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• 综述 •

降糖药物骨代谢效应及对糖尿病患者牙种植的影响

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【摘要】 2型糖尿病(type 2 diabetes mellitus, T2DM)患者的牙种植修复需求较大,但T2DM患者机体的病理环境影响了该人群的牙种植效果。牙种植术前控制血糖稳定可提高该人群的种植成功率,然而个体的早期骨结合强度仍有待提高,增强T2DM患者种植体的早期骨结合是当前口腔种植医生急需解决的问题之一。降糖药物的骨代谢效应各不相同,可能会对种植体周围骨组织产生不同的干预作用,但是目前缺乏降糖药物对种植体周围骨组织保护作用的直接临床证据。文章整合了临床内科研究和种植牙研究中降糖药物的骨代谢效应,为即将接受种植手术的T2DM患者提出用药指导,建议在不违反临床用药准则的前提下,种植期间尽量避免使用可能不利于骨组织的药物,如钠-葡萄糖协同转运蛋白2抑制剂及噻唑烷二酮类;选择对骨代谢有益的降糖药物,如胰岛素、二甲双胍及GLP-1受体激动剂。但这些药物对牙种植体周围骨作用的临床效应对比尚需要进一步阐明。建议选取适宜的(肠促胰岛素类药物)进行增强T2DM患者牙种植体早期骨结合的深入研究。

【关键词】 2型糖尿病; 血糖; 降糖药物; 胰岛素; 二甲双胍; 胰高血糖素样肽-1; 骨代谢; 种植牙; 骨结合

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【Abstract】 Patients with type 2 diabetes mellitus (T2DM) have a large demand for dental implants, but the pathologic state of T2DM patients could compromise the efficacy of implant treatment. Glycemic control can improve the success rate of implants in the T2DM population, but the early osseointegration of individuals still needs to be improved. Strengthening early osseointegration in patients with T2DM is one of the urgent problems for clinicians. The pharmacological mechanisms of hypoglycemic drugs on the market for bone metabolism are different and may require different interventions on the bone around the implant, but there is a lack of direct clinical evidence of the protective effect of hypoglycemic drugs. This review integrated the bone metabolic effect of drugs in clinical medical research and dental implant research. The aim was to provide medication guidance for T2DM patients who require implant surgery, and it is recommended to avoid the use of drugs with negative effects on bone as far as possible without violating the clinical medication guidelines, including SGLT-2 inhibitors and thiazolidinediones. Instead, they should choose glucose-lower-

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ing drugs that are beneficial to bone metabolism, such as insulin, metformin and GLP-1 receptor agonists. However, the comparative clinical effects of these drugs on periimplant bone need to be further elucidated. The researcher should select appropriate drugs (incretin drugs) to enhance the early osseointegration of implants in patients with T2DM.

【Key words】 type 2 diabetes mellitus; blood glucose; hypoglycemic medication; insulin; metformin; glucagon-like peptide1; bone metabolism; dental implant; osseointegration

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1 2型糖尿病患者牙种植研究概况

2型糖尿病(type 2 diabetes mellitus, T2DM)患者是一个数量庞大的群体,2019年全世界约9.3%(4.63亿)的成人(20~79岁)患有T2DM^[1]。T2DM患者常伴有严重的牙列缺损,与牙周病变的发生有一定关联^[2]。T2DM缺牙患者有较大的种植修复需求,但血糖异常且难以控制属于种植治疗的禁忌症,即使得到控制之后治疗效果仍比正常患者稍差^[3]。T2DM一方面影响了机体钙磷代谢等骨生化反应^[4],另一方面引起了晚期糖基化产物(advanced glycation end products, AGEs)、活性氧(reactive oxygen species, ROS)与慢性炎症相互促进的恶性循环^[5],影响成骨^[6]。T2DM患者种植体骨结合的形成速度和质量不如正常机体,T2DM患者的早期骨结合还需要增强^[7]。

仅通过血糖控制并不足以纠正糖尿病机体的异常骨代谢。随着降糖药物的多样化和机制研究的不断深入,各种降糖药物的骨代谢效应越来越显著。种植体的骨结合需要良好的骨质基础,降糖药物对骨质的影响可能会波及种植体的骨结合。但是降糖药物对种植体周围骨结合作用主要集中在动物研究中,暂时没有随机、大样本和长期随访的研究报道。

