性,糖尿病患者的 AGEs 的蓄积可加快成骨细胞凋亡,导致骨形成受抑制[12]。慢性高血糖导致 AGEs 积聚,使骨蛋白及骨细胞分化受到影响,进一步造成骨代谢平衡失调,容易诱发骨质疏松。慢性炎症因子 IL-1、IL-6、TNF-α 被认为与糖尿病并发骨质疏松密切相关,AGEs 结合细胞表面的 RAGE 可产生过多的 IL-1、IL-6、TNF-α 因子,诱导脾细胞、外周单核细胞分化为破骨细胞[13]。BMP-2 在成骨细胞分化过程中起着非常重要的作用,它是骨诱导活性最强的一种[14,15]。薛昊罡等[16]动物实验研究发现,糖尿病大鼠的 AGEs 与 BMP-2mRNA 呈显著负相关,两者均参与了糖尿病骨质疏松的发生发展。

此外,高血糖可刺激甲状旁腺素(PTH)分泌,激活破骨细胞,动员骨钙、磷、促使骨吸收增强。高糖环境可使细胞渗透性增强,造成钙、磷、镁等微量元素随尿液排出,肾小管无法完成重吸收,使机体产生负钙平衡。低血钙和低血镁又促进 PTH 功能亢进,使钙、磷、镁动员能力变强,破骨细胞活性增加,导致骨密度减小,骨量减少,引起骨质疏松[17]。

2 胰岛素对骨代谢的影响

无论是 I 型糖尿病还是 II 型糖尿病患者,其体内胰岛素都存在分泌失调或作用障碍。胰岛素抵抗、高胰岛素血症、胰岛素分泌绝对不足或相对不足,都会引起骨代谢的紊乱。

胰岛素分泌不足可造成骨代谢紊乱,导致骨质疏松,并且胰岛素水平越低,骨代谢异常越明显。胰岛素分泌不足会引起维生素 D 的减少,研究发现,维生素 D 不仅存在于肠道中,还存在于胰岛 β 细胞中,而且维生素 D 与胰岛素敏感性密切相关[18,19]。在 Yoho 等[20]临床研究中发现,糖尿病患者的血清维生素 D 水平明显低于正常人。胰岛素缺乏时肾脏 1-α 羟化酶的活性降低,致使 1,25-$(OH)_2D_3$ 的合成减少,钙、镁吸收减少,刺激 PTH 分泌,破骨细胞活性增强,导致骨密度减小,骨量减少,引起骨质疏松。因此,胰岛素也可通过维生素 D 来调节 PTH,影响骨代谢。

胰岛素可直接刺激成骨细胞,促进其细胞内的氨基酸蓄积、骨胶原及骨基质的合成分泌。此外 BGP 有成骨细胞分泌,是骨代谢中一个十分重要的调节因子,可通过减弱破骨细胞的活性,使骨吸收减慢。当胰岛素分泌不足,成骨细胞及 BGP 水平都会降低,将有利于骨吸收[21,22]。

此外,胰岛素还可通过腺苷酸环化酶(减少 cAMP 合成)促进骨吸收[23],高血糖对 BMSCs 的毒性作用促进骨吸收等[24]。

胰岛素能够改善糖尿病患者的骨代谢影响,在 KM 等[25]研究中发现,II 型糖尿病初期,存在胰岛素抵抗和高胰岛素血症的患者,其骨密度反而会增高,骨量累积。而胰岛素并不一定能降低高血糖,在张菱等[26]研究中发现,胰岛素分泌延迟和胰岛素水平过高,其血糖水平并无差异,且远远高于正常人。

高血糖有利于骨吸收,从而导致骨质疏松,胰岛素水平高则有利于骨形成,可预防骨质疏松。而 II 型糖尿病初期,同时存在高血糖和高胰岛素的状况时,其骨密度是增加,骨量是累积的,其相关机制有待进一步研究。

3 高血脂环境对骨代谢的影响

肥胖已成为 II 型糖尿病的主要致病危险因素之一,对于肥胖型的糖尿病患者,肥胖对骨代谢影响的结论具有较大争议。有研究表明 BMI 的增加对骨密度及骨形成不利,且肥胖程度越大,骨折风险也越大[27]。在 YH 等[28]临床研究发现,不管是男性还是女性,其体脂比例与骨量减少和非脊柱性骨折呈正相关。JL 等[29]研究中提出相反的结论,BMI 降低骨折风险增加,肥胖女性骨折风险只有正常体重者的 1/3。原因是体重的快速下降,减少了骨骼的应力负荷,机械刺激降低,而不利于骨密度增加[30]。

