

运动干预调控脂质代谢重编程缓解 糖尿病肌少症的机制与策略*

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摘要 糖尿病肌少症 (diabetic sarcopenia, DS) 是糖尿病患者常见且易被忽视的骨骼肌并发症, 主要表现为骨骼肌质量减少、肌力下降和身体功能衰退, 可进一步增加患者跌倒、失能、代谢紊乱及不良预后的风险。近年来, 研究表明, DS 的发生发展并非单纯由高血糖或增龄因素导致, 脂质代谢紊乱及病理性脂质代谢重编程与 DS 的发生发展密切相关, 其通过驱动慢性炎症、氧化应激、线粒体功能障碍和肠道菌群紊乱等多个关键病理环节, 与疾病进程形成复杂的双向恶性循环, 共同加速骨骼肌质量的减少和功能衰退。与此同时, 运动干预作为一种重要的非药物干预手段, 已被证实能够改善胰岛素敏感性, 促进脂肪酸氧化, 减少异位脂肪沉积和脂毒性产物积累, 重塑骨骼肌代谢状态, 纠正病理性脂质代谢重编程, 从而对 DS 产生积极的干预作用。因此, 本文基于公开数据集的探索性分析与相关文献证据, 系统综述脂质代谢紊乱参与 DS 发生发展的病理机制, 重点阐述运动干预通过调控脂质代谢重编程改善 DS 的潜在分子机制及运动干预策略, 以期对 DS 的早期识别、机制研究和运动疗法的临床转化提供理论依据。

关键词 运动干预, 糖尿病肌少症, 脂质代谢重编程, 脂质代谢紊乱, 骨骼肌

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糖尿病肌少症 (diabetic sarcopenia, DS) 作为糖尿病 (diabetes mellitus, DM) 常见且严重的并发症之一, 以骨骼肌质量下降、肌力减退及躯体功能受损加速为核心特征, 严重影响患者的生活质量^[1]。随着全球老龄化进程的加快和 DM 患病率的持续攀升, DS 已成为导致患者衰弱、失能、跌倒风险与死亡率增加的关键因素, 进而对医疗和社会经济造成沉重的负担^[2-3], 因此亟须寻找有效的预防和治疗方式。近年来, DS 的机制研究正逐步从“单纯肌量减少”转向“代谢失衡驱动的肌肉衰退”。除糖代谢紊乱、蛋白质稳态失衡、慢性炎症等多种致病机制外, 脂代谢紊乱、脂毒性及其背后的脂质代谢重编程, 可能在 DS 的发生发展中扮演着重要角色。研究表明, DS 患者的脂质转运与储存方式改变, 脂肪酸 β 氧化及线粒体脂质处理能力相对不足, 促使肌内脂滴异常堆积, 并伴随脂毒性产物的积累, 进而导致肌肉加速流失^[4]。值得注意的是, DS 脂质代谢重编程是指为应对脂质代谢

紊乱所造成的损害, 通过改变糖酵解、氧化磷酸化和脂质合成、分解及运输等途径, 重新分配代谢资源, 从而适应环境压力、维持生存与增殖的一种代偿性调节机制^[5]。然而, 当这种重编程持续存在并失代偿时, 则可能由生理性脂质代谢重编程转变为病理性脂质代谢重编程, 进一步推动脂毒性损伤和肌肉衰退。因此, 以脂质代谢重编程为切入点, 深入探索 DS 的病理机制并据此优化治疗策略, 是当前 DS 治疗潜在的研究方向。

目前, 在 DS 的治疗方面虽取得了一些进展, 但单纯的药物治疗或营养补充存在疗效局限, 潜在副作用以及长期成本高昂等问题, 难以形成可持续的干预方案。运动作为一种安全性较高、成本效益突出的非药物干预手段, 已被证实能够有效重塑脂

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代谢、降低脂毒性产物、增加脂肪细胞因子、改善线粒体功能并提升胰岛素敏感性,从而缓解DS进程^[6]。此外,本研究团队前期发现,运动能够通过调控缺口受体1/自噬信号改善DM伴非酒精性脂肪肝小鼠脂质代谢异常,降低其肝脏脂肪沉积和炎症水平,提示运动干预调控脂质代谢改善DS可能是潜在的研究方向^[7]。然而,运动诱导的脂质代谢重编程的具体分子机制以及现有研究在运动类型与剂量的反应关系上尚未完全阐明。本文旨在系统综述运动干预调控脂质代谢重编程以缓解DS的最新研究进展,阐明脂质代谢重编程在DS发生发展中的关键作用,探讨相关的运动干预策略,以期为运动干预在DS临床防治中的转化提供理论依据。

1 糖尿病肌少症与脂质代谢紊乱

1.1 糖尿病肌少症中脂质代谢紊乱——基于数据库分析

为探索DM状态下骨骼肌的代谢异常及其与肌少症表型相关的潜在分子机制,本文从GEO数据库(<https://www.ncbi.nlm.nih.gov/geo/>)中检索并下载数据集GSE202295和GSE268372。其中,GSE202295包含17名健康对照者和21名瘦体重减少的2型糖尿病(type 2 diabetes mellitus, T2DM)患者的骨骼肌样本^[8],用于分析DM状态下骨骼肌转录谱的变化。GSE268372包含3只健康对照大鼠和3只DS模型大鼠的骨骼肌样本,且模型组表现出肌纤维萎缩及肌纤维横截面积的显著降低^[9],用于进一步探索DS潜在的分子机制。采用R 4.4.1中GEOquery 2.72.0包获取表达矩阵及平台注释文件,并完成探针注释、基因名转换、log₂转换及标准化处理。随后采用limma 3.60.6包进行差异表达分析,以 $|\log_2FC|>0.5$ 且 $P<0.05$ 为筛选标准,比较T2DM组与健康对照组、DS组与正常对照组之间的差异表达基因(differentially expressed genes, DEGs),且仅作为趋势性结果展示。进一步采用Benjamini-Hochberg方法进行多重检验校正,以 $P_{\text{adjust}}<0.05$ 为显著性标准,并通过clusterProfiler 4.12.6包对DEGs进行基因本体(gene ontology, GO)及京都基因与基因组百科全书(Kyoto encyclopedia of genes and genomes, KEGG)富集分析。对于大鼠数据集,在进行跨物种比较时,先将大鼠基因转换为相应的人类同源基因后再进行共同通路层面的比较。

GSE202295数据集共筛选出476个DEGs,其

中T2DM患者较健康人群有232个基因上调,244个基因下调。而GSE268372共筛选出2 947个DEGs,DS模型相对于健康对照中有1 484个基因上调,1 463个基因下调(图1a, b)。此外,KEGG富集分析结果显示,DEGs参与炎症、醚酯代谢、Apelin信号通路、磷脂酰肌醇3激酶/蛋白激酶B(phosphatidylinositol-3-kinase/protein kinase B, PI3K/Akt)信号通路、丝裂原活化蛋白激酶信号通路、细胞因子-细胞因子受体相互作用等通路。GO富集分析结果同样显示:在生物过程(biological process, BP)方面,基因主要涉及白细胞分化正向调控、淋巴细胞活化正向调控、有氧呼吸、氧化磷酸化等代谢及炎症反应过程;在细胞组分(cellular component, CC)方面,基因参与合成免疫球蛋白复合体及细胞质核糖体;在分子功能(molecular function, MF)方面,基因主要富集于抗原结合、核糖体结构成分及细胞外基质结构成分(图1c~f)。基于以上结果发现,无论是T2DM患者还是DS动物模型,在肌肉减少的同时,伴随着表达谱的重塑,且显著影响脂质代谢、炎症反应等生物学过程,但DS的多种病理因素与脂质代谢紊乱、炎症反应等生物学过程的具体分子机制仍需进一步探讨。

1.2 脂质代谢紊乱对糖尿病肌少症的影响

当前研究认为,与增龄性肌少症相比,DS具有更为突出的代谢异常特征。增龄性肌少症主要与衰老过程中蛋白质合成能力下降、神经肌肉功能退化等因素有关。而DS除受到衰老相关因素影响外,还长期处于高血糖、脂质沉积、脂毒性及晚期糖基化终末产物(advanced glycation end products, AGEs)积累等异常代谢环境中。这些代谢因素可进一步诱发炎症反应、氧化应激、线粒体功能障碍及蛋白质稳态失衡等病理改变,从而加速肌肉量下降、肌力减退和躯体功能受损^[10](图2)。

1.2.1 脂质代谢紊乱与胰岛素抵抗

胰岛素抵抗(insulin resistance, IR)是DS的核心病理特征之一。脂质代谢紊乱则是诱发和加重骨骼肌IR的重要因素。脂质组学研究显示,DM患者已出现明显的血浆磷脂谱改变,其中醚键磷脂及缩醛磷脂相关脂质水平异常与糖代谢受损、肥胖和IR密切相关^[11],这与本研究基于GEO数据库的探索性分析一致。此外,二酰甘油、神经酰胺等脂毒性分子的蓄积使骨骼肌逐渐出现IR,导致胰岛素(insulin, INS)及胰岛素样生长因子-1(insulin-