2 降糖药物全身骨质代谢效应对牙种植的指导意义

2.1 降糖药物的全身骨代谢作用差异

T2DM患者骨质条件较差,骨质量和骨组织的微结构受损,骨小梁孔隙变大^[8]。T2DM患者骨质疏松的发生风险较高,骨折风险较高^[9]。降糖药物会对T2DM个体骨质有一定干预作用,目前评价降糖药物骨代谢效应的指标包括用药者骨密度、骨生化指标和骨折风险的变化^[10]。T2DM的临床用药参照但不限于指南^[11],以二甲双胍单药使用为

首选用药,血糖无法控制时根据患者情况选择胰高血糖素样肽-1(glucagon-like peptide1, GLP-1)受体激动剂、磺脲类、钠-葡萄糖协同转运蛋白(sodium-glucose cotransporter 2, SGLT2)抑制剂以及胰岛素等药物。

二甲双胍和噻唑烷二酮类(Thiazolidinediones, TZDs)都是胰岛素增敏剂。二甲双胍有一定的骨质保护作用,可以降低骨折风险;而TZDs类药物对骨骼的不良影响较为明确,会增加使用者的骨折风险,降低骨密度^[12]。研究证实TZDs会激活骨髓细胞中的过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ , PPAR γ)和核因子 κ B受体活化因子配体(receptor activator of nuclear factor- κ B ligand, RANKL)等不利于成骨的因子,抑制成骨细胞分化,刺激破骨细胞分化,进而阻碍新骨形成^[13]。TZDs对骨组织的不良影响还有可能与雌激素有关,女性患者中骨折风险较高^[14]。这种不良影响随着停药会逐渐消失,但骨密度丧失却无法恢复^[15]。可以推测,T2DM患者在种植期间最好也避免使用TZDs类药物。

磺脲类药物和SGLT-2抑制剂的骨代谢效应研究较少。少数研究显示磺脲类药物有降低骨折风险的潜力,但也有报道提出相反意见^[16]。关于SGLT-2抑制剂对骨的影响较少,但有研究表明卡那列啉可能会降低患者髋部的骨密度,增加四肢的骨折风险^[17],可能与改变了甲状旁腺素的分泌与钙磷代谢有关。

胰岛素和GLP-1的骨保护效应潜力较大。多数研究表明胰岛素在控制血糖的同时,可以保护骨密度^[18],但也有研究认为使用胰岛素可能会增加骨折风险^[19]。GLP-1相关的药物包括GLP-1受体激动剂和二肽基肽酶4(dipeptidyl peptidases-4, DPP-4)抑制剂。GLP-1受体激动剂可以保护骨密度,且比其他降糖药物更能降低骨折风险^[20],可预

防糖尿病机体并发的骨质疏松,并改善糖尿病骨质疏松机体的骨密度和骨代谢^[21]。DPP-4抑制剂的临床数据较少,相关研究倾向于认为DPP-4抑制剂对T2DM患者骨折风险影响不大^[22]。

2.2 降糖药物全身骨代谢研究的局限性

1型糖尿病的骨密度低于正常患者,然而T2DM患者的骨密度有可能和正常患者相似或偏高^[23],所以骨密度变化并不能准确反映药物的骨代谢效应。T2DM骨折风险一方面来自于皮质骨强度降低和骨小梁孔隙变大,另一方面可能是因为药物的低血糖反应和T2DM严重并发症导致摔倒风险增加^[24],所以骨折风险也不一定能准确反映药物对骨质改变的影响。在骨密度及骨折风险等全身骨质的研究指标存在一定局限性的情况下,降糖药物对种植体周围骨的作用可作为对全身骨质干预效果的参考指标。