脂肪细胞和成骨细胞都源于 BMSCs,骨髓内脂肪细胞增加可影响成骨细胞的分化和功能,增加破骨细胞活性,影响骨矿化[31]。脂肪组织作为一种内分泌器官能分泌前炎症因子 IL-6、CPR 及促炎细胞因子 TNF-α,这些炎症因子会引起骨代谢异常导致

骨量丢失[32,33]。此外,高脂饮食造成的肥胖会干扰肠道对钙、磷和维生素 D 等成骨元素的吸收,游离脂肪酸可形成不可吸收的不溶性钙化灶,影响钙吸收,加速骨质疏松[31]。

瘦素和脂联素是脂肪细胞分泌的两个重要因子,对糖尿病患者的骨代谢产生一定的影响。

瘦素主要由脂肪细胞分泌的多功能蛋白类激素,是调节体质量的重要因子之一[34]。肥胖程度越高,瘦素水平也越高。瘦素可影响骨代谢,瘦素分泌过多对骨代谢产生不利影响。Cirmanova 等[35]研究发现,ob 小鼠的血清瘦素水平明显高于野生型小鼠,其 BMD、小梁骨体积以及皮质骨的厚度都低于野生型小鼠。瘦素对骨代谢的效应可能取决于血浆瘦素水平及血脑屏障的通透性。

瘦素的分泌受多种因素调节,其中包括胰岛素,瘦素水平与胰岛素呈相关,瘦素抵抗和胰岛素抵抗常共同存在[36]。反之,瘦素能够抑制胰岛 β 细胞生物合成和分泌胰岛素,当瘦素分泌过多时,胰岛素的活性也会被抑制[37]。Muller 等[38]动物实验研究中发现,大鼠脂肪细胞置于高浓度的瘦素溶液中,高浓度的瘦素损害了胰岛素的代谢活动,当瘦素 > 30nmol/ L 时,胰岛素的活性几乎完全被抑制。

脂联素是脂肪细胞分泌的另一个重要细胞因子,研究证实,脂联素水平与骨密度呈负相关[39]。汪学军等[40]研究中发现,脂联素与 II 型糖尿病肥胖患者的胰岛素抵抗发生有关,脂联素降低易导致胰岛素抵抗。

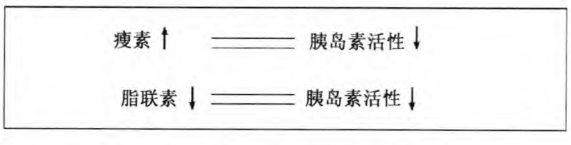

图 1 瘦素、脂联素与胰岛素之间的关系

Fig. 1 The relationship among leptin, adiponectin, and insulin

瘦素、脂联素与胰岛素之间相互影响。当瘦素分泌水平较高,脂联素分泌水平较低时,将抑制胰岛素的分泌及其活性。相较于高血糖环境,胰岛素、瘦素与脂联素对骨代谢的影响更加关键,三者之间的相关影响机制尚不是很明确。

4 运动对糖尿病患者骨代谢的影响

运动能促进身体健康,改善体质,维持或增加骨代谢水平,预防骨质疏松[41]。对于糖尿病患者,适宜的运动不仅能改善血糖、血脂水平,还可以调节胰岛素、瘦素及脂联素水平,有利于骨代谢[42]。

运动可提高胰岛素敏感性,改善胰岛素抵抗现象[43]。原因可能是提高了糖原合成相关酶的活性和数量、改善胰岛素受体后的信号转导过程,上调肌肉葡萄糖转运蛋白等机制来提高胰岛素敏感性[44]。程守科等[45]研究发现,剧烈运动后短时间内胰岛素的敏感性下降,运动中过度氧化是胰岛素敏感下降的重要原因。过度氧化也抑制成骨细胞分化,促进其凋亡,有利于骨吸收[46]。

衣雪洁等[47]研究中发现,耐力训练可明显降低体脂和血瘦素水平,上调脂肪的瘦素受体的基因表达,有效地缓解瘦素抵抗。中等强度的运动也可明显增加血液脂联素水平,一次性急性运动对瘦素和脂联素水平改善没有显著作用[48]。

剧烈运动对胰岛素、瘦素及脂联素的调节没有改善作用,运动中的过度氧化也会抑制成骨细胞的分化,有利于骨吸收。中低强度的有氧运动对胰岛素、瘦素及脂联素调节具有促进作用,也有利于体脂的消耗。

5 总结

糖尿病患者由于胰岛素分泌缺陷或胰岛素作用障碍从而引起高血糖代谢疾病,胰岛素分泌水平影响骨代谢;同时,瘦素、脂联素分泌水平对骨代谢影响也有较大;瘦素、脂联素分别作用于胰岛素,共同引发糖尿病患者的骨质疏松问题。长期的有氧运动有利于调节胰岛素、瘦素和脂联素水平,增加胰岛素的敏感性,改善糖尿病患者的骨质疏松问题。

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