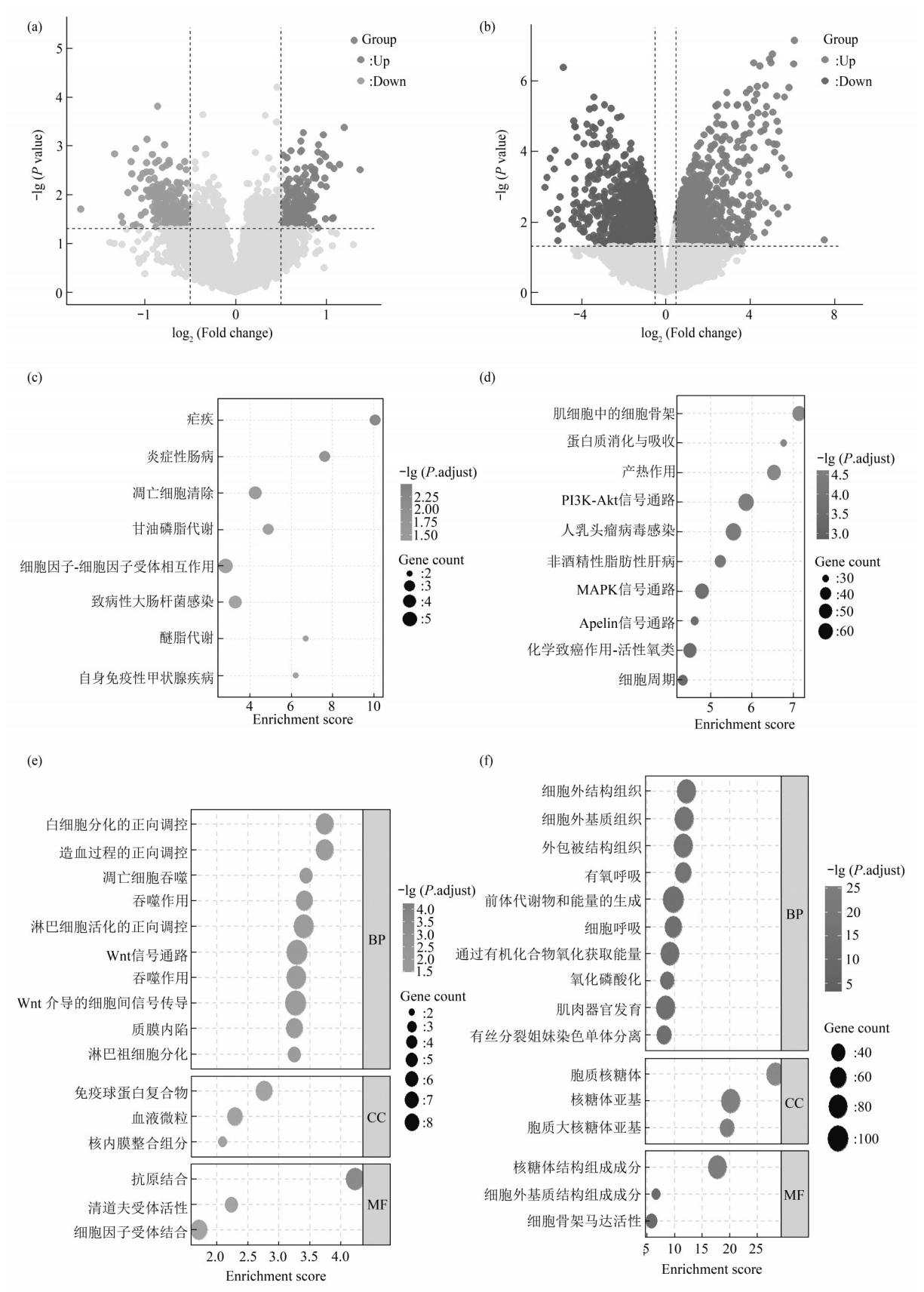


Fig. 1 Bioinformatics analysis of GSE202295 and GSE268372

图1 GSE202295和GSE268372的生物信息学分析

(a, b) GSE202295和GSE268372差异基因火山图。Down: 下调的差异表达基因; Up: 上调的差异表达基因。(c, d) GSE202295和GSE268372 KEGG富集分析结果。(e, f) GSE202295和GSE268372 GO富集分析结果。富集基因数目由气泡图中每个气泡的大小表示。

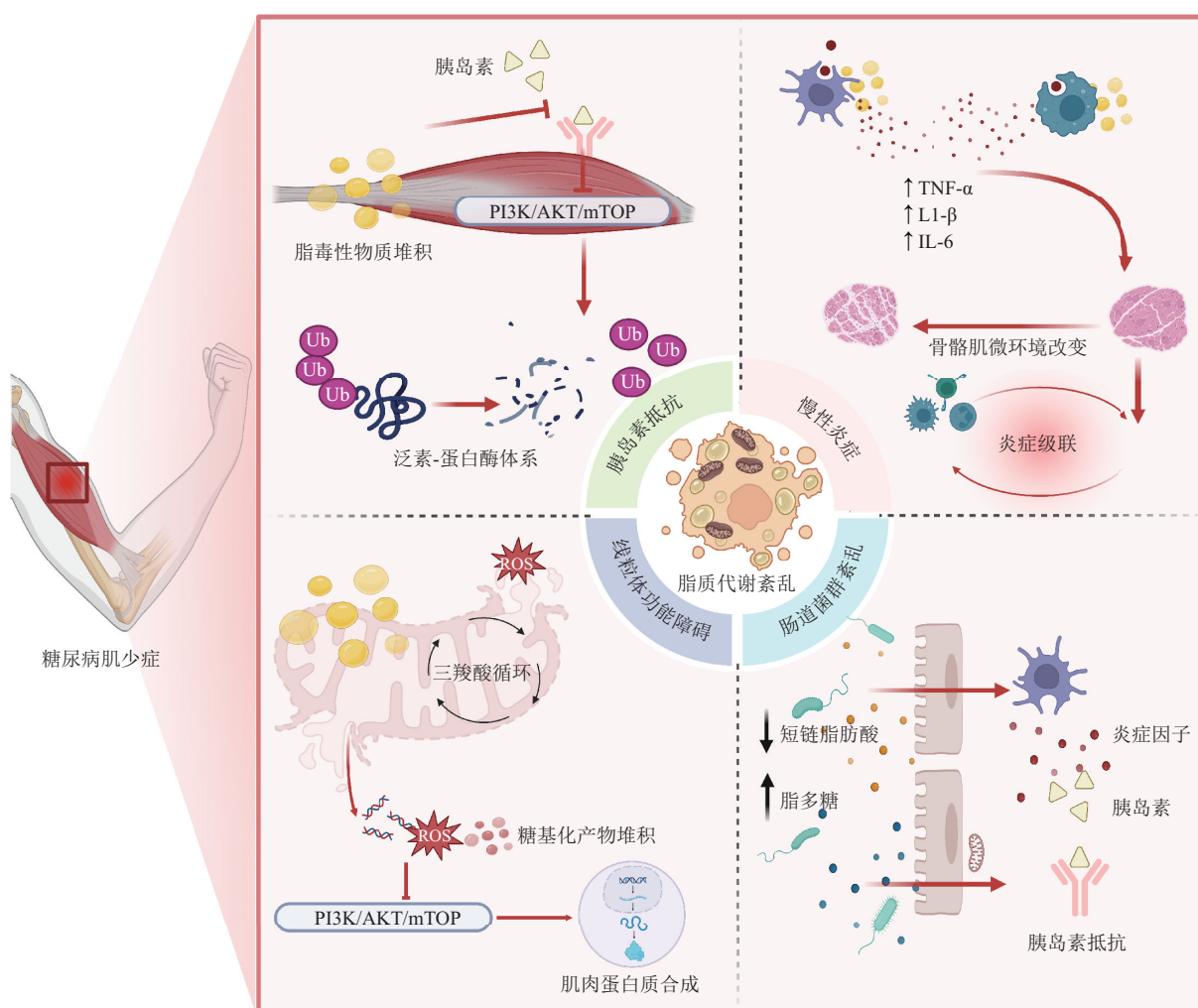


Fig. 2 Effects of lipid metabolism dysregulation on diabetic sarcopenia

图2 脂质代谢紊乱对糖尿病肌少症的影响

PI3K/AKT/mTOR: 磷脂酰肌醇3激酶/蛋白激酶B/哺乳动物雷帕霉素靶蛋白 (phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin); Ub: 泛素 (ubiquitin); TNF- α : 肿瘤坏死因子- α (tumor necrosis factor- α); IL-1 β : 白介素-1 β (interleukin-1 β); IL-6: 白介素-6 (interleukin-6); ROS: 活性氧类 (reactive oxygen species)。

like growth factor-1, IGF-1) 信号减弱, 下游PI3K/Akt/哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 信号通路活性受抑, 葡萄糖转运蛋白4 (glucose transporter-4, GLUT4) 易位减少, 骨骼肌对葡萄糖的摄取和氧化利用能力下降, 机体长期处于“能量利用障碍”状态^[12]。同时, INS的合成代谢作用减弱, 使其促进氨基酸摄取、核糖体翻译及蛋白质合成的能力下降, 最终导致肌肉蛋白合成减少, 加速DS的发生发展。目前相关证据虽多来源于DM及骨骼肌IR相关研究, 但为解释DS中脂质代谢异常与肌肉功能下降提供了间接依据。另有研究发现, DS患者Akt信号的减弱会解除对叉头样转录因子 (forkhead Box O,

FoxO) 的抑制作用, 促使FoxO入核并上调泛素-蛋白酶体系 (ubiquitin-proteasome system, UPS) 相关肌萎缩基因, 如肌肉萎缩盒F基因 (muscle atrophy F-box protein, MAFbx/Atrogin-1) 和肌肉特异性环指蛋白1 (muscle-specific ring finger protein 1, MuRF-1) 的表达, 从而加速骨骼肌蛋白降解, 导致肌肉丢失和肌力下降^[13]。这为阐释DS的病理机制提供了直接依据, 未来仍需更多DS动物模型和临床实验进一步验证。此外, 肌间脂肪组织 (intermuscular adipose tissue, IMAT) 浸润也与DS的进展密切相关^[14]。在骨骼肌中, IMAT分解主要依赖甘油三酯脂肪酶 (adipose triacylglyceride lipase, ATGL) 和激素敏感性脂肪酶 (hormone

sensitive lipase, HSL) 的协同作用。在 DM 环境下, ATGL 和 HSL 活性失衡可导致局部脂解异常, 使脂毒性代谢产物进一步积聚, 加重骨骼肌细胞的脂毒性损伤和 IR^[15]。目前关于 IMAT 参与 DS 进展的直接证据仍相对有限, 相关机制仍需进一步明确。综上, 脂质代谢紊乱促进脂毒性代谢产物积聚、干扰 INS 及 IGF-1 信号转导、抑制葡萄糖摄取利用并破坏蛋白质合成与降解平衡, 可能是推动 DS 的重要机制之一。

