膝骨关节炎与肌少症的关系及膝骨关节炎合并肌少症治疗方法的研究进展

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摘　要　膝骨关节炎（knee osteoarthritis,KOA）是肌少症发生的危险因素,而肌少症能够诱发 KOA 并加速 KOA 发展,二者在影响因素、病理表现和发生机制方面存在密切联系。本文对 KOA 与肌少症的关系及 KOA 合并肌少症治疗方法的研究进展进行了综述。

关键词　骨关节炎,膝;肌肉衰减征;运动疗法;饮食疗法;中医药疗法;综述

膝骨关节炎（knee osteoarthritis,KOA）以膝关节疼痛和功能障碍为主要临床表现,主要病理特征包括软骨缺失、软骨下骨硬化、半月板磨损、膝关节间隙改变等[1]。肌肉力量和质量的降低会诱导 KOA 发生、加剧 KOA 发展[2-3]。肌少症是一种以四肢骨骼肌力量和质量缓慢下降为主要特征的综合征。60 ~ 70 岁老年人群中,肌少症的患病率为 5% ~ 13%[4]。肌少症患者股四头肌横截面积较正常人群减少 12% ~ 19%[5],而肌力较正常人群下降 20% ~ 40%[6]。相关研究[7-9]的结果表明,KOA 与肌少症之间存在密切联系。本文对 KOA 与肌少症的关系及 KOA 合并肌少症治疗方法的研究进展进行了综述。

1　KOA 与肌少症的关系

1.1　KOA 与肌少症的共同影响因素

1.1.1　炎症因子　炎症因子是肌少症发生的危险因素之一。随着机体衰老,机体长期处于慢性炎症状态,血液中的白细胞介素（interleukin,IL）-6、肿瘤坏死因子（tumor necrosis factor,TNF）-α 等炎症因子含量增加,引起肌肉分解[10]。Rom 等[11]研究发现,在泛素-蛋白酶体系统（ubiquitinproteasome system,UPS）中,肌萎缩蛋白和肌肉环指蛋白 1 可调控肌肉中蛋白质的分解。TNF-α 等炎症因子能够促进肌萎缩蛋白与肌肉环指蛋白 1 的表达,进而促进肌肉的分解,导致肌肉量减少[10]。Kauppinen 等[12]研究发现,IL-1 与 TNF-α 还可以通过核因子-κB（nuclear factor-κB,NF-κB）信号通路促进肌肉分解。

炎症因子能够诱发 KOA 发生或加剧 KOA 发展。肌肉中炎症因子含量增加会引起肌肉僵硬,进而导致关节活动障碍;IL-1、TNF-α 等炎症因子能够激活转化生长因子 β 活化激酶 1,进而诱导细胞外基质中聚蛋白多糖的降解,导致软骨细胞外基质降解,引起关节软骨损伤,加剧 KOA 发展[13]。Ismail 等研究[14-15]发现,部分炎症因子可激活 NF-κB 信号通路,促进肌肉和关节软骨分解。

1.1.2　胰岛素抵抗　骨骼肌是胰岛素的重要靶器官之一。生理状态下,胰岛素可激活磷脂酰肌醇 3 激酶/蛋白激酶 B（protein kinase B,AKT）信号通路,抑制体内半胱氨酸天冬氨酸蛋白酶（cysteine aspartic acid specific protease,Caspase）-3 的活性和 UPS,从而维持肌肉的质量[16]。此外,胰岛素还可通过 p38 促分裂原活化的蛋白激酶、哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin,mTOR）/p70S6 激酶途径抑制蛋白水解,维持肌肉的质量[17-19]。当胰岛素抵抗发生时,Caspase-3 与 UPS 被激活,促进肌肉分解,导致肌少症的发生[16]。

