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·综 述·

糖尿病和高糖血症在骨性关节炎中的作用

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[摘 要] 骨性关节炎是最常见骨关节疾病,严重危害人类健康。随着对骨性关节炎认识的加深,人们逐渐意识到蛋白质、脂肪、碳水化合物等物质发生代谢紊乱所导致的代谢综合征(Mets)与骨性关节炎病程的密切关系,其中2型糖尿病和高糖血症被认为是骨性关节炎病情进展的重要风险因素,对骨性关节炎的影响越来越受到人们重视。有大量体内外试验显示高糖暴露对关节组织具有局部毒性,可导致局部氧化应激、促炎细胞因子、蛋白水解酶的产生和晚期糖基化终末产物(AGEs)的积累,进而加快骨性关节炎进程。因此,本文就糖尿病和高糖血症对骨性关节炎的影响及其可能机制进行整理总结。

[关键词] 骨性关节炎;糖尿病;高血糖症;代谢综合征

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Role of diabetes or hyperglycemia in osteoarthritis

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Abstract: Osteoarthritis (OA) is the most common osteoarticular disease, which seriously endangers human health. With the deepening of the understanding of OA, people gradually realized that metabolic syndrome (MetS) caused by metabolic disorders of protein, fat, carbohydrate and other substances was closely related to the course of OA. Type 2 diabetes and hyperglycemia are considered as important risk factors for the progression of OA, and their influence on OA are attracting more and more attention. A large number of in vitro and in vivo experiments have shown that high glucose exposure has local toxicity to joint tissues, which can lead to local oxidative stress, the production of proinflammatory cytokines, proteolytic enzymes and the accumulation of advanced glycosylation products (AGE) and accelerate the progression of OA. In this review, the potential mechanisms and the effects of diabetes or hyperglycemia on OA are summarized.

Keywords: osteoarthritis; diabetes; hyperglycemia; metabolic syndrome

骨性关节炎(osteoarthritis, OA)是导致关节疼痛、僵硬和残疾的最常见骨关节疾病,严重危害人类健康,并对公共健康提出巨大挑战[1]。骨性关节炎是慢性退行性关节疾病,其病理特征包括软骨丢失、骨质增生、骨硬化和关节滑膜炎症。在很长一段时间,老龄和机械应力被认为是骨性关节炎的风险因素。但随着对骨性关节炎认识的加深,人们逐渐意识到蛋白质、脂肪、碳水化合物等物质发生代谢紊乱所导致的代谢综合征(metabolic syndrome, MetS)与骨性关节炎的病程有密切联系,从而定义了一种新的骨性关节炎亚型,即代谢性骨性关节炎,其范围比肥胖相关性骨性关节炎更为广泛[2]。有荟萃分析报告显示,2型糖尿病是骨性关节炎的风险因素[3-4]。过去几年里的体内外实验进一步研究了高血糖和胰岛素抵抗对关节组织的影响,结果提示高糖暴露对关节组织具有局部毒性,可导致局部氧化应激、促炎细胞因子、蛋白水解酶的产生和晚期糖基化终末产物(advanced glycation end products, AGEs)的积累[5-7]。此外,一项关于糖尿病患者滑膜组织的研究发现,糖尿病患者的滑膜组织具有胰岛素抵抗性,因此降低了胰岛素的抗炎和抗降解作用[8]。基于目前的研究,本文就糖尿病和高糖血症对骨性关节炎的影响及其可能机制综述如下。

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1 糖尿病和高糖血症对骨性关节炎的影响

早在上个世纪60年代,人们就开始关注高糖血症和骨性关节炎之间的关系[9]。直到今天,越来越多的大规模流行病学研究开始关注高血糖对骨性关节炎的影响,其中有研究得出了血糖水平升高与骨性关节炎发病率之间存在正相关的结论[9-13],但也有研究发现二者之间不存在明确的相关性[14]。由于研究结果仍存争议,并很可能受年龄和BMI等其他因素所影响,因此目前还不能确定高血糖是骨性关节炎的一个独立危险因素,但是综合来看,骨性关节炎和高血糖之间可能存在一个潜在的独立相关关系[15]。