1.2.2 脂质代谢紊乱与慢性炎症

慢性炎症是脂质代谢紊乱导致骨骼肌损伤的关键中介环节。骨骼肌内脂毒性微环境, 不仅直接损害肌细胞代谢功能, 还可激活多种炎症信号通路, 如核因子- κ B (nuclear factor kappa-B, NF- κ B) 信号通路, 并产生白介素-6 (interleukin-6, IL-6)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、干扰素- γ (interferon- γ , IFN- γ) 等促炎因子, 这些炎症因子又可反过来进一步激活 NF- κ B 及其他应激通路, 形成自我放大的炎症级联反应, 持续破坏骨骼肌内环境稳态。研究表明, T2DM 患者 IL-6、TNF- α 及 C 反应蛋白与骨骼肌质量、力量呈负相关, 且这些炎症因子会加重 IR, 抑制 PI3K/Akt/mTOR 信号通路, 激活 UPS 系统, 最终引起蛋白质分解, 为炎症反应参与 DS 进展提供了间接证据^[16]。此外, IFN- γ 通过 Janus 激酶 1/转录激活因子 1 通路使胰岛 β 细胞损伤, 亦可与 TNF- α 协同促进肌肉萎缩^[17]。这提示相关炎症因子可能通过影响骨骼肌代谢参与 DS 进展。另有研究表明, 脂肪酸代谢异常还可激活 NOD 样受体家族含 pyrin 结构域蛋白 3 炎症小体, 促进白介素-1 β (interleukin-1 β , IL-1 β) 释放。IL-1 β 可通过诱导 INS 受体底物丝氨酸位点磷酸化, 抑制 INS 下游信号转导, 进一步加重 IR。提示脂质代谢紊乱与炎症反应之间存在密切的双向促进作用^[18]。炎症因子的分泌增加会加剧 IMAT 浸润, 同时会抑制脂联素的表达, 进一步影响肌肉功能^[19]。综上, 脂质代谢紊乱可能通过激活慢性炎症反应, 加重 IR、抑制蛋白质合成并促进蛋白降解, 进而导致 DS 的发生发展。需要指出的是, 该机制目前更多来源于 T2DM、肥胖及骨骼肌 IR 相关研究, 其在 DS 发生发展中的特异性作用仍需进一步验证。因此, 靶向改善骨骼肌脂质代谢紊乱、降低炎症反应, 可能是干预 DS 的潜在方向。

1.2.3 脂质代谢紊乱与线粒体功能障碍

线粒体功能障碍和脂质代谢紊乱与 DS 发生发展密切相关。研究发现, 游离脂肪酸升高及骨骼肌内脂质异常沉积, 能够干扰线粒体脂肪酸摄取、 β 氧化及电子传递链功能, 进而引发线粒体形态和功能的改变^[20]。线粒体功能障碍释放过量活性氧类 (reactive oxygen species, ROS), 可直接攻击细胞膜脂质和蛋白质, 并激活 C-Jun 氨基末端激酶、NF- κ B 等信号通路, 导致脂质蓄积, 从而形成脂质代谢紊乱与氧化应激的恶性循环^[21]。同时, 过量的 ROS 抑制 Akt/mTOR 通路, 激活 UPS 系统, 加速骨骼肌蛋白质的降解^[22]。这为解释 DS 中线粒体功能障碍与肌肉流失之间的联系提供了重要依据。值得注意的是, 已有直接证据表明, DS 大鼠模型线粒体动力学平衡被破坏, 微管相关蛋白 I 轻链 3 等自噬相关调控蛋白表达水平下降, 细胞自噬活性降低, 导致错误折叠的蛋白质积聚^[23]。而高脂喂养大鼠使用自噬抑制剂氯喹处理后, 肌萎缩标志物 Atrogin-1 表达升高^[24]。这提示脂质代谢异常背景下, 自噬功能受损可能促进骨骼肌蛋白降解和肌萎缩, 为阐释 DS 中脂质代谢紊乱、线粒体功能障碍与自噬异常之间的关系提供了间接机制依据。此外, 脂质代谢紊乱产生的 AGEs 可在骨骼肌、韧带和神经等多种组织中沉积, 严重影响组织的生物学功能。进一步研究发现, AGEs 可通过受体介导的 AMP 依赖的蛋白激酶 (adenosine 5'-monophosphate (AMP)-activated protein kinase, AMPK) 下调 Akt 信号通路从而导致肌肉萎缩以及肌肉功能的缺陷^[25]。同时, AGEs 诱发炎症反应, 并激活 NADPH 氧化酶, 增加循环中 ROS 的含量, 促进蛋白激酶样内质网激酶 (protein kinase R-like endoplasmic reticulum kinase, PERK) 和 FoxO 的磷酸化, 导致腓肠肌 MAFbx 表达升高, 这表明 AGEs 通过介导 PERK/FoxO1 信号通路诱导骨骼肌萎缩^[26-27], 为 DS 发生发展提供了间接依据。综上, 脂质代谢紊乱、线粒体功能障碍、氧化应激与自噬之间相互作用、彼此放大, 可能共同构成推动 DS 进展的重要病理基础。

1.2.4 脂质代谢紊乱与肠道菌群失调

近年来, 肠道菌群作为人体“第二基因组”而备受关注, 其通过影响胆汁酸代谢、调节短链脂肪酸 (short-chain fatty acids, SCFAs) 形成, 在脂质代谢中发挥重要作用^[28]。已有研究表明, T2DM、肌少症和肠道微生物群通过 IR、炎症等途径相互

关联,提示肠道菌群失衡可能参与DS的发生发展^[29]。在DS状态下,异常的脂质代谢可重塑肠道菌群结构与功能,主要体现为肠道菌群 α 生物多样性的下降,丁酸盐菌减少及潜在致病菌增多,并伴随肠屏障功能受损^[30-31]。值得注意的是,肠道屏障的受损,导致肠源性脂多糖(lipopolysaccharide, LPS)入血,引起系统性炎症和代谢失调,进一步损害骨骼肌质量与功能。同时,过多的LPS会激活Toll样受体4信号,促进Atrogin-1和MuRF-1的表达,诱导肌管细胞萎缩^[32]。需要指出的是,目前多数研究来源于DM、肌少症相关研究,其在DS中的作用机制仍需进一步验证。另有研究表明,SCFAs可通过“肌肠轴”调控G蛋白偶联受体41等相关受体调节INS敏感性、能量代谢和炎症反应等多种途径影响肌肉代谢状态^[33-34]。而DM患者SCFAs生成减少,SCFAs可通过血液循环与骨骼肌细胞上的游离脂肪酸受体2/3结合,促进葡萄糖摄取和利用,并激活IGF-1/PI3K/Akt/mTOR通路,刺激肌肉蛋白质合成。此外,在SAMP8肌少症小鼠模型中,SCFAs通过抑制FoxO3a/Atrogin-1,并激活mTOR通路,减弱脂肪浸润,改善蛋白质合成^[35-36]。因此,SCFAs可能是连接肠道菌群失调、脂代谢异常和肌肉功能下降的重要环节,但需要指出的是,目前多数证据来自DM模型或肌少症模型,针对DS的直接证据尚少,未来研究可进一步探讨DS肠道菌群在脂质代谢中的潜在中介机制。综上,脂质代谢紊乱可能通过肠道菌群结构与功能异常,引发肠屏障破坏、慢性炎症及菌群代谢产物失衡,进而影响DS的进展,提示以脂质代谢与肠道菌群为靶点的干预策略,可能为DS的治疗提供新的思路。

2 运动干预调节脂质代谢重编程改善糖尿病肌少症的分子机制

上述机制表明,脂质代谢紊乱与IR、慢性炎症、线粒体功能障碍、肠道菌群紊乱等病理过程密切相关。运动干预DS的意义不同于一般增龄性肌少症。对于增龄性肌少症而言,运动干预强调增加肌肉量、提升肌力和改善躯体功能;而在DS中,运动干预除改善肌肉功能外,还需兼顾重塑脂质代谢状态,恢复生理性脂质代谢重编程和骨骼肌代谢灵活性(图3)。因此,系统阐明运动干预调节脂质代谢重编程改善DS的分子机制,对于深入理解其发生发展规律及探索精准运动干预策略具有重要

理论价值和现实意义。

2.1 运动调控脂质代谢重编程缓解胰岛素抵抗

病理性脂质代谢重编程是IR的重要诱因之一。不同形式的运动模式均可调节基础代谢,纠正病理性脂质代谢重编程,即减少脂毒性代谢产物堆积,改善IR,缓解肌肉萎缩^[37]。研究表明,在db/db模型鼠,即瘦素受体基因缺陷导致的自发性T2DM模型鼠中,每天1次,每周5d,持续6周的中等强度有氧运动可通过增加糖酵解、脂肪酸分解代谢和脂肪酸 β 氧化途径,改善伴肌少症db/db模型小鼠INS敏感性,纠正病理性脂质代谢重编程,从而增加肌细胞密度和肌纤维面积^[38]。临床研究同样表明,每周3次,每次40min的抗阻运动,可改善DS患者IR,并恢复 β 细胞功能,减少大腿肌肉的IMAT,从而缓解肌肉萎缩^[39]。Alexander等^[40]研究同样发现,每周5次,持续12周的高强度间歇训练(high-intensity interval training, HIIT)和每周3次,持续12周的渐进式抗阻运动均有助于降低小腿部位的IMAT含量,并可显著增加老年受试者肌肉含量和空腹INS水平。

