

SGLTs 抑制剂对骨代谢的影响及其机制

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【摘要】 新型降糖药物钠-葡萄糖协同转运蛋白 2(SGLT2)抑制剂能够改变矿物质水平、影响骨转换标志物、降低骨密度、破坏骨微结构、加速骨转换以及可能增加跌倒风险,提示其可能对骨代谢及糖尿病患者骨折结局产生影响,探讨其潜在机制并评估接受该药治疗的骨折风险对临床实践中的药物选择有重要的指导意义。

【关键词】 钠-葡萄糖协同转运蛋白;钠-葡萄糖协同转运蛋白 2 抑制剂;2 型糖尿病;骨代谢;骨折
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Impact of SGLTs inhibitors on bone metabolism and its mechanism Qian Beibei¹, Yan Caifeng².

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【Abstract】 Sodium-glucose transporter 2 (SGLT2) inhibitors, the novel anti-diabetic drugs, can change the levels of minerals, affect bone turnover markers, reduce bone mineral density, disrupt bone microarchitecture, accelerate bone turnover and may increase the susceptibility to falls. It suggests that it may have an impact on bone metabolism and fracture outcomes in patients with diabetes mellitus. It is of great significance to explore its potential mechanisms and evaluate the risk of fractures caused by the drug for selection of drug in clinical practice.

【Key words】 Sodium-glucose transporter; Sodium-glucose transporter 2 inhibitors; Type 2 diabetes mellitus; Bone metabolism; Fracture

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糖尿病是一种以高血糖为特征的慢性代谢性疾病。糖尿病患者骨折风险升高,提示疾病本身以及降糖药物对骨骼的潜在影响^[1]。因此,研究降糖药物对骨代谢的影响对临床实践中的药物选择有重要意义。钠-葡萄糖协同转运蛋白 2(SGLT2)抑制剂是一种新型降糖药物,主要作用于肾脏近曲小管的 SGLT2 受体,抑制肾小管内葡萄糖重吸收,增加肾脏尿糖排泄,以非胰岛素依赖机制降低血糖及糖化血红蛋白水平,并有多项研究证实具有心血管及肾脏获益,已成为治疗 2 型糖尿病(T2DM)的新支柱^[2-3]。最近,欧盟批准索格列净(Sotagliflozin)作为 1 型糖尿病(T1DM)治疗中胰岛素的辅助用药^[4]。虽然索格列净具体的心血管结局试验仍在进行中,但目前的研究显示,其似乎具有 SGLT2 抑制剂的所有优点,并且与 SGLT2 抑制剂相比具有延缓肠道葡

萄糖吸收的额外优势,在降低餐后血糖方面效果更优,提示 SGLT1/2 双抑制剂是未来降糖药物市场发展的新方向,但它们对骨代谢及糖尿病患者骨折结局的影响尚不清楚^[5-6]。本文就 SGLT 抑制剂对骨代谢的影响及其潜在机制进行综述。

1 SGLT 的生物学特性

肾脏对葡萄糖的重吸收与 SGLT 和葡萄糖转运蛋白(GLUT)有关,其中 SGLT1 主要分布于肠黏膜上皮细胞的刷状缘,在肠道葡萄糖和半乳糖的吸收中发挥重要作用,亦表达于肾脏近曲小管远端 S3 段,重吸收葡萄糖,是一种低转运能力、高亲和力的转运蛋白。SGLT2 主要分布在肾脏近曲小管 S1 段,是一种低亲和力、高转运能力的转运蛋白,其主要生理功能是在肾脏近曲小管完成肾小球滤过液 90% 葡萄糖的重吸收,其余 10% 由 SGLT1 完成,可见

