

脂代谢紊乱与骨性关节炎的关系研究进展

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【摘要】 骨性关节炎的发病机制与年龄相关的退行性病变、创伤、代谢等因素有关,其中脂代谢紊乱在骨性关节炎的发生发展中扮演关键的角色。本文主要对脂代谢紊乱与骨性关节炎的关系进行综述,着重阐述可能的相关机制。在脂代谢过程中,脂肪因子促进关节发生炎症反应、激活蛋白水解酶,加速关节软骨的破坏;胆固醇逆转运途径异常导致胆固醇在软骨细胞内超负荷积累,致使软骨细胞肥大、软骨骨化,加重软骨退变的严重程度;低密度脂蛋白氧化能够促进软骨骨赘形成、促进炎症反应及加速软骨细胞凋亡,在骨性关节炎的病理改变中起到关键作用。本文着重介绍脂代谢紊乱与骨性关节炎发生发展的作用机制,为探索骨性关节炎的治疗提供新的思路。

【关键词】 脂代谢; 骨性关节炎

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骨性关节炎(osteoarthritis, OA)是一种慢性、关节退行性疾病,与性别、年龄、关节损伤、遗传及代谢综合征相关^[1]。近年来,多项研究表明代谢因素与 OA 密切相关,代谢综合征包括肥胖、胰岛素抵抗型糖尿病、脂代谢紊乱和高血压病等^[2],其中肥胖、胰岛素抵抗型糖尿病与 OA 的相关性已经被证实^[3,4],有关脂代谢紊乱与 OA 联系的研究较少。本文主要阐述脂代谢紊乱与骨性关节炎发生发展的可能作用机制及相关治疗展望。

脂代谢紊乱的发病机制

血脂是血浆中的中性脂肪和类脂的总称,其中中性脂肪包括甘油三酯和胆固醇,类脂包括磷脂、糖脂、固醇、类固醇,血脂是生命细胞的基础代谢必需物质,广泛存在于人体中。血脂和蛋白质组成脂蛋白,脂蛋白分为乳糜微粒、极低密度脂蛋白、低密度脂蛋白(low density lipoprotein, LDL)、高密度脂蛋白。脂代谢紊乱临床分型可分为高胆固醇血症、高甘油三酯血症、混合型高脂血症及低高密度脂蛋白胆固醇血症^[5]。脂质来源增多及脂质分解代谢减少是引起脂代谢紊乱的主要原因,脂质分解代谢异常原因包括 LDL 转运与分解代谢异常、高密度脂蛋白介导胆固醇逆转运异常、乳糜微粒和极低密度脂蛋白分解代谢异常^[5]。探究脂肪因子及脂质代谢途径异常引起 OA 的相关机制有助于为 OA 的治疗提供新的思路。

脂肪因子与骨性关节炎

脂肪因子包括瘦素、脂联素、内脂素、抑制素等,基本由脂肪细胞释放,具有控制血压、参与止血、消耗能量、参与细胞代谢与炎症反应等功能。除了脂肪细胞,其他的关节组织包括软骨、滑膜、骨赘及半月板等也能产生特定的脂肪因子,尤其在 OA 患者的关节组织中^[6]。脂代谢紊乱能促进脂肪因子的分泌,研究发现高脂血症的患者会分泌大量的脂肪因子,这些脂肪细胞因子可通过与基质金属蛋白酶(matrix metalloproteinase,

MMP)-9 和 MMP-13 等软骨基质降解酶因子的协同作用加速骨关节炎后期软骨退变过程,其本身也可作为促炎因子,参与骨性关节炎的炎症反应过程,与 OA 的病理过程密切相关^[7]。

一、瘦素

瘦素对软骨细胞增殖具有分解代谢作用,可以促进软骨细胞分泌更高水平的软骨降解关键介质如肿瘤坏死因子- α 、白细胞介素-1 β 、白细胞介素-6、白细胞介素-8、生长相关的癌基因及单核细胞趋化蛋白-1^[8]。软骨的合成代谢与成纤维细胞生长因子有关,而瘦素可以通过下调成纤维细胞生长因子进而影响软骨的合成代谢^[9]。有研究发现 OA 软骨下骨成骨细胞瘦素异常增多,而瘦素合成的增加能使成骨细胞中的转化生长因子- β 1、骨钙蛋白、碱性磷酸酶表达异常,进而引起 OA 软骨下骨成骨细胞功能异常,促进骨赘生成^[10]。关节软骨主要由蛋白聚糖和 II 型胶原纤维组成,软骨细胞嵌入其内。瘦素能上调 MMP-1、MMP-3 和 MMP-13 的表达,促使在 OA 患者滑液中的浓度上升,从而促进软骨蛋白聚糖和胶原蛋白的降解,导致软骨的破坏^[11]。软骨蛋白聚糖对软骨胶原组织具有保护作用,可使软骨避免发生退变,有研究发现,人软骨细胞中的瘦素使蛋白聚糖酶(ADAMTS-4, ADAMTS-5, ADAMTS-9)基因表达增加,而使软骨降解产物-蛋白聚糖减少,进而加速软骨退变^[12]。