此外,运动可增强INS受体底物磷酸化水平,促进PI3K/Akt/mTOR/GLUT4信号级联激活,增加骨骼肌与脂肪组织对葡萄糖的摄取和利用,抑制脂解作用,恢复生理性脂质代谢重编程,下调Atrogin-1和MuRF-1的表达,从而减轻DS骨骼肌蛋白降解和萎缩^[41]。同时,HIIT和混合强度运动训练均可提高T2DM患者骨骼肌中AMPK磷酸化水平,并改善血脂异常和IR,重塑骨骼肌耐力^[42]。另有研究表明,运动还能增加脂联素、鸢尾素、Apelin等运动因子的表达,形成肌肉与其他组织间的内分泌串扰参与脂质代谢重塑和IR,进而促进肌肉生长^[43]。综上,运动及运动因子可通过激活相关信号通路,改善骨骼肌糖脂代谢并促进骨骼肌代谢向生理性重编程恢复,可能成为延缓DS进展的重要干预靶点。

2.2 运动调控脂质代谢重编程降低慢性炎症

病理性脂质代谢重编程与慢性炎症之间联系密切。有氧运动已被证明可减少肌少症患者内脏及骨骼肌内脂肪堆积介导的炎症反应,降低患者TNF- α 和IL-6水平^[44]。每周3次,持续6周的抗阻运动可抑制DS大鼠模型NF- κ B和炎症因子的释放,进而下调MuRF-1和Atrogin-1的表达,减少由炎症引起的蛋白质降解^[45]。此外,持续8周的渐进式抗阻运动可改善糖脂代谢紊乱,降低脂代谢相关酶的表

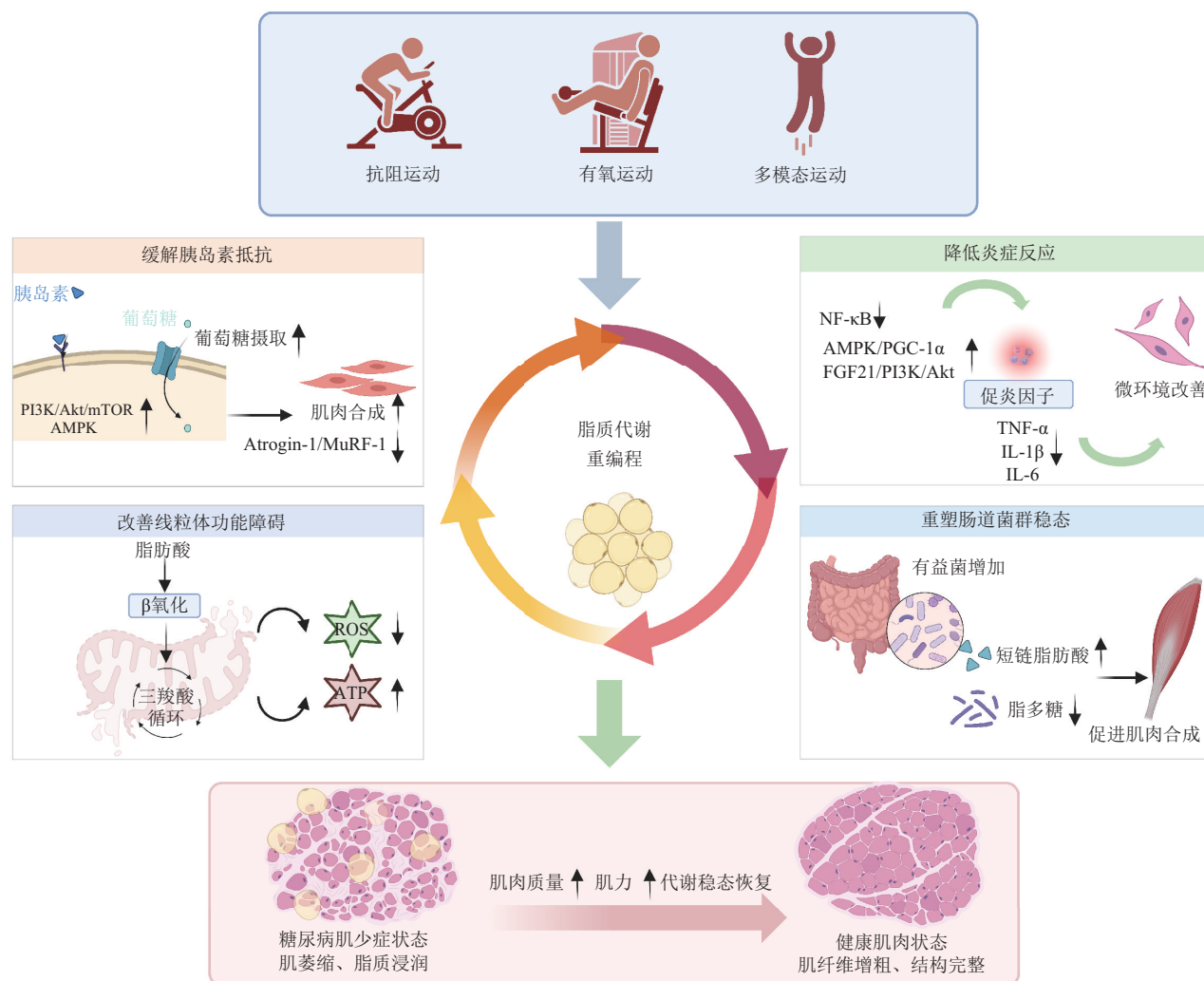


Fig. 3 Effects of exercise intervention on regulating lipid metabolism reprogramming in diabetic sarcopenia

图3 运动干预调控脂质代谢重编程对糖尿病肌少症的影响

PI3K/AKT/mTOR: 磷脂酰肌醇3-激酶/蛋白激酶B/哺乳动物雷帕霉素靶蛋白 (phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin); Atrogin-1: 肌肉萎缩盒F基因 (muscle atrophy F-box protein); MuRF-1: 肌肉特异性环指蛋白1 (muscle-specific ring finger protein 1); AMPK/PGC-1α: AMP依赖的蛋白激酶/过氧化物酶体增殖物激活受体γ辅激活因子1α (adenosine 5'-monophosphate (AMP)-activated protein kinase/peroxisome proliferator-activated receptor γ coactivator 1-alpha); FGF21: 成纤维细胞生长因子21 (fibroblast growth factor 21); ROS: 活性氧类 (reactive oxygen species); ATP: 三磷酸腺苷 (adenosine triphosphate); NF-κB: 核因子-κB (nuclear factor kappa-B); TNF-α: 肿瘤坏死因子-α (tumor necrosis factor-α); IL-1β: 白介素-1β (interleukin-1β); IL-6: 白介素-6 (interleukin-6)。

达, 如甾醇调节元件结合转录因子、3-羟基-3-甲基戊二酰辅酶A还原酶, 纠正病理性代谢重编程, 并激活成纤维细胞生长因子21 (fibroblast growth factor 21, FGF21) /PI3K/Akt信号通路抑制炎症、肌萎缩及肌纤维化蛋白的表达, 缓解T2DM伴肌少症小鼠肌萎缩^[46]。同时, 规律运动还可增强AMPK和过氧化物酶体增殖物激活受体γ辅激活因子1α (peroxisome proliferator-activated receptor γ coactivator 1-alpha, PGC-1α)等代谢调控通路活

性, 促进脂肪氧化, 减少脂肪组织巨噬细胞浸润, 推动骨骼肌内环境由促炎状态向代谢稳态恢复^[47-48]。由此可见, AMPK/PGC-1α和PI3K/Akt可能是运动介导脂质代谢重编程、改善DS的重要信号轴。

另有研究表明, 每周2次, 持续8周的中等强度有氧运动提升体内IGF-1水平, 增强肌少症患者骨骼肌质量并优化内脏脂肪分布^[49]。适度的有氧运动和HIIT能通过释放脂肪因子或肌因子, 提高

T2DM患者脂肪酸氧化能力并减少脂肪酸合成酶乙酰辅酶A羧化酶的活性,降低瘦素水平,调控脂肪褐变相关途径,恢复生理性脂质代谢重编程^[50]。这提示运动因子可能是运动恢复脂质代谢重编程、炎症反应及肌肉退行性改变的重要介质,未来需要进一步探究运动因子改善DS的分子机制。综上所述,运动干预可通过调节脂质代谢重编程与慢性炎症之间的相互作用,促进脂肪酸氧化,改善脂肪分布和骨骼肌代谢微环境,抑制炎症信号通路,进而减轻由炎症介导的蛋白质分解代谢,为阐释DS的运动疗法提供了新的思路。

