

2型糖尿病肌少症与血糖稳定性研究进展

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摘 要

2型糖尿病(T2DM)与肌肉减少症(Sarcopenia)密切相关, 二者并存可形成恶性循环, 加剧病情。本文综述了二者关联的最新研究进展。T2DM相关的代谢紊乱(如胰岛素抵抗、慢性炎症)通过促进肌肉蛋白质分解抑制合成, 加速肌少症发生。反之, 肌少症导致的骨骼肌质量与功能下降会进一步削弱葡萄糖处置能力, 加剧胰岛素抵抗, 增加血糖控制难度。深入探讨T2DM患者合并肌少症的临床特征与危险因素, 并探索通过改善肌肉健康来优化血糖管理的策略, 对于打破上述恶性循环、改善患者预后具有重大临床意义。

关键词

2型糖尿病(T2DM), 肌肉减少症

Research Progress on Type 2 Diabetes with Sarcopenia and Glycemic Stability

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Abstract

Type 2 diabetes mellitus (T2DM) is closely associated with sarcopenia, and their coexistence can form a vicious cycle that exacerbates the condition. This article reviews the latest research advances in the relationship between these two conditions. Metabolic disturbances related to T2DM (such as insulin resistance and chronic inflammation) promote muscle protein breakdown and inhibit synthesis, accelerating the onset of sarcopenia. Conversely, the reduction in skeletal muscle mass and

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function caused by sarcopenia further impairs glucose disposal capacity, worsens insulin resistance, and increases the difficulty of glycemic control. In-depth exploration of the clinical characteristics and risk factors of sarcopenia in T2DM patients, along with strategies to optimize glycemic management by improving muscle health, is of great clinical significance for breaking this vicious cycle and improving patient prognosis.

Keywords

Type 2 Diabetes Mellitus (T2DM), Sarcopenia

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1. 引言

2 型糖尿病(Type 2 Diabetes Mellitus, T2DM)是一种以慢性高血糖、胰岛素抵抗和进行性胰岛素分泌缺陷为特征的代谢性疾病。随着全球生活方式的显著变化,其患病率持续攀升,已成为重大公共卫生问题[1]。肌肉减少症(Sarcopenia)则是一种与年龄增长密切相关的综合征,主要表现为以进行性骨骼肌质量减少、肌肉力量下降和躯体功能减退为主要特征,与跌倒、虚弱和死亡风险增加有关[2]。近年来研究发现,T2DM 患者中肌少症的患病率显著高于同龄非糖尿病人群,肌少症现已被认定为 T2DM 的重要并发症之一[3][4]。骨骼肌作为人体最大的胰岛素敏感器官,负责餐后约 80%的葡萄糖摄取与利用,对维持全身血糖稳态至关重要。近年来,学者们逐渐认识到,血糖稳定性,尤其是餐后血糖波动是连接 T2DM 与肌少症双向关系的核心病理生理枢纽。一方面,T2DM 特有的代谢紊乱,