二、内脂素

内脂素可以通过产生炎症介质肿瘤坏死因子- α 、白细胞介素-1 β 、白细胞介素-6 途径和破坏维持软骨细胞表型所需相关蛋白表达的方式参与 OA 的病理过程^[13-15]。此外,内脂素还可以调节去乙酰化酶-1,而去乙酰化酶-1 与软骨生物学及 OA 的发病机制有关^[16]。

三、脂联素

脂联素通过刺激软骨和软骨细胞产生白细胞介素-6、白细胞介素-8、MMP-1、前列腺素 E2、一氧化氮合酶 2 及血管内皮生长因子引起炎症反应^[17]。脂联素还可增加软骨细胞中的血管细

胞黏附分子-1 的表达,使炎性 OA 关节软骨的降解过程持续存在^[18]。

四、抑制素

抑制素可以下调软骨细胞中 II 型胶原蛋白和聚蛋白多糖的表达,并且上调蛋白聚糖酶 4 (ADAMTS-4)、MMP-1 和 MMP-3 的表达,加速软骨的破坏^[19]。抑制素还可以刺激软骨细胞产生炎症因子,如白细胞介素-6、肿瘤坏死因子- α 、前列腺素 E2 等,加重关节的炎症反应^[20]。

胆固醇与骨性关节炎

脂代谢紊乱更容易发展高胆固醇血症,与正常人相比,OA 患者的关节滑膜液中含有较高的胆固醇和胆固醇晶体^[21],高胆固醇血症已经被证实与 OA 的发生发展存在联系^[22],高胆固醇血症主要是指胆固醇和低密度脂蛋白的升高。在小鼠模型的实验中发现采用高胆固醇饮食会增加自发性软骨损伤,滑膜巨噬细胞中高胆固醇聚集可以增加软骨骨赘的形成,诱发或者加重 OA^[23-24]。软骨中胆固醇的升高与胆固醇逆转途径异常有关,胆固醇逆转是指机体将外周除供生理需求外的多余胆固醇通过高密度脂蛋白运回肝脏内进行代谢的生理过程^[25],即细胞内游离胆固醇和磷脂通过三磷酸腺苷结合盒转运子 A1 (ATP-binding cassette transporter A1, ABCA1) 到达细胞外,与贫脂载脂蛋白 AI 结合形成不成熟的高密度脂蛋白,随后不成熟的高密度脂蛋白经卵磷脂胆固醇酰基转移酶和固醇酯转运蛋白作用酯化形成成熟的高密度脂蛋白。成熟的高密度脂蛋白通过与清道夫受体-B1 结合,然后在肝脏内进一步代谢成胆汁酸排出体外。胆固醇逆转过程中的异常会导致外周组织胆固醇沉积,而关节软骨中也存在胆固醇逆转过程,胆固醇异常引起 OA 的发病机制可能与软骨中胆固醇相关转运基因的表达下降有关,该基因的表达减少可以导致软骨细胞中脂质沉积,进而导致细胞毒性增加,诱发 OA 的发生^[26]。高密度脂蛋白是维持脂代谢平衡的关键蛋白,促进胆固醇逆转过程,从而提高胆固醇流出率,流行病学研究表明,与正常人相比,OA 患者的高密度脂蛋白胆固醇明显减少,说明高密度脂蛋白与 OA 的发病机制存在潜在的联系^[27],高密度脂蛋白是 OA 发病机制中的关键部分^[28]。

一、载脂蛋白 AI

载脂蛋白 AI 是高密度脂蛋白的主要结构蛋白,在胆固醇逆转中十分重要^[29]。有研究认为载脂蛋白 AI 能促进巨噬细胞胆固醇逆转过程,促进巨噬细胞胆固醇外流,具有抗动脉粥样硬化的功能,能抑制或逆转粥样硬化过程^[30]。最近也有研究通过静脉注射模拟载脂蛋白 AI 于动脉粥样硬化患者,发现模拟载脂蛋白 AI 能增加高密度脂蛋白介导的胆固醇的外流、减少脂蛋白脂质过氧化^[31-32]。高胆固醇诱导的脂质沉积引起软骨损害可能与动脉粥样硬化具有类似的机制^[33],有研究发现 OA 患者的载脂蛋白 AI 明显减少^[34]。但有关载脂蛋白 AI 是否也能通过促进软骨细胞胆固醇的流出从而对抗 OA 的进展的研究甚少,若增加关节中载脂蛋白 AI 含量能促进软骨胆固醇转运,这将为 OA 的治疗提供新方法。