2.3 运动调控脂质代谢重编程改善线粒体功能障碍

线粒体功能障碍是DS发生发展的重要机制之一,而病理性脂质代谢重编程则是诱发线粒体损伤的关键上游因素。线粒体质量控制是维持骨骼肌代谢稳态的重要机制,主要包括线粒体生物发生、线粒体动力学、线粒体自噬及受损线粒体清除等过程。研究表明,运动干预能够促进线粒体生物合成,调节葡萄糖和脂质代谢,纠正病理性代谢重编程^[51]。Wu等^[52]研究发现,每周5次,持续8周的有氧运动上调 β 羟丁酸脱氢酶1可改善T2DM小鼠腓肠肌糖脂代谢紊乱和线粒体质量控制,并减轻氧化应激和肌纤维化。而Ma等^[46]也发现,每周3次,共8周的抗阻运动上调FGF21/PI3K/Akt通路,改善糖脂代谢、促进PGC-1 α 等线粒体生物发生相关因子表达,缓解T2DM伴肌少症小鼠骨骼肌萎缩。此外,8周有氧运动可上调PGC-1 α 表达,提高骨骼肌葡萄糖摄取、脂肪酸氧化和线粒体氧化能力,改善糖脂代谢稳态,恢复生理性代谢重编程并促进肌纤维生长和肌肥大,进一步提示其在运动改善骨骼肌代谢功能中的重要作用^[53-54]。另有研究表明,运动因子同样参与线粒体生物发生。鸢尾素、脑源性神经营养因子在骨骼肌中可通过激活PGC-1 α 的表达,上调其下游靶基因核呼吸因子1和线粒体转录因子A,从而促进线粒体生物发生并增强脂质氧化能力,为肌纤维再生及功能维持提供充足的能量支持^[35]。FGF21在骨骼肌中可通过激活核因子 κ B/IRF3/IRF7/IRF8/IRF9/IRF10/IRF11/IRF12/IRF13/IRF14/IRF15/IRF16/IRF17/IRF18/IRF19/IRF20/IRF21/IRF22/IRF23/IRF24/IRF25/IRF26/IRF27/IRF28/IRF29/IRF30/IRF31/IRF32/IRF33/IRF34/IRF35/IRF36/IRF37/IRF38/IRF39/IRF40/IRF41/IRF42/IRF43/IRF44/IRF45/IRF46/IRF47/IRF48/IRF49/IRF50/IRF51/IRF52/IRF53/IRF54/IRF55/IRF56/IRF57/IRF58/IRF59/IRF60/IRF61/IRF62/IRF63/IRF64/IRF65/IRF66/IRF67/IRF68/IRF69/IRF70/IRF71/IRF72/IRF73/IRF74/IRF75/IRF76/IRF77/IRF78/IRF79/IRF80/IRF81/IRF82/IRF83/IRF84/IRF85/IRF86/IRF87/IRF88/IRF89/IRF90/IRF91/IRF92/IRF93/IRF94/IRF95/IRF96/IRF97/IRF98/IRF99/IRF100/IRF101/IRF102/IRF103/IRF104/IRF105/IRF106/IRF107/IRF108/IRF109/IRF110/IRF111/IRF112/IRF113/IRF114/IRF115/IRF116/IRF117/IRF118/IRF119/IRF120/IRF121/IRF122/IRF123/IRF124/IRF125/IRF126/IRF127/IRF128/IRF129/IRF130/IRF131/IRF132/IRF133/IRF134/IRF135/IRF136/IRF137/IRF138/IRF139/IRF140/IRF141/IRF142/IRF143/IRF144/IRF145/IRF146/IRF147/IRF148/IRF149/IRF150/IRF151/IRF152/IRF153/IRF154/IRF155/IRF156/IRF157/IRF158/IRF159/IRF160/IRF161/IRF162/IRF163/IRF164/IRF165/IRF166/IRF167/IRF168/IRF169/IRF170/IRF171/IRF172/IRF173/IRF174/IRF175/IRF176/IRF177/IRF178/IRF179/IRF180/IRF181/IRF182/IRF183/IRF184/IRF185/IRF186/IRF187/IRF188/IRF189/IRF190/IRF191/IRF192/IRF193/IRF194/IRF195/IRF196/IRF197/IRF198/IRF199/IRF200/IRF201/IRF202/IRF203/IRF204/IRF205/IRF206/IRF207/IRF208/IRF209/IRF210/IRF211/IRF212/IRF213/IRF214/IRF215/IRF216/IRF217/IRF218/IRF219/IRF220/IRF221/IRF222/IRF223/IRF224/IRF225/IRF226/IRF227/IRF228/IRF229/IRF230/IRF231/IRF232/IRF233/IRF234/IRF235/IRF236/IRF237/IRF238/IRF239/IRF240/IRF241/IRF242/IRF243/IRF244/IRF245/IRF246/IRF247/IRF248/IRF249/IRF250/IRF251/IRF252/IRF253/IRF254/IRF255/IRF256/IRF257/IRF258/IRF259/IRF260/IRF261/IRF262/IRF263/IRF264/IRF265/IRF266/IRF267/IRF268/IRF269/IRF270/IRF271/IRF272/IRF273/IRF274/IRF275/IRF276/IRF277/IRF278/IRF279/IRF280/IRF281/IRF282/IRF283/IRF284/IRF285/IRF286/IRF287/IRF288/IRF289/IRF290/IRF291/IRF292/IRF293/IRF294/IRF295/IRF296/IRF297/IRF298/IRF299/IRF300/IRF301/IRF302/IRF303/IRF304/IRF305/IRF306/IRF307/IRF308/IRF309/IRF310/IRF311/IRF312/IRF313/IRF314/IRF315/IRF316/IRF317/IRF318/IRF319/IRF320/IRF321/IRF322/IRF323/IRF324/IRF325/IRF326/IRF327/IRF328/IRF329/IRF330/IRF331/IRF332/IRF333/IRF334/IRF335/IRF336/IRF337/IRF338/IRF339/IRF340/IRF341/IRF342/IRF343/IRF344/IRF345/IRF346/IRF347/IRF348/IRF349/IRF350/IRF351/IRF352/IRF353/IRF354/IRF355/IRF356/IRF357/IRF358/IRF359/IRF360/IRF361/IRF362/IRF363/IRF364/IRF365/IRF366/IRF367/IRF368/IRF369/IRF370/IRF371/IRF372/IRF373/IRF374/IRF375/IRF376/IRF377/IRF378/IRF379/IRF380/IRF381/IRF382/IRF383/IRF384/IRF385/IRF386/IRF387/IRF388/IRF389/IRF390/IRF391/IRF392/IRF393/IRF394/IRF395/IRF396/IRF397/IRF398/IRF399/IRF400/IRF401/IRF402/IRF403/IRF404/IRF405/IRF406/IRF407/IRF408/IRF409/IRF410/IRF411/IRF412/IRF413/IRF414/IRF415/IRF416/IRF417/IRF418/IRF419/IRF420/IRF421/IRF422/IRF423/IRF424/IRF425/IRF426/IRF427/IRF428/IRF429/IRF430/IRF431/IRF432/IRF433/IRF434/IRF435/IRF436/IRF437/IRF438/IRF439/IRF440/IRF441/IRF442/IRF443/IRF444/IRF445/IRF446/IRF447/IRF448/IRF449/IRF450/IRF451/IRF452/IRF453/IRF454/IRF455/IRF456/IRF457/IRF458/IRF459/IRF460/IRF461/IRF462/IRF463/IRF464/IRF465/IRF466/IRF467/IRF468/IRF469/IRF470/IRF471/IRF472/IRF473/IRF474/IRF475/IRF476/IRF477/IRF478/IRF479/IRF480/IRF481/IRF482/IRF483/IRF484/IRF485/IRF486/IRF487/IRF488/IRF489/IRF490/IRF491/IRF492/IRF493/IRF494/IRF495/IRF496/IRF497/IRF498/IRF499/IRF500/IRF501/IRF502/IRF503/IRF504/IRF505/IRF506/IRF507/IRF508/IRF509/IRF510/IRF511/IRF512/IRF513/IRF514/IRF515/IRF516/IRF517/IRF518/IRF519/IRF520/IRF521/IRF522/IRF523/IRF524/IRF525/IRF526/IRF527/IRF528/IRF529/IRF530/IRF531/IRF532/IRF533/IRF534/IRF535/IRF536/IRF537/IRF538/IRF539/IRF540/IRF541/IRF542/IRF543/IRF544/IRF545/IRF546/IRF547/IRF548/IRF549/IRF550/IRF551/IRF552/IRF553/IRF554/IRF555/IRF556/IRF557/IRF558/IRF559/IRF560/IRF561/IRF562/IRF563/IRF564/IRF565/IRF566/IRF567/IRF568/IRF569/IRF570/IRF571/IRF572/IRF573/IRF574/IRF575/IRF576/IRF577/IRF578/IRF579/IRF580/IRF581/IRF582/IRF583/IRF584/IRF585/IRF586/IRF587/IRF588/IRF589/IRF590/IRF591/IRF592/IRF593/IRF594/IRF595/IRF596/IRF597/IRF598/IRF599/IRF600/IRF601/IRF602/IRF603/IRF604/IRF605/IRF606/IRF607/IRF608/IRF609/IRF610/IRF611/IRF612/IRF613/IRF614/IRF615/IRF616/IRF617/IRF618/IRF619/IRF620/IRF621/IRF622/IRF623/IRF624/IRF625/IRF626/IRF627/IRF628/IRF629/IRF630/IRF631/IRF632/IRF633/IRF634/IRF635/IRF636/IRF637/IRF638/IRF639/IRF640/IRF641/IRF642/IRF643/IRF644/IRF645/IRF646/IRF647/IRF648/IRF649/IRF650/IRF651/IRF652/IRF653/IRF654/IRF655/IRF656/IRF657/IRF658/IRF659/IRF660/IRF661/IRF662/IRF663/IRF664/IRF665/IRF666/IRF667/IRF668/IRF669/IRF670/IRF671/IRF672/IRF673/IRF674/IRF675/IRF676/IRF677/IRF678/IRF679/IRF680/IRF681/IRF682/IRF683/IRF684/IRF685/IRF686/IRF687/IRF688/IRF689/IRF690/IRF691/IRF692/IRF693/IRF694/IRF695/IRF696/IRF697/IRF698/IRF699/IRF700/IRF701/IRF702/IRF703/IRF704/IRF705/IRF706/IRF707/IRF708/IRF709/IRF710/IRF711/IRF712/IRF713/IRF714/IRF715/IRF716/IRF717/IRF718/IRF719/IRF720/IRF721/IRF722/IRF723/IRF724/IRF725/IRF726/IRF727/IRF728/IRF729/IRF730/IRF731/IRF732/IRF733/IRF734/IRF735/IRF736/IRF737/IRF738/IRF739/IRF740/IRF741/IRF742/IRF743/IRF744/IRF745/IRF746/IRF747/IRF748/IRF749/IRF750/IRF751/IRF752/IRF753/IRF754/IRF755/IRF756/IRF757/IRF758/IRF759/IRF760/IRF761/IRF762/IRF763/IRF764/IRF765/IRF766/IRF767/IRF768/IRF769/IRF770/IRF771/IRF772/IRF773/IRF774/IRF775/IRF776/IRF777/IRF778/IRF779/IRF780/IRF781/IRF782/IRF783/IRF784/IRF785/IRF786/IRF787/IRF788/IRF789/IRF790/IRF791/IRF792/IRF793/IRF794/IRF795/IRF796/IRF797/IRF798/IRF799/IRF800/IRF801/IRF802/IRF803/IRF804/IRF805/IRF806/IRF807/IRF808/IRF809/IRF810/IRF811/IRF812/IRF813/IRF814/IRF815/IRF816/IRF817/IRF818/IRF819/IRF820/IRF821/IRF822/IRF823/IRF824/IRF825/IRF826/IRF827/IRF828/IRF829/IRF830/IRF831/IRF832/IRF833/IRF834/IRF835/IRF836/IRF837/IRF838/IRF839/IRF840/IRF841/IRF842/IRF843/IRF844/IRF845/IRF846/IRF847/IRF848/IRF849/IRF850/IRF851/IRF852/IRF853/IRF854/IRF855/IRF856/IRF857/IRF858/IRF859/IRF860/IRF861/IRF862/IRF863/IRF864/IRF865/IRF866/IRF867/IRF868/IRF869/IRF870/IRF871/IRF872/IRF873/IRF874/IRF875/IRF876/IRF877/IRF878/IRF879/IRF880/IRF881/IRF882/IRF883/IRF884/IRF885/IRF886/IRF887/IRF888/IRF889/IRF890/IRF891/IRF892/IRF893/IRF894/IRF895/IRF896/IRF897/IRF898/IRF899/IRF900/IRF901/IRF902/IRF903/IRF904/IRF905/IRF906/IRF907/IRF908/IRF909/IRF910/IRF911/IRF912/IRF913/IRF914/IRF915/IRF916/IRF917/IRF918/IRF919/IRF920/IRF921/IRF922/IRF923/IRF924/IRF925/IRF926/IRF927/IRF928/IRF929/IRF930/IRF931/IRF932/IRF933/IRF934/IRF935/IRF936/IRF937/IRF938/IRF939/IRF940/IRF941/IRF942/IRF943/IRF944/IRF945/IRF946/IRF947/IRF948/IRF949/IRF950/IRF951/IRF952/IRF953/IRF954/IRF955/IRF956/IRF957/IRF958/IRF959/IRF960/IRF961/IRF962/IRF963/IRF964/IRF965/IRF966/IRF967/IRF968/IRF969/IRF970/IRF971/IRF972/IRF973/IRF974/IRF975/IRF976/IRF977/IRF978/IRF979/IRF980/IRF981/IRF982/IRF983/IRF984/IRF985/IRF986/IRF987/IRF988/IRF989/IRF990/IRF991/IRF992/IRF993/IRF994/IRF995/IRF996/IRF997/IRF998/IRF999/IRF1000/IRF1001/IRF1002/IRF1003/IRF1004/IRF1005/IRF1006/IRF1007/IRF1008/IRF1009/IRF1010/IRF1011/IRF1012/IRF1013/IRF1014/IRF1015/IRF1016/IRF1017/IRF1018/IRF1019/IRF1020/IRF1021/IRF1022/IRF1023/IRF1024/IRF1025/IRF1026/IRF1027/IRF1028/IRF1029/IRF1030/IRF1031/IRF1032/IRF1033/IRF1034/IRF1035/IRF1036/IRF1037/IRF1038/IRF1039/IRF1040/IRF1041/IRF1042/IRF1043/IRF1044/IRF1045/IRF1046/IRF1047/IRF1048/IRF1049/IRF1050/IRF1051/IRF1052/IRF1053/IRF1054/IRF1055/IRF1056/IRF1057/IRF1058/IRF1059/IRF1060/IRF1061/IRF1062/IRF1063/IRF1064/IRF1065/IRF1066/IRF1067/IRF1068/IRF1069/IRF1070/IRF1071/IRF1072/IRF1073/IRF1074/IRF1075/IRF1076/IRF1077/IRF1078/IRF1079/IRF1080/IRF1081/IRF1082/IRF1083/IRF1084/IRF1085/IRF1086/IRF1087/IRF1088/IRF1089/IRF1090/IRF1091/IRF1092/IRF1093/IRF1094/IRF1095/IRF1096/IRF1097/IRF1098/IRF1099/IRF1100/IRF1101/IRF1102/IRF1103/IRF1104/IRF1105/IRF1106/IRF1107/IRF1108/IRF1109/IRF1110/IRF1111/IRF1112/IRF1113/IRF1114/IRF1115/IRF1116/IRF1117/IRF1118/IRF1119/IRF1120/IRF1121/IRF1122/IRF1123/IRF1124/IRF1125/IRF1126/IRF1127/IRF1128/IRF1129/IRF1130/IRF1131/IRF1132/IRF1133/IRF1134/IRF1135/IRF1136/IRF1137/IRF1138/IRF1139/IRF1140/IRF1141/IRF1142/IRF1143/IRF1144/IRF1145/IRF1146/IRF1147/IRF1148/IRF1149/IRF1150/IRF1151/IRF1152/IRF1153/IRF1154/IRF1155/IRF1156/IRF1157/IRF1158/IRF1159/IRF1160/IRF1161/IRF1162/IRF1163/IRF1164/IRF1165/IRF1166/IRF1167/IRF1168/IRF1169/IRF1170/IRF1171/IRF1172/IRF1173/IRF1174/IRF1175/IRF1176/IRF1177/IRF1178/IRF1179/IRF1180/IRF1181/IRF1182/IRF1183/IRF1184/IRF1185/IRF1186/IRF1187/IRF1188/IRF1189/IRF1190/IRF1191/IRF1192/IRF1193/IRF1194/IRF1195/IRF1196/IRF1197/IRF1198/IRF1199/IRF1200/IRF1201/IRF1202/IRF1203/IRF1204/IRF1205/IRF1206/IRF1207/IRF1208/IRF1209/IRF1210/IRF1211/IRF1212/IRF1213/IRF1214/IRF1215/IRF1216/IRF1217/IRF1218/IRF1219/IRF1220/IRF1221/IRF1222/IRF1223/IRF1224/IRF1225/IRF1226/IRF1227/IRF1228/IRF1229/IRF1230/IRF1231/IRF1232/IRF1233/IRF1234/IRF1235/IRF1236/IRF1237/IRF1238/IRF1239/IRF1240/IRF1241/IRF1242/IRF1243/IRF1244/IRF1245/IRF1246/IRF1247/IRF1248/IRF1249/IRF1250/IRF1251/IRF1252/IRF1253/IRF1254/IRF1255/IRF1256/IRF1257/IRF1258/IRF1259/IRF1260/IRF1261/IRF1262/IRF1263/IRF1264/IRF1265/IRF1266/IRF1267/IRF1268/IRF1269/IRF1270/IRF1271/IRF1272/IRF1273/IRF1274/IRF1275/IRF1276/IRF1277/IRF1278/IRF1279/IRF1280/IRF1281/IRF1282/IRF1283/IRF1284/IRF1285/IRF1286/IRF1287/IRF1288/IRF1289/IRF1290/IRF1291/IRF1292/IRF1293/IRF1294/IRF1295/IRF1296/IRF1297/IRF1298/IRF1299/IRF1300/IRF1301/IRF1302/IRF1303/IRF1304/IRF1305/IRF1306/IRF1307/IRF1308/IRF1309/IRF1310/IRF1311/IRF1312/IRF1313/IRF1314/IRF1315/IRF1316/IRF1317/IRF1318/IRF1319/IRF1320/IRF1321/IRF1322/IRF1323/IRF1324/IRF1325/IRF1326/IRF1327/IRF1328/IRF1329/IRF1330/IRF1331/IRF1332/IRF1333/IRF1334/IRF1335/IRF1336/IRF1337/IRF1338/IRF1339/IRF1340/IRF1341/IRF1342/IRF1343/IRF1344/IRF1345/IRF1346/IRF1347/IRF1348/IRF1349/IRF1350/IRF1351/IRF1352/IRF1353/IRF1354/IRF1355/IRF1356/IRF1357/IRF1358/IRF1359/IRF1360/IRF1361/IRF1362/IRF1363/IRF1364/IRF1365/IRF1366/IRF1367/IRF1368/IRF1369/IRF1370/IRF1371/IRF1372/IRF1373/IRF1374/IRF1375/IRF1376/IRF1377/IRF1378/IRF1379/IRF1380/IRF1381/IRF1382/IRF1383/IRF1384/IRF1385/IRF1386/IRF1387/IRF1388/IRF1389/IRF1390/IRF1391/IR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后其肠道拟杆菌含量增多且骨骼肌力量明显提高^[63]。拟杆菌丰度增加, 改善葡萄糖代谢及脂质代谢水平, 并降解支链氨基酸和复合糖聚合物, 进而改善肌肉衰老。此外, 8周HIIT和抗阻运动均可以提升菌群多样性, 并增加拟杆菌属丰度^[64-65]。另有研究表明, 在db/db小鼠模型中定向移植运动供体的粪菌, 可改善受体鼠的葡萄糖稳态、肠道SCFAs代谢、内皮功能, 并提高握力和转棒停留时间^[66]。以上结果提示, 不同运动方式均可能通过调节肠道菌群的组成、纠正病理性脂质代谢重编程提高骨骼肌的功能。