有体内外试验研究发现,高血糖可引起骨性关节炎相关的局部和全身毒性反应[5-7,16]。在局部,高血糖通过氧化应激和AGEs介导对软骨产生有害影响,可导致基质硬化、软骨下骨破坏和软骨细胞功能障碍等。具体来说,高血糖降低了脱氢抗坏血酸进入软骨细胞

的转运,影响了Ⅱ型胶原的合成,提高了活性氧和炎症介质的水平,从而介导了软骨的破坏[17-20]。AGEs 也可以在软骨细胞膜上结合其受体 RAGE,从而触发促炎和促降解介质的过度表达[21-23]。高血糖引起的全身性低度炎症与软骨丢失直接相关,并且可加剧氧化应激,导致局部毒性[24]。而葡萄糖积累引起的肌肉运动和感觉功能障碍可能是导致骨性关节炎发病的另一个系统性因素[25]。骨性关节炎患者可出现肌无力和关节振动感觉丧失等症状[26]。有研究通过对比髋关节骨性关节炎患者和健康人群的振动感觉发现,振动感觉功能障碍可能存在于局部或全身,这表明周围神经系统受到了系统性的影响,而糖尿病神经病变是一种系统性的周围神经系统改变,可能导致骨性关节炎患者出现肌肉无力和关节松弛等症状[27]。

2 糖尿病和高糖血症对关节软骨的影响

目前关于高糖对关节组织作用的认识主要集中在高糖对软骨的影响。软骨是一种无血管、无淋巴、无神经支配的组织,处于低氧环境,通过关节腔与软骨下骨和滑膜液相连接而获得营养。软骨细胞是软骨组织中的单一细胞,属于糖酵解细胞,表达葡萄糖转运蛋白(glucose transporter,GLUT),特别是 GLUT-1、GLUT-3 和 GLUT-9[28]。软骨细胞能够感知环境中的葡萄糖浓度,并调节 GLUT 的表达及其与细胞膜的结合水平。在葡萄糖缺失的条件下,正常软骨细胞 GLUT-1 表达量增加并与细胞膜结合;反之,在高糖条件下正常软骨细胞 GLUT-1 表达量则减少。然而,正常软骨细胞适应局部葡萄糖水平的能力在骨性关节炎过程中逐渐减弱,这是导致高葡萄糖摄取和潜在葡萄糖毒性的原因[29]。并且,GLUT 的表达受多种因素影响,在促炎因子 TNF-α 和 IL-1β 的刺激下可通过激活磷酸激酶 C 上调 GLUT 的表达,同时,GLUT 在骨性关节炎有关或者高表达的代谢和缺氧因子的影响下也可上调[30]。

局部高糖环境的刺激亦会减少间充质干细胞、肌肉干细胞和脂肪干细胞的软骨分化,这可能会进一步降低骨性关节炎中已经下降的软骨再生潜能[31-33]。与非糖尿病人群的脂肪干细胞相比,糖尿病患者脂肪干细胞自发的软骨分化潜能更低。此外,慢性高糖环境对软骨细胞的代谢有不良影响。在 IL1-β 刺激下,糖尿病患者的软骨比非糖尿病人群的软骨可产生更多的 IL-6 和 PGE2,而自噬和血红素氧化酶表达则减少[34-35]。同时,在高糖环境下 IL1-β 可通过氧化应激途径导致软骨细胞产生更多的 IL-6 和 PGE2[35]。

同样,高糖环境能诱导骨性关节炎患者软骨细胞产生的 MMP 增加,并减少Ⅱ型胶原的生成。而过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors,PPARs)γ-受体激动剂可以抑制高糖对软骨细胞的促炎和促降解的作用[36]。在高糖环境的细胞和组织中,AGEs 也可能参与糖尿病相关的骨性关节炎。在体外,AGEs 通过 AGE 受体(RAGE)和 toll 样受体诱导软骨细胞的促炎和促分解代谢表型。这些软骨受体的激活诱导了 PPARs-γ 的下降,并且激活了 Nf-κB 和 MAP 激酶通路[37-39]。一项动物体内研究表明,AGEs 的集聚随着年龄的增长而增加,使得骨关节炎软骨的机械性能发生变化,与非糖尿病大鼠相比,AGEs 在糖尿病链脲霉素(streptozotocin,STZ)大鼠的软骨中积累,进一步提示高糖血症与骨性关节炎的相关性[36]。