二、三磷酸腺苷结合盒转运子 A1

ABCA1 是胆固醇逆转过程中的关键基因,在起始环节发挥作用,参与细胞内胆固醇外流的调节。该基因异常会影响胆

固醇逆转,进而造成细胞胆固醇沉积^[35]。

1. 过氧化体增殖物激活型受体

过氧化体增殖物激活型受体 (peroxisome proliferator-activated receptor, PPAR) 是一种配体依赖性的转录因子,主要由 PPAR α 、PPAR γ 和 PPAR β/δ 3 种亚型组成,属于核受体超家族。PPAR 激动剂能促进 ABCA1 mRNA 的表达,从而增加胆固醇流出。其中 PPAR γ 和 PPAR α 参与调节脂代谢,激活两者能改善 OA 脂代谢紊乱^[36]。有研究通过敲除 PPAR γ 基因的小鼠模拟实验研究过氧化体增殖物激活型受体 γ /雷帕霉素靶蛋白信号通路异常对小鼠关节软骨的影响,发现 PPAR γ 基因敲除会使小鼠软骨细胞退变及凋亡现象明显,同时软骨自噬基因表达增多^[37]。PPAR γ 的表达在 OA 的关节组织中是减少的,PPAR γ 激动剂能减少软骨细胞和滑膜细胞的促炎因子及分解代谢介质的产生,从而对软骨具有保护作用。

2. 肝 X 受体

肝 X 受体 (liver X receptor, LXR) 也属于核激素受体超家族,LXR 位于 PPAR γ 的下游,能诱导 ABCA1 基因的转录。与正常软骨相比,OA 患者软骨细胞中的 LXR、ABCA1 的表达水平明显减少,激动 LXR 可通过上调 ABCA1 表达,促进胆固醇流出,促进 OA 软骨细胞胆固醇流出,消除软骨细胞内脂质沉积^[26]。

PPAR 反应元件存在于 LXR 基因启动子,激动 PPAR α 或 PPAR γ 能促进 LXR mRNA 表达,PPAR 激动剂的作用途径通过活化 LXR 因子,诱导 ABCA1 基因转录^[38]。LXR/PPAR/ABCA1 信号通路参与 OA 软骨胆固醇逆转,通过激活 PPAR、LXR 有望为 OA 提供基因靶向治疗。

3. 微小 RNA-33a

有研究表明固醇调节元件结合蛋白-2 是调节胆固醇代谢的重要转录因子,可以激活胆固醇代谢和生物合成基因,参与 OA 的发病机制。在 OA 胆固醇合成的观察中发现固醇调节元件结合蛋白-2 通路通过磷脂酰肌醇 3 激酶/蛋白激酶 B (PI3K/Akt) 途径被转化生长因子- β 激活,从而增加了胆固醇的合成^[39]。微小 RNAs (microRNAs, miRNAs) 可以调控 OA 中相关基因的表达^[40],miRNA-33a 是胆固醇和脂肪酸代谢的主要调控因子之一,位于人类固醇调节元件结合蛋白-2 基因的内含子中,能通过固醇调节元件结合蛋白-2 基因下调胆固醇转运基因 ABCA1 水平,从而调控胆固醇的流出。因此通过抑制内源性 miRNA-33a,可以促进 ABCA1 的表达从而治疗血脂异常^[41]。但是 miRNA-33a 在 OA 中能否对胆固醇的调控起到作用至今尚未明确,有研究发现 miRNA-33a 在 OA 软骨细胞中的表达水平较正常软骨明显增高,在转化生长因子- β 1 的诱导下调控 OA 软骨细胞胆固醇合成及流出相关基因^[42]。抑制 miRNA-33a 可能有助于减少 OA 的发生发展,miRNA-33a 将成为一种治疗 OA 的新型的靶点。

三、氧化低密度脂蛋白

高胆固醇血症的另一个特点,是低密度脂蛋白的清除减少^[43],在小鼠模型实验的研究中发现高 LDL 水平会促进滑膜炎及异位成骨,促进 OA 的发生发展^[44]。近年来流行病学和实验研究表明,脂质过氧化参与了 OA 的发病机制^[22],尤其是氧化低密度脂蛋白 (oxidized LDL, ox-LDL)。许多因素可以诱导低密度脂蛋白氧化,如鞘磷脂酶,活性氧及脂酶等,其中活性氧是主要因素^[45]。oxLDL 可以被内皮细胞、成纤维细胞和巨噬细