另一方面, 运动促进SCFAs生成可能是连接肠道菌群、脂质代谢重编程和骨骼肌功能改善的重要环节。具体而言, 运动可提高双歧杆菌、乳酸杆菌、拟杆菌、阿克曼菌以及*Faecalibacterium*、*Roseburia*、*Lachnospiraceae*和*Ruminococcaceae*等SCFAs相关菌群的丰度, 从而增加乙酸、丙酸和丁酸等代谢物生成^[67]。SCFAs进入循环后, 可通过作用于骨骼肌及代谢相关组织中的游离脂肪酸受体, 或通过抑制组蛋白去乙酰化酶活性, 激活AMPK/PGC-1 α 信号, 促进线粒体生物发生、脂肪酸氧化和GLUT4介导的葡萄糖摄取; 同时, SCFAs还可降低肠屏障破坏和LPS介导的炎症反应, 减少NF- κ B信号激活, 从而改善IR、脂质沉积和肌肉蛋白分解状态^[68]。此外, 研究表明, 有氧运动能通过调节增加SCFAs水平, 进而影响蛋白质合成途径, 增加腺苷三磷酸生成和肌肉蛋白质的摄入, 促进骨骼肌合成^[69]。而12周的HIIT训练亦可通过增加SCFAs水平改善DM患者的糖脂代谢紊乱, 即SCFAs增加促进小鼠乙酰辅酶A羧化酶的磷酸化, 增加脂肪组织和骨骼肌中PGC-1 α 的表达, 上调解偶联蛋白1, 进而恢复生理性代谢重编程^[70]。Okamoto等^[71]报道, 抗生素处理后C57BL/6小鼠运动耐力下降, 而持续输注乙酸可以恢复其运动能力, 提示肠道菌群作用是运动发挥抗肌萎缩作用的重要途径。需要指出的是, 目前研究主要来源于DM模型、衰老性肌少症模型或一般肌萎缩模型, 针对DS的直接研究SCFAs仍相对有限。因此, 现有研究更多是从糖代谢紊乱、肌肉衰退和菌群代谢异常等相关病理环节出发, 为解释DS中肠道菌群失衡与病理性脂质代谢重编程提供间接依据。未来仍需在DS特异性模型及临床人群中进一步验证运动干预对肠道菌群结构、SCFAs生成、脂质代谢重编程及骨骼肌功能改善之间的因果