胰岛素抵抗可通过加快滑膜细胞及软骨细胞的损伤,诱导 KOA 发生。有研究[20]发现,胰岛素可以与滑膜细胞上的受体结合,抑制膝关节内的炎症反应,发挥保护滑膜细胞的作用;当胰岛素抵抗发生时,膝关节内炎症反应无法被抑制,关节内 TNF-α 表达量增加,进一步损害滑膜细胞。此外,发生胰岛素抵抗的患者,往往并发高胰岛素血症,血液中胰岛素含量增高会导致关节软骨破坏,进而诱发或加重 KOA[21]。血液中胰岛素含量的增加会导致 AKT 与 mTOR 处于高激活状态,抑制叉头框蛋白 O 激活自噬体,导致自噬体数量减少[13]。自噬体具有清除细胞内受损物质、

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稳定细胞内微环境的作用,自噬体数量减少会严重降低软骨细胞的功能,与 KOA 发展密切相关[22-23]。

1.1.3　肥胖　脂联素是脂肪细胞释放的脂肪因子之一,具有调节食欲和促进机体能量消耗的作用;脂联素能够激活 AMP 活化蛋白激酶(AMP-activated protein kinase,AMPK)信号通路促进脂肪酸氧化,增加骨骼肌对胰岛素的敏感性[24]。此外,脂联素还能抑制 TNF-α 和 IL-γ 的分泌,减少机体炎症反应[25]。当机体处于肥胖状态时,血清中脂联素水平下降,会降低骨骼肌对胰岛素敏感性、增加机体的炎症反应,最终导致骨骼肌质量下降,诱导肌少症发生或加重肌少症发展[24-25]。

肥胖导致人体关节承受重力增加,加速关节内软骨磨损;软骨磨损会引起关节无菌性炎症的发生,导致关节内炎症因子积累,进而激活转化生长因子-β-激活激酶 1 引起聚蛋白多糖降解,导致关节软骨破坏,加剧 KOA 发展[13,26]。

1.2　KOA 与肌少症的相互影响　研究表明,肌少症与 KOA 的严重程度之间存在相关性[5]。随着肌肉力量和质量下降,关节的生物力学结构会发生变化,导致关节稳定性降低,进而加速关节软骨的退化。动物实验研究发现,肌肉萎缩会导致小鼠关节软骨下骨微观结构发生改变[8],增加兔关节内炎症细胞的数量[27]。人体对疼痛的忍耐程度与肌肉质量相关,肌少症会导致人体对疼痛的耐受度降低[28]。Andrews 等[29-30]研究发现,四肢肌肉总质量下降的 KOA 患者的膝关节疼痛更为严重。因此,肌少症能够诱发 KOA 并加速 KOA 发展,同时也是加重 KOA 患者疼痛的重要因素。

研究发现,KOA 患者肌肉中Ⅱa/x 型纤维、细胞外基质的含量较健康人多,卫星细胞密度较健康人明显降低[31]。Ⅰ型肌纤维向Ⅱa/x 型肌纤维转化表明肌肉力量和质量的下降;KOA 患者的股外侧肌中的Ⅱa/x 型肌纤维百分比随 KOA 的发展逐渐增加,进而导致肌少症的发生[31]。骨骼肌细胞外基质的增多会降低肌肉力量[32],而卫星细胞在促进肌肉修复再生[33]、减少细胞外基质[34]中发挥关键作用。Tsukada 等[35]采用双侧 CT 分析 KOA 患者的肌肉体积,结果发现 KOA 患者膝关节周围肌肉体积明显减少。Cunha 等[36]研究发现,KOA 模型小鼠股四头肌横截面积较对照组明显减少。因此,KOA 是肌少症发生的危险因素,二者的病理表现与发生机制存在密切联系。