许多使用 1 型(STZ 模型)或 2 型(高脂肪饮食)糖尿病模型的体内动物实验探索了糖尿病对骨性关节炎的作用。Atayde 等[40]首次报道了 STZ 诱导的 1 型糖尿病大鼠模型尽管有更低的体质量,但是却有更严重的自发性软骨基质丢失。这一结果在后来被 El Karib 等[41]的研究再次证实,并进一步发现持续的 STZ 诱导可导致显著的大鼠关节软骨损伤,且这种软骨损伤是可以通过胰岛素或胰岛素类似物进行预防的,而吡格列酮作为 PPARs-γ 的受体激动剂可能是通过抑制系统性炎症减轻 STZ 糖尿病小鼠的骨性关节炎。此外,Onur 等[42]发现 2 型糖尿病大鼠亦可发生自发性的骨性关节炎。而在 2 型糖尿病伴内侧半月板不稳定骨性关节炎的小鼠模型中,通过使用雷帕霉素激活自噬,可阻止糖尿病诱导骨性关节炎的进展[43]。

3 糖尿病和高糖血症对关节滑膜的影响

目前,关于高糖血症和滑膜关系的研究较少。高糖通过氧化应激、PI3K、Akt、c-Jun 和 AP-1 等信号通路增加人滑膜成纤维细胞中血管内皮生长因子(VEGF)等促血管生成因子的表达[44]。而滑膜组织的血管化被认为是诱导促炎细胞的重要原因。一些糖尿病动物模型的体内研究表明,糖尿病动物的滑膜组织更容易诱发滑膜炎症[43]。这些结果与使用超声检查发现的糖尿病患者膝关节骨性关节炎滑膜炎症重于非糖尿病患者的临床观察一致[45]。Hamada 等[8]也证实了这一结果,其研究表明 2 型糖尿病肥胖小鼠在高脂饮食下产生自发性骨性关节炎,部分是由肥胖糖尿病小鼠滑膜过度分泌 TNF 介导的。此外,该研究还发现人骨性关节炎成纤维细胞样滑膜细胞(fibroblast like-synoviocytes,FLS)表达了胰岛素受体,并对胰岛素产生应答,从而部分抵消了 TNF 的促炎、促降解作用[8]。由于糖尿病患者 FLS 的胰岛素反应较非糖尿病患者减弱,TNF 的表达较非糖尿病患者高,再加上糖尿病患者的胰岛素

抵抗状态,其 FLS 对局部过量产生的 TNF 更敏感。

4 糖尿病和高糖血症对软骨下骨的影响

众所周知,糖尿病和高糖血症可以减少骨骼重塑,因此大多数关于骨骼和糖尿病之间关系的研究都是在骨质疏松症的背景下发生的,而关注软骨下骨与糖尿病特异性的研究很少。但有研究通过 MRI 检测发现,空腹血糖浓度与女性膝关节骨髓病变(bone marrow lesions,BML)相关[46],而 BML 被认为是可用于预测骨性关节炎结构损伤的因素[47]。在晚期膝关节骨性关节炎合并糖尿病、高血压需要进行关节置换术的患者中,软骨下骨丢失表现为较低的骨密度和较高的孔隙率,而与体质量无关[48]。而另一项研究发现,AGEs 在糖尿病患者软骨下骨的累积多于非糖尿病患者,这可能会影响软骨下骨的机械抗力,并表现为促炎作用[49]。

5 展望

骨性关节炎是一种多因素的全关节、全身性疾病,其发病机制与各种物质的代谢因素密切相关[50]。将代谢性骨性关节炎作为骨性关节炎的一种亚型,可以指导临床上更好地进行个性化骨性关节炎治疗,其中糖代谢作为物质和能量代谢的基础,对生命活动本就非常关键。因此,进一步关注糖代谢异常在骨性关节炎病程中的作用有助于加深对骨性关节炎的认识,对指导临床工作具有重要意义。

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