关系, 以明确该调控轴在DS防治中的实际作用和应用价值。

3 脂质代谢重编程改善糖尿病肌少症的运动干预策略

DS兼具糖脂代谢异常与骨骼肌质量、力量及功能下降的双重特征, 因此其运动干预不宜仅以降糖或增肌为单一目标, 而应以纠正病理性脂质代谢重编程、减少异位脂肪沉积并维持肌肉功能为综合导向。近年来, 亚洲肌少症工作组(Asian working group for sarcopenia, AWGS)在2025年更新共识中进一步强调, 应从单纯的肌少症诊断和治疗转向全生命周期的肌肉健康促进, 并重视运动、营养与功能维护的综合管理理念^[72]。基于此, 运动类型、强度与频率的精准组合是调控脂质代谢重编程, 缓解DS发生发展的关键。

3.1 运动类型

从运动类型看, 抗阻运动是DS干预中证据较为充分的运动形式之一, 尤其适用于改善肌肉力量、肌肉量及糖代谢相关指标。随机对照试验研究(randomized controlled trial, RCT)显示, 抗阻运动对老年T2DM患者的糖化血红蛋白(glycosylated hemoglobin, HbA1c)、肌力及体成分均具有积极影响, 且能够重塑脂质谱, 降低甘油三酯、总胆固醇的含量, 且在部分人群中, 其对血糖控制和身体成分改善的作用甚至优于单纯有氧运动^[73]。这为抗阻运动干预DS提供了间接依据。Chien等^[74]对40例50岁以上DS患者进行12周渐进性抗阻运动, 显著改善了HbA1c、骨骼肌量和小腿围。Takenami等^[75]同样发现, 每周2次、持续16周的抗阻运动, 可增加DS患者大腿围度和肌力, 减少脂肪量并降低HbA1c。从机制上看, 抗阻运动不仅可改善肌肉量和肌力, 还可能通过激活PI3K/Akt/mTOR信号促进蛋白质合成, 并抑制MuRF-1、Atrogin-1介导的蛋白降解^[41]。同时, 抗阻运动还可通过抑制NF- κ B炎症信号、激活FGF21/PI3K/Akt通路, 改善糖脂代谢紊乱、炎症反应和肌纤维化^[45]。上述研究说明, 抗阻运动在改善DS相关肌肉表型和糖脂代谢异常方面具有重要价值。

此外, HIIT同样有助于降低小腿部位的IMAT含量, 并可显著改善老年人空腹INS水平和糖耐量^[40]。而热量限制联合有氧运动可以改善DM患者全身INS敏感性、增加线粒体生物发生、能量代

谢以及肌肉合成^[76],提示有氧训练及HIIT同样具有重要的代谢调节价值。尽管目前相关证据多来源于T2DM、老年人或代谢异常人群,直接针对DS患者的研究仍相对有限,但上述研究为不同模式运动干预DS提供了借鉴依据。相比之下,联合训练兼具抗阻运动和有氧运动的特点,综合获益可能更具优势。参考AWGS 2025共识正式建议采用“多模态运动干预”(即有氧与抗阻运动结合),可能更符合DS复合病理特征下的综合干预需求^[77]。研究显示,T2DM患者进行多模态运动干预可同时降低空腹血糖、餐后血糖、INS和HbA1c,并改善血脂谱、下肢肌力^[78]。另一项12周RCT同样显示,相对于单纯运动,多模态运动干预后,HbA1c、血糖、血脂谱、四肢骨骼肌指数和体适能均显著改善^[79]。从机制角度看,多模态运动可整合抗阻运动对PI3K/Akt/mTOR和蛋白质代谢的调节作用,以及有氧运动对AMPK/PGC-1 α 、脂肪酸氧化和线粒体功能的改善作用,从而同时干预IR、异位脂肪沉积和肌肉萎缩等多个环节。然而,需要指出的是,目前关于多模态运动干预对DS的直接研究仍较少,部分证据主要来自T2DM、老年肌少症或老年代谢异常人群,其相对于单一训练方式在DS干预上的优势仍需更多高质量RCT进一步验证。综上,DS运动类型的选择不应简单追求某一种固定模式,而应根据患者的主要问题进行分层设计,整合遗传风险及患者偏好,以实现疗效最大化。对于有特定症状需求的患者而言,可针对性选择已验证有优势的运动类型。

3.2 运动强度

运动强度是制定运动方案的核心参数。抗阻运动强度与血糖控制、血脂代谢、肌肉力量和瘦体重改善密切相关,但不同强度对不同结局指标的作用并不完全一致。研究表明,75%~100% 1RM的中高强度抗阻运动能够在改善T2DM患者HbA1c和IR的同时增加瘦体重、降低总胆固醇、甘油三酯水平^[80]。而低强度训练并不意味着干预效应较弱,对于高龄、体能下降或合并慢性疾病的DS患者而言,低强度慢速抗阻运动同样可改善糖脂代谢和骨骼肌功能指标,并具有较好的安全性和依从性。与高强度运动相比,中等强度抗阻运动(65%~80% 1RM)在改善DS患者肌肉减少的同时,在改善IR、三酰甘油和总胆固醇方面可能更具优势,其原因可能在于高强度运动增加了游离脂肪酸和儿茶酚胺的含量,造成氧化应激损伤,从而对GLUT4表

达产生了负面作用^[81]。Su等^[82]研究同样发现,70%~80% 1RM抗阻训练可显著降低患者HbA1c和空腹血糖。从机制上看,适宜强度运动可有效激活AMPK/PGC-1 α 、PI3K/Akt等代谢信号,促进脂肪酸氧化、葡萄糖摄取和线粒体功能改善,而过高强度运动可能增加氧化应激和炎症负荷,反而不利于脂质代谢重编程恢复^[47-48]。因此,运动强度并非越高越好,而应兼顾代谢获益、肌肉适应和运动安全性。尤其是DS患者常伴高龄、肌力下降、关节退变、心血管风险或DM并发症,不宜在干预初期直接采用高强度训练。

针对有氧运动,研究表明,中等强度有氧运动训练通过增加糖酵解、脂肪酸分解代谢和脂肪酸 β 氧化途径,改善db/db伴肌少症小鼠INS敏感性,从而增加肌细胞密度和肌纤维面积^[38]。RCT研究同样显示,50%~80%最大摄氧量的有氧运动后能明显改善体成分、HbA1c等指标^[83],提示中等强度有氧运动可能是改善DS的合适强度。需要指出的是,目前有氧运动干预DS的最佳强度仍缺乏直接证据,研究部分借鉴DM患者,有氧运动处方制定过程中最佳强度范围仍需结合患者年龄、心肺功能、并发症风险和运动耐受能力进行个体化调整。而对于多模态运动干预而言,强度控制相对更为复杂。有氧运动与抗阻运动在强度指标、训练容量、间歇时间和恢复需求上存在差异且目前仍缺乏针对多模态运动强度效应的相关研究。综上,运动强度的设定并非越高越好,而应根据患者的代谢状态、肌肉功能和耐受能力进行个体化设定。基于现有研究提示,中低强度抗阻运动或有氧运动,在改善IR、血脂代谢及骨骼肌功能方面可能更具优势,其应作为DS运动处方制定的重要参考。

3.3 运动频率和时间

DS运动干预的效果并不只取决于运动类型本身,还与训练剂量的累积密切相关。Shultz等^[84]发现16周,每次60 min的高频-中等强度抗阻运动(60%~85% 1RM)可降低脂肪含量并减轻炎症反应。另有研究表明,每周3次及以上,每次时间超过30 min,共12周的抗阻运动能够显著改善T2DM的血糖和总胆固醇水平,且当运动频率超过每周3次时,对总胆固醇的改善更为明显^[85]。McLeod等^[86]也发现,每周3次以上的抗阻运动比每周1次能带来更显著的力量增长。针对DS人群,陈丽妹等^[87]建议患者应进行12周,每周3次,每次间隔48 h的抗阻运动。上述研究提示,抗阻运动需要