3 部分降糖药物对种植体骨结合的影响

研究表明,在血糖稳定的前提下,二甲双胍、胰岛素及GLP-1类药物可以控制骨折风险,并且保护骨密度,可能具有促进T2DM种植体骨结合的潜力。

3.1 二甲双胍

二甲双胍是T2DM治疗的一线用药,主要通过激活腺苷酸活化蛋白激酶(adenosine monophosphate activated protein kinase, AMPK)来提高胰岛素敏感性^[25]。此外,二甲双胍可以通过降低ROS和AGEs的作用来促进骨形成^[26]。近来有研究对植入种植体的糖尿病大鼠使用了二甲双胍,认为二甲双胍可提高糖尿病大鼠种植体周围新骨形成,增加种植体周围骨组织中骨保护素(osteoprotegerin, OPG)的表达,降低RANKL水平来促进成骨及抑制破骨,提高种植体骨结合水平^[27]。但是也有研究认为二甲双胍对糖尿病个体的骨结合没有作用^[28];甚至还有研究认为二甲双胍可能会损害糖尿病个体的种植体骨结合^[29]。这种争议可能是因为其口服用药方式使其对骨组织的作用剂量不稳定,而二甲双胍对骨的作用可能有剂量和作用时间的依赖性^[25]。

3.2 胰岛素

皮下注射胰岛素类药物是T2DM的经典治疗方式。胰岛素可上调成骨因子RUNX2和抑制破骨因子RANKL的表达,促进骨形成^[30]。考虑到胰岛素受体分布广泛,相比局部使用方式,胰岛素的全

身使用方式可能分散了胰岛素作用强度而对骨结合改善有限。于是有研究尝试了胰岛素的局部使用途径,在T2DM动物的骨折部位局部使用胰岛素后可以促进骨愈合且不影响血糖稳定^[31],提示局部使用胰岛素可能在发挥其骨靶点效应的同时不影响糖尿病的临床治疗。有研究对正常大鼠种植体的周围局部使用胰岛素,发现实验组大鼠的种植体骨结合效率大幅度提高^[32]。还有研究者在动物实验中使用了含胰岛素涂层的种植体,结果发现胰岛素涂层可增强骨结合^[33]。这些研究都提示了在种植体周围局部使用胰岛素是有优势的。由于T2DM机体的胰岛素抵抗现象,还有一部分关于胰岛素促进T2DM骨结合的研究倾向于联合用药增强胰岛素的成骨效果,也取得了一定成效,如维生素D3^[34]。

3.3 GLP-1类药物

GLP-1类药物属于口服药物控制血糖效果不佳时的二线药物,作用靶点是糖尿病机体内受损的肠促胰岛素功能^[35]。GLP-1是内源性胰高血糖素样肽的一种,可在降血糖的同时提高骨密度和改善骨质量^[36]。GLP-1可上调Wnt通路和抑制骨硬化素的表达作用于干细胞^[37]。GLP-1受体缺乏的大鼠骨质条件变差,骨吸收指标升高,且降钙素的表达被抑制^[38]。GLP-1受体激动剂可使正常大鼠的OPG/RANKL比值增高,骨密度和新骨形成增加^[39]。还有研究发现GLP-1类药物exendin-4可以促进干细胞成骨分化以及抑制脂肪分化,促进骨缺损的新骨再生^[40]。GLP-1类药物的积极骨代谢效应使其成为促进种植体骨结合的潜力药物。

有研究在T2DM动物植入种植体后使用GLP-1受体激动剂,结果也证明GLP-1受体激动剂可提高血清中成骨因子ALP的含量^[41],有利于种植体周围成骨。种植体早期骨结合还需要成骨细胞通过黏附蛋白等吸附在植入物表面形成早期附着。T2DM会干扰黏附蛋白与整合素的表达进而影响种植体骨结合,而GLP-1受体激动剂可提高种植体周围的黏附蛋白和整合素水平^[42],这提示了GLP-1受体激动剂有增强种植体早期骨结合的潜力。

4 小结与展望

部分降糖药物对骨组织的作用会影响种植体的骨结合,建议T2DM患者在准备接受种植手术期间尽量避免使用对骨质有不良影响的药物,如噻唑烷二酮类、磺脲类及SGLT-2抑制剂,而是尽量选

择对骨代谢有益的降糖药物,如胰岛素、二甲双胍及GLP-1受体激动剂等。这些药物对种植体周围骨作用的临床效应尚需要进一步阐明,目前的临床证据不足以给出支持其优先级顺序的建议。下一步研究目标是糖尿病种植患者的降糖药物和种植体周围骨水平变化的相关性,并通过种植体周围骨的变化检验降糖药物全身骨代谢作用,为临床用药指导提供参考。

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