胞,通过清道夫受体吸收,如清道夫受体-A、凝集素样氧化低密度脂蛋白受体 1(lectin-type oxLDL receptor 1, LOX-1),不同细胞吸收 ox-LDL 后的反应不同。ox-LDL 与 OA 的滑膜活化、骨赘形成、炎症反应及软骨细胞凋亡有关。研究表明 ox-LDL 可以减少软骨细胞蛋白多糖的合成及关节软骨细胞的活力^[46],ox-LDL 通过清道夫受体,如 LOX-1,导致激活和分泌不同的蛋白酶和炎症介质^[24]。OA 关节软骨 ox-LDL 和 LOX-1 的含量与软骨损伤程度相关,且与正常软骨细胞相比有明显的升高^[47]。软骨细胞外基质的破坏和关节炎症反应与 ox-LDL/LOX-1 通路存在一定的联系,ox-LDL 通过不同的受体被巨噬细胞吸收,尤其是 LOX-1,并诱导巨噬细胞表型向促炎型转变,产生炎症和趋化因子,刺激单核细胞涌入,导致炎症加重,从而促进软骨的损伤^[24,48]。有研究在 LDL 受体缺乏鼠模型中发现 ox-LDL 能激活合成代谢因子如转化生长因子- β ,从而导致骨赘形成,并且 ox-LDL 还可以刺激纤维母细胞产生分解酶如 MMP-1, MMP-3,从而导致胶原蛋白减少,这表明 ox-LDL 通路可能与骨性关节炎的发病机制有关^[44,49]。在 OA 中软骨细胞凋亡的增多被认为是软骨关节退变的标志^[50],有研究表明包括肿瘤坏死因子- α 在内的许多刺激都参与了软骨细胞凋亡过程^[51],ox-LDL 可以促进肿瘤坏死因子- α 通过自噬相关通路介导软骨细胞死亡,从而参与 OA 的病理过程^[52]。

骨性关节炎的治疗及展望

目前骨性关节炎的治疗原则包括药物改善疼痛、晨僵等症状、软骨保护剂延缓细胞外基质降解进程。已有研究表明^[53],如非甾体类抗炎药、糖皮质激素等通过抑制炎症因子,减轻炎症反应,从而缓解疼痛等不适症状,透明质酸钠作为软骨保护剂的代表性药物,适用于软骨磨损严重的患者,通过关节给药保护和润滑关节、促进软骨修复作用及降低炎症反应。近年来,多项研究证明,OA 不仅是与年龄相关的软骨退化性疾病,也被证明是一种代谢性疾病^[54]。他汀类药物具有保护关节软骨的作用,可以延缓软骨细胞退变,防止细胞外基质降解,这可能与它汀促进胆固醇逆转运机制相关^[55]。但由于长期口服他汀类药物会导致血糖异常、肌病、肝酶异常、记忆和认知障碍等严重不良反应,选择合适的给药途径,缩短治疗疗程,以降低不良反应增强药物疗效是未来他汀用于 OA 治疗的研究重点之一。考虑到 OA 机制的多样性,还可以通过抑制关节滑膜中瘦素、脂联素等脂肪因子,刺激载脂蛋白 AI 表达、降低低密度脂蛋白的氧化作用,为 OA 的治疗提供精准靶向治疗途径。

综上所述,骨性关节炎是一种多因素参与的慢性代谢性疾病,脂代谢紊乱干扰胆固醇逆转运的过程。超负荷的脂质堆积在软骨细胞中,导致细胞肥大、软骨骨化等病理状态,进一步加剧 OA 细胞外基质降解进程。因此,脂代谢紊乱与骨性关节炎密切相关,调控脂代谢紊乱相关的软骨细胞外基质脂质代谢微环境已作为新的 OA 诊疗思路。

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Compression socks during exercise

BACKGROUND AND OBJECTIVE While compression garments have been used to improve circulation, similar garments are worn during sports to improve performance. This study assessed the effect of compression socks worn during a five km run.

METHODS This counterbalanced, crossover design study included 12, well-trained, male runners. All were asked to maintain constant dietary patterns prior to each of three sessions. At each session, the runners performed a standardized warm-up, followed by a five km timed trial and a one-hour recovery before a second warm-up and five km timed trial.

The runners completed one session wearing compression socks for the first warm-up and timed trial and one session with no compression socks. Blood lactate concentration was measured, with samples collected at completion of each stage of the warm-up protocol, as well as three minutes after completion of the runs.

RESULTS The declines in run performance between the first and second runs were moderate in the control group and significantly greater than in the compression stockings group ($P < 0.01$). No significant difference was found between the conditions on measures of oxygen consumption, blood lactate or calf volume.

CONCLUSION This study of well-trained runners found that wearing compression stockings while running can reduce deterioration in performance one hour later.

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