达到一定训练剂量后,才更可能在肌力、脂代谢和炎症改善方面产生稳定获益。

有氧运动方面,研究表明,12周,每周2~3次,每次30 min的有氧运动改善老年肌少症患者脂肪异位分布和容量,并减少跌倒与骨折风险,带来远期效益^[88]。Prior等^[89]研究同样发现,24周,每周3次,每次30~45 min的有氧运动有助于降低小腿部位的IMAT含量。根据以上结果,DS运动干预的效果不仅取决于运动类型,还高度依赖训练频率、单次时长及干预周期等剂量因素。针对多模态运动干预,每周3次,每次40 min,共6个月的多模态运动干预已被证明可同时降低空腹血糖、餐后血糖、INS和HbA1c,并改善血脂谱和下肢肌力^[90]。另一项12周RCT同样显示,每周2~3次,每次50 min的多模态运动干预后,相对于单纯运动,HbA1c、血糖、血脂谱、四肢骨骼肌指数和体能均显著改善^[91]。从机制上看,运动频率和干预周期决定了短暂代谢信号能否转化为稳定适应。持续规律运动有助于维持AMPK/PGC-1 α 介导的脂肪酸氧化和线粒体生物发生,并促进PINK1/Parkin、ULK1等线粒体质量控制过程,从而改善脂毒性负荷和骨骼肌代谢稳态^[58-59]。此外,肠道菌群结构和SCFAs生成也依赖较长周期的规律运动刺激,可能进一步参与脂质代谢和炎症反应调节^[67-68]。不过,鉴于DS直接研究仍较有限,上述频率和时间建议仍需结合T2DM、老年肌少症及老年代谢异常人群的研究结果谨慎外推。综上,DS的运动干预强调长期、规律和可持续的训练剂量。现有研究提示,12周以上的持续干预收益更稳定,其中抗阻运动以每周3次、每次30 min,间隔48 h较为适宜,有氧运动采用每周2~3次、每次30 min以上更具可行性,而多模态运动干预则应在控制总运动量和恢复时间的基础上,将抗阻、有氧等训练合理组合。总体来看,规律、足量、长期坚持的运动方案更有利于改善DS患者的脂代谢紊乱、异位脂肪沉积及肌肉功能下降。

4 总结与展望

本文系统探讨了脂质代谢紊乱驱动IR、慢性炎症、线粒体功能障碍、肠道菌群失衡及蛋白质稳态破坏等多个关键病理环节在DS发生发展中的核心作用及运动干预改善脂质代谢紊乱,重塑骨骼肌代谢模式,恢复生理性脂质代谢重编程调控DS的潜在机制和干预策略,为DS的预防、干预和长期

管理提供新的依据。尽管研究已初步揭示运动干预对于纠正病理性脂质代谢重编程缓解DS的积极作用,但尚有大量科学问题亟待解决。其一,DS的诊断标准和分层依据尚未完全统一,不同疾病阶段的脂质代谢异常特征及其动态变化仍不清晰。其二,运动干预影响脂质代谢重编程的关键酶、信号通路及其上下游调控网络尚未充分阐明。其三,不同运动方式、强度、频率和周期在调控脂质代谢重编程方面的差异及其剂量-效应关系尚未完全明确。因此,未来研究应在规范DS诊断标准和评价体系的基础上,结合转录组学、脂质组学、代谢组学及单细胞测序等技术,系统解析DS不同阶段脂质代谢重编程的分子特征及运动干预的调控网络。同时,应进一步比较不同运动模式在不同人群和疾病阶段中的干预效果,明确关键剂量参数和适宜运动方案,推动运动处方由经验推荐向精准干预转变。总体而言,运动干预恢复生理性脂质代谢重编程是改善DS进展新的潜在研究路径。随着技术的进步和研究的深入,有望揭示这一复杂调控网络的全貌,为DS的治疗提供新的思路和方法。

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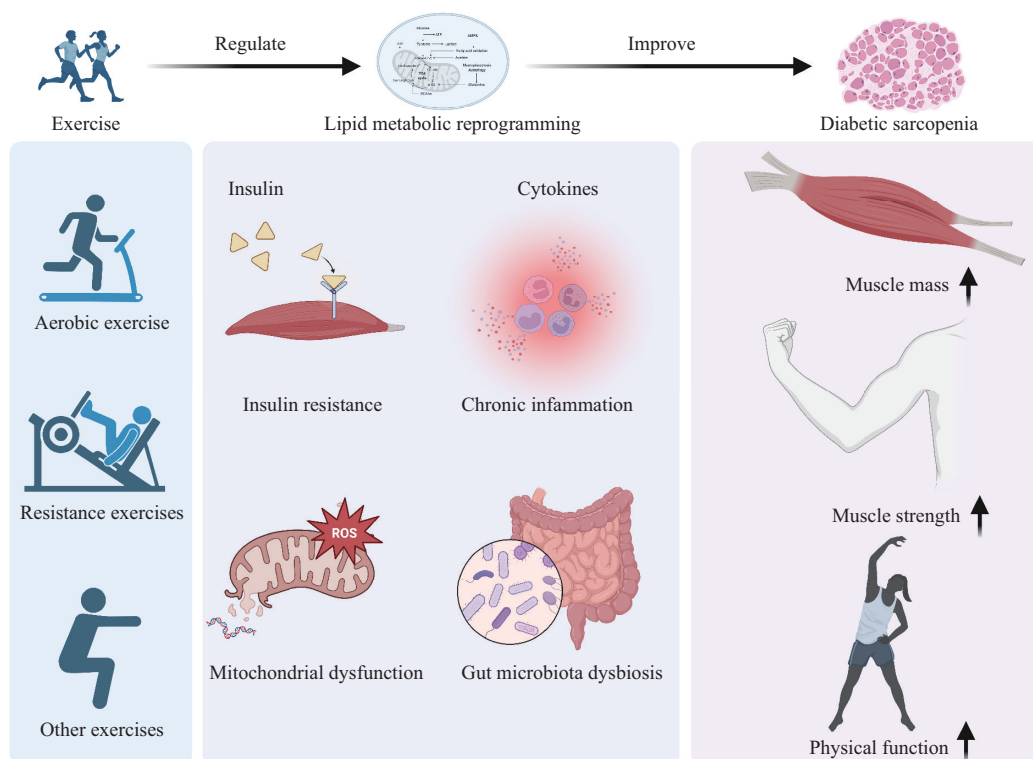
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Exercise Intervention Alleviates Diabetic Sarcopenia by Regulating Lipid Metabolic Reprogramming: Mechanisms and Strategies*

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Graphical abstract



Abstract Diabetic sarcopenia (DS) is a common but often ignored skeletal muscle complication in individuals with diabetes mellitus. It is characterized by progressive loss of skeletal muscle mass, reduced muscle strength, and impaired physical performance, which may further increase the risk of falls, disabilities, metabolic disorders, and adverse clinical outcomes. Traditionally, DS has been attributed mainly to hyperglycemia, insulin resistance, aging-related muscle decline, and chronic complications of diabetes. However, increasing evidence suggests that lipid metabolic disturbance and pathological lipid metabolic reprogramming are not merely secondary

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consequences of diabetes, but may actively participate in the initiation and progression of DS. Under diabetic conditions, impaired fatty acid uptake, transport, oxidation, and storage disrupt skeletal muscle metabolic homeostasis, leading to ectopic lipid deposition and accumulation of lipotoxic intermediates. These lipid-derived metabolites can aggravate insulin resistance, impair mitochondrial energy production, enhance oxidative stress, activate chronic low-grade inflammation, and disturb protein synthesis and degradation balance, thereby accelerating skeletal muscle atrophy and functional decline. Lipid metabolic dysregulation may also interact with multiple pathological processes involved in DS, including mitochondrial dysfunction, inflammatory signaling, oxidative damage, impaired autophagy, and gut microbiota imbalance. These mechanisms do not occur independently; instead, they form a complex bidirectional vicious cycle with diabetes-related metabolic disorders. Specifically, mitochondrial dysfunction reduces fatty acid oxidative capacity, which further promotes lipid accumulation and lipotoxicity. Inflammatory activation can impair insulin signaling and muscle protein metabolism, while lipid overload may in turn amplify inflammatory responses. Similarly, gut microbiota dysbiosis and altered microbial metabolites may influence systemic inflammation, lipid metabolism, and skeletal muscle homeostasis. Therefore, lipid metabolic reprogramming provides an important mechanistic perspective for understanding the progression of DS from metabolic disturbance to structural and functional muscle impairment. Exercise intervention is an effective and clinically feasible non-pharmacological strategy for the prevention and management of DS. Both aerobic exercise and resistance training have been shown to improve insulin sensitivity, enhance fatty acid oxidation, increase mitochondrial biogenesis, reduce ectopic lipid deposition, and attenuate lipotoxic metabolite accumulation. These adaptations not only improved glucose and lipid metabolism, but also increased the preservation of muscle mass, muscle strength, and physical function. Moreover, combined exercise strategies may provide complementary benefits by integrating the metabolic advantages of aerobic exercise with the anabolic and functional effects of resistance training. Based on analyses of publicly available datasets and literature evidences, this review systematically summarizes the role of lipid metabolic disorders in the pathogenesis of DS, with particular attention to the molecular mechanisms linking lipid dysregulation to insulin resistance, chronic inflammation, oxidative stress, mitochondrial dysfunction, and gut microbiota disturbance. Furthermore, this review discusses the potential mechanisms by which exercise intervention improves DS through the regulation of lipid metabolic reprogramming, and outlines exercise prescription strategies in terms of modality, intensity, frequency, and duration. Understanding the interaction between lipid metabolism and skeletal muscle dysfunction may provide new theoretical evidence for early identification, mechanistic research, and precision exercise therapy in DS. Overall, targeting pathological lipid metabolic reprogramming through exercise intervention represents a promising and clinically actionable approach for improving muscle health and prognosis in individuals with DS.

Key words exercise intervention, diabetic sarcopenia, lipid metabolic reprogramming, lipid metabolism disorder, skeletal muscle

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