2　KOA 合并肌少症的治疗方法

2.1　运动疗法　久坐不动的生活方式与软骨病变密切相关,运动疗法对于 KOA 和肌少症均具有良好疗效。Bricca 等[37]研究发现,运动后血清中 C 反应蛋白、TNF-α 等炎症因子及Ⅱ型胶原 C 端肽、软骨寡聚基质蛋白等软骨破裂相关标志物的含量均降低。重负荷高强度阻力训练可以增加骨骼肌的质量和力量[38],是防治肌少症的重要干预措施。但 KOA 患者对重负荷高强度阻力训练的依从性较差,治疗效果并不理想。游泳、骑自行车等低负荷阻力训练能够缓解 KOA 患者膝关节疼痛,改善膝关节功能,且患者依从性好。Alkatan 等[39]研究发现,KOA 患者接受游泳或骑自行车运动疗法治疗后,患者 6 min 内步行距离显著增加,膝关节周围肌肉力量显著增强。Takarada 等[40-41]研究发现,血流受限训练联合低负荷运动能够显著增加肌肉细胞内 H^+、乳酸、腺苷一磷酸等代谢物的含量,并促进垂体分泌生长激素;且运动过程中肌肉组织消耗大量氧气,能够促进肌纤维的转化,进而提高肌肉中Ⅰ型肌纤维的比例,增强肌肉组织的力量。Fujita 等[42]的研究结果表明,健康老年人在采用血流受限训练联合低负荷运动训练 3 h 后,肌肉蛋白合成量增加,血清中 AKT、mTOR 及 p70S6K 的磷酸化水平升高。采用运动疗法治疗 KOA 合并肌少症,疗效确切。但临床上尚无统一的治疗方法,常根据患者自身情况进行个性化定制。常用的运动疗法有游泳、骑自行车、血流受限训练联合低负荷运动、太极拳、五禽戏、八段锦、易筋经、股四头肌肌力训练联合坐立行姿态矫正训练、股四头肌等长收缩联合自主训练等[39,43-50]。部分运动疗法的具体方案见表 1。这些针对 KOA 患者的运动疗法均能够显著改善患者的肌肉力量和质量。然而,对于合并 KOA 的肌少症型肥胖患者,应慎重选择运动治疗,如选择运动治疗,需在康复医师及营养师的指导下进行,以免加重肌肉组织的流失。

2.2　饮食疗法　饮食疗法是改善肌肉状态的重要方法,补充充足的必需氨基酸、蛋白质、维生素 D 等营养成份是维持肌肉质量的必要条件[51]。欧洲临床和营养代谢学会推荐,老年人群每日应补充 1.2 ~ 1.5 $g \cdot kg^{-1}$ 富含必需氨基酸的优质蛋白[52]。Manoy 等[53-54]研究

表 1　部分运动疗法的具体方案

运动名称	运动频次	单次运动时间/min	疗程/周
游泳[39]	每日 1 次,每周 3 次	45	12
骑自行车[39]	每日 1 次,每周 3 次	45	12
血流受限训练联合低负荷运动[44]	每周 2 次	4～5	8
太极拳[45]	每周 2 次	30～40	12
五禽戏[46]	每周 5 次	20	24
八段锦[47]	每周 5 次	30	12
易筋经[48]	每周 5 次	40	24
股四头肌肌力训练联合坐立行姿态矫正训练[49]	每日早晚各 1 次	≥20	4

发现,补充适量的维生素 D 能够改善 KOA 患者的肌肉质量、缓解关节疼痛,提高患者的生活质量。欧洲骨质疏松症和骨关节炎临床经济协会推荐,老年骨关节炎患者每天应摄入不低于 800 IU 的维生素 D[55]。