SGLT2在葡萄糖重吸收中起主要作用^[7]。

目前国内上市的SGLT2抑制剂包括达格列净(Dapagliflozin)、恩格列净(Empagliflozin)、卡格列净(Canagliflozin)。

2 SGLT 抑制剂对矿物质代谢的影响

现有的研究表明,SGLT抑制剂通过影响矿物质水平间接调节骨吸收。Blau等^[8]认为,SGLT2抑制剂通过抑制钠和葡萄糖的共转运和再吸收,增加肾小管上皮细胞膜内外钠的电化学梯度,使钠、磷共转运增强,刺激近端小管的磷酸盐重吸收,增加的血清磷酸盐触发成纤维细胞生长因子23(FGF23)分泌,FGF23通过抑制1-25(OH)₂维生素D₃减少胃肠道对钙的吸收,从而促进甲状旁腺激素(PTH)分泌,使骨吸收增强。研究者进行的一项单盲、随机、交叉研究,共有25名健康志愿者接受卡格列净或安慰剂治疗5d,结果与安慰剂组相比,卡格列净组钠排泄增加与血清磷酸盐明显升高相关,尿钙排泄量增加,但未引起明显血清钙的变化,FGF23和PTH水平升高,且与磷酸盐增加相关,而1-25(OH)₂维生素D₃水平持续下降。对T2DM患者的研究显示,卡格列净与血清磷酸盐水平升高有关^[9]。此外,在T1DM小鼠模型中,与对照组相比,卡格列净组血清FGF23水平升高^[10]。

在一项对T2DM合并早期糖尿病肾病患者进行的双盲、随机、交叉试验中也得出相似的结果,与安慰剂组相比,达格列净组血清磷酸盐、PTH和FGF23水平分别升高了9%、16%和19%^[11]。

与此相反, Samadfam等^[12]研究发现,使用SGLT1/2双抑制剂SAR7226处理Sprague-Dawley鼠,其尿钙水平增加,血钙维持正常,血磷略有升高,PTH、1,25(OH)₂维生素D₃和骨转换标志物(BTM)显著减少,骨密度增加,提示SGLT1/2抑制剂SAR7226对钙、磷稳态有显著影响,对骨量和骨强度有正向影响,并且在使用SGLT1抑制剂SAR474832处理后的Sprague-Dawley鼠中也观察到相似的结果。

SGLT2抑制剂可促进骨吸收,这可能是由于血清钠浓度降低对破骨细胞的直接影响导致的。实验研究表明,低钠血症可以刺激破骨细胞,使其活性增强和数量增加,促进骨吸收^[13]。另外,骨骼中高表达的电压门控Na⁺通道作用增强也可以刺激破骨细胞,使其活性增强^[14]。Barsony等^[13]研究发现,持续的低钠血症使破骨细胞作用增强,Na⁺从骨骼中释放,而骨骼中高表达的电压门控Na⁺通道易受骨组织细胞外液变化的影响,因此骨质疏松可能与骨骼中可交换Na⁺增多有关。低钠血症时,破骨细胞促

进骨吸收,使Na⁺从骨骼中释放,以维持血浆Na⁺平衡,其作用机制与低钙血症时Ca²⁺由骨骼中释放很相似^[15]。

此外,低钠血症还会增加氧化应激生物标志物如8-羟基-2'-脱氧鸟嘌呤核苷(8-OHdG)水平,而氧化应激增加可能与骨质疏松和骨折风险有关^[16]。

3 SGLTs 抑制剂对 BTM 的影响

骨质量主要由破骨细胞骨吸收的速率和成骨细胞骨形成的速率决定。BTM能及时反映全身骨骼的代谢状态,分为骨形成标志物和骨吸收标志物,前者反映成骨细胞的活性和骨形成的状态,包括I型前胶原N端前肽、I型前胶原C端前肽、碱性磷酸酶、骨特异性碱性磷酸酶、骨钙素和骨保护素;后者代表破骨细胞活性和骨吸收水平,包括I型胶原交联羧基端肽区(CTX)、I型胶原交联氨基端肽区、抗酒石酸酸性磷酸酶-5b、脱氧吡啶啉、吡啶啉和羟脯氨酸。骨吸收标志物异常与骨折风险增加有关^[17]。在一项对T2DM患者为期104周的临床药物试验研究显示,卡格列净治疗组在52周时出现CTX和骨钙素的增多^[18]。在对糖尿病小鼠的研究中,与对照组相比,卡格列净组骨吸收标志物RatLAPs增加^[10,19]。然而,也有研究显示,与安慰剂组相比,达格列净组P1NP、CTX水平没有变化^[20]。