2.3　中药内服疗法　KOA 的病机为肝脾肾亏虚、卫表不固、邪气入里、痰凝血瘀;KOA 的治疗以补肝益肾健脾为主,兼用活血行气、祛痰通络、祛风寒热湿之品。肌少症的病机为正气不足、脾胃失和、气血亏虚;肌少症的治疗以固护脾胃、补气养血为要,辅以补肝益肾、疏通筋脉、调和阴阳的药物[56]。KOA 和肌少症的病机中,肝脾肾亏虚为本,腠理空虚易感风寒湿热邪、瘀血痰饮阻滞筋络为标[57]。KOA 合并肌少症患者的辨证分型多为肝肾亏虚证、血瘀寒凝证、寒湿痹阻证、阳虚寒凝证、气滞血瘀证[58-59]。在治疗 KOA 合并肌少症时,应重在“治骨”,辅以“调肌”,以达到“除痹”的目的,用药时以补益肝脾肾药物为主,仔细辨证,分清三者主次,合理运用散寒、利湿、化瘀、行气之法,适当配伍减痛、消痰、增肌、壮骨之药[60]。

2.4　其他潜在治疗药物

2.4.1　二甲双胍　研究表明,二甲双胍能够通过抑制 mTOR 信号通路、激活 AMPK 信号通路发挥抗炎、维持骨骼肌质量和力量的作用[61]。Saisho[62]研究发现,KOA 合并肌少症的肥胖患者通过口服二甲双胍控制血糖,患者体重降低,膝关节疼痛得到缓解。Wang 等[63]对 818 例 KOA 患者进行了为期 6 年的随访观察,部分患者长期口服二甲双胍,结果显示长期口服二甲双胍的 KOA 患者疼痛缓解、膝关节内侧软骨损伤减轻,KOA 进程延缓。

2.4.2　血管紧张素转化酶抑制剂　肾素-血管紧张素系统在抑制炎症因子表达、提高胰岛素样生长因子 1 水平等方面发挥重要作用;肾素-血管紧张素系统的失调会影响神经肌肉骨骼系统,增加肌少症发生的风险[64]。血管紧张素转化酶抑制剂能够调节肾素-血管紧张素系统的平衡[65]。目前,通过阻断肾素-血管紧张素系统治疗 KOA 的方法尚存在争议[66],但部分动物实验研究[67-70]证实了该方法的有效性。

2.4.3　雌激素替代药物　雌激素替代药物疗法是一种针对绝经后女性 KOA 合并肌少症患者的治疗方案,该方法能够增加患者的肌肉力量和质量[71-72]。但是需要警惕的是,雌激素会增加乳腺癌[73]以及心脑血管疾病[74]发生的风险。因此,该方法在临床上的应用受到一定的限制。

2.4.4　其他　MicroRNAs 在调控肌细胞增殖、分化、凋亡和再生过程中发挥重要作用,也是维持软骨、韧带、肌腱等关节组织生理状态的重要参与者[75-76]。生长激素释放肽可增加肌肉质量,并保护软骨[77-78]。过氧化物酶体增殖物激活受体-γ 共激活因子既可通过抑制 IL-1β 防止软骨变性,又可通过调节线粒体活性降低肌肉蛋白分解[79]。抗肌肉生长抑制素可以增加肌肉质量和力量,同时降低血液与滑囊中生长抑制素浓度[80],而血液与滑囊中生长抑制素浓度与 KOA 严重程度密切相关[81]。磷酸二酯酶抑制剂可通过增加骨骼肌中环磷酸腺苷含量维持肌肉力量[82],并且减少 IL-1β 诱导生成的 NO,进而达到保护软骨的目的[83]。这些物质均表现出治疗 KOA 合并肌少症的潜力,可为 KOA 合并肌少症的治疗提供新思路。

3　小　结

KOA 与肌少症之间关系密切,炎症因子、胰岛素抵抗、肥胖是 KOA 和肌少症的共同影响因素。肌少症能够诱发 KOA 并加速 KOA 发展,而 KOA 是肌少症发生的危险因素,二者在病理表现和发生机制方面相互影响。目前,治疗 KOA 合并肌少症的主要方法有运动疗法、饮食疗法、中药内服疗法等。二甲双胍、血管紧张素转化酶抑制剂、雌激素替代药物等均表现出治疗 KOA 合并肌少症的潜力,为 KOA 合并肌少症的治疗提供了新思路。

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