到目前为止,还没有证据表明这些BTM的改变是SGLT2抑制剂与骨组织直接结合的结果。研究发现,在破骨细胞中未检测到SGLT1和SGLT2,在任何成骨细胞中均未检测到SGLT2,在分化的成骨细胞MC3T3-E1中检测到SGLT1,但其水平仅为肾脏中观察到的水平的1%^[10]。另一项研究显示,用4-[¹⁸F]氟-达格列净正电子发射断层扫描绘制啮齿类动物SGLT2功能蛋白的分布,未见骨组织与静脉注射的4-[¹⁸F]氟-达格列净结合^[21]。因此,与SGLT2相关的骨骼效应可能是骨骼-矿物质稳态和血糖的变化间接导致的,而不是骨细胞中SGLT2依赖的葡萄糖转运破坏导致的;与SGLT1相关的骨骼效应是否与骨细胞中SGLT1依赖的葡萄糖转运相关需进一步的研究证实。

4 SGLT2 抑制剂对骨密度的影响

低骨密度是骨折发生的一个独立危险因素。在一项对T2DM患者的随机、双盲、对照试验中,卡格列净100mg和300mg在治疗104周后全髋部骨密度与安慰剂组相比分别下降0.9%和1.2%,差异有统计学意义,但股骨颈、腰椎和前臂远端的骨密度差异无统计学意义。体重变化在该统计分析中是一个重要的协变量($P = 1.2 \times 10^{-8}$),其可以解释约40%

的全髌关节骨密度下降。因此研究者认为,全髌部骨密度下降的原因可能是由体重减轻导致的,而不是药物直接对骨密度的影响^[18]。此外,雌二醇水平降低可能是导致骨密度下降的一个原因,已有研究显示,卡格列净可以降低女性患者的雌二醇水平,但其机制尚未完全阐明^[18]。然而,也有研究显示达格列净组与安慰剂组在腰椎、股骨颈和全髌部骨密度差异均无统计学意义^[20]。Rosenstock等^[22]报道,埃格列净(ertugliflozin)治疗 26 周后对腰椎、股骨颈、髌部和前臂远端的骨密度无影响。

5 SGLT2 抑制剂对骨微结构的影响

研究显示,长期糖尿病与股骨小梁骨微结构缺损有关,包括骨小梁数目减少、小梁间距增加、皮质厚度减少、皮质孔隙度增加^[23]。糖尿病骨病小鼠应用卡格列净治疗 10 周后,血糖水平改善了约 35%,但血糖改善没有修复糖尿病相关的骨缺损,也没有提高股骨或腰椎的抗骨折能力^[23]。在非糖尿病小鼠中,与赋形剂对照组相比,卡格列净组股骨小梁体积分数、小梁数目和小梁组织矿物密度降低,小梁间距增加,因此卡格列净可能对骨微结构有不利影响^[23]。然而,目前尚缺乏 SGLT2 抑制剂对人类骨微结构改变的研究,以及其如何影响骨基质矿化和胶原纤维分布的研究。

6 SGLT2 抑制剂减轻体重,间接加速骨转换

SGLT2 抑制剂可通过减轻体重间接加速骨转换。据报道,SGLT2 抑制剂可以适度减轻体重^[24]。体重减轻可显著增加骨钙素和 CTX 浓度,加速骨转换,促进骨吸收,并且骨吸收增加与体重减轻的程度正相关^[18]。脂肪组织产生的脂联素和瘦素对成骨细胞和破骨细胞有一定的作用^[25-26]。在肥胖青少年中,脂联素/瘦素比值与骨钙素呈正相关,促进骨形成^[27]。一项对非糖尿病肥胖患者的研究显示,瑞格列净(remogliflozin)治疗 8 周后显著降低瘦素/脂联素比值^[28]。此外,研究表明,体重下降可以不依赖瘦素调节骨量^[29]。目前尚无 SGLT2 抑制剂影响脂联素和瘦素的综合数据。脂联素/瘦素比值与骨钙素的关系有助于临床上了解骨转换情况。

7 SGLT2 抑制剂对骨折结局的影响

目前 SGLT2 抑制剂对骨折风险的影响尚无一致结论。卡格列净心血管评估研究(CANVAS)随机临床试验(RCT)显示,卡格列净可降低髌关节骨密度,增加骨折风险^[30]。Watts等^[31]指出,CANVAS中卡格列净组观察的剂量相关性血容量不足导致的不良事件(如体位性眩晕、直立性低血压、晕厥)可能和卡格列净治疗早期发生的跌倒相关的骨折有关,

但报道的跌倒相关的不良事件发生率很低,并且没有系统地收集关于跌倒的数据,因此该研究的数据不能作为最终结论。一项纳入 9 项 RCT 的荟萃分析显示,与安慰剂、格列美脲或西格列汀相比,卡格列净明显增加骨折风险^[31]。然而,一项队列研究显示,与胰高血糖素样肽 1 受体激动剂相比,卡格列净不增加肱骨、前臂、骨盆和髌部的骨折风险(总 $HR = 0.98, 95\% CI: 0.75 \sim 1.26$)^[32]。Wiviott等^[33]对接受达格列净治疗的 17 160 例 T2DM 患者进行观察,发现达格列净组和安慰剂组的骨折风险相似。Toullis等^[34]对 22 618 例 T2DM 患者为期 12 个月的随访发现,达格列净不增加骨折风险。研究显示,恩格列净组和安慰剂组的骨折风险相似^[35]。在一项巢式病例对照研究中,与二甲双胍 + 二肽基肽酶 4 抑制剂相比,使用二甲双胍 + SGLT2 抑制剂不增加上肢或下肢骨折风险($OR = 1.00, 95\% CI: 0.72 \sim 1.39; OR = 0.99, 95\% CI: 0.71 \sim 1.37$)^[36]。一项纳入 27 项 RCT 的荟萃分析显示,SGLT2 抑制剂不增加骨折风险(总 $RR = 1.02, 95\% CI: 0.81 \sim 1.28$),进一步亚组分析发现,不同类型的 SGLT2 抑制剂与骨折风险无关,达格列净、卡格列净、恩格列净及埃格列净的 RR 分别为 1.33 (95% $CI: 0.70 \sim 2.51$)、1.21 (95% $CI: 0.74 \sim 1.97$)、0.89 (95% $CI: 0.67 \sim 1.20$)及 1.16 (95% $CI: 0.39 \sim 3.49$)^[37]。有 4 篇荟萃分析均未发现使用 SGLT2 抑制剂对骨折风险有影响^[38-41]。

综上,作为新型降糖药物,SGLT2 抑制剂对 T2DM 患者的血糖、心血管和肾脏预后等均有显著改善作用,其在临床中的使用地位逐步上升。虽然一些研究证实 SGLT2 抑制剂能改变人体骨代谢水平,促进骨吸收,但是这些改变与骨折风险之间的相关性仍然存在争议。上述大量的荟萃分析和其他多项研究显示,在一些研究中观察到的骨折风险增加很可能是偶然发生的,尚未得到证实。考虑到骨骼健康问题和骨折带来的巨大经济和社会负担,在缺乏充分证据的情况下,应在使用该药物前充分评估患者跌倒风险,对血容量减少患者应先纠正血容量,对有骨折史或老年糖尿病患者应考虑检测骨密度、评估椎体骨折风险及治疗骨质疏松症,建议对高骨折风险、糖尿病晚期及肾功能不全的患者慎用 SGLT2 抑制剂。SGLT1/2 双抑制剂和选择性 SGLT1 抑制剂对骨量和骨强度有正向影响,但相关研究很少且仅限于动物实验水平。目前,SGLTs 抑制剂对骨骼的影响及其机制尚未完全阐明,因此,仍需进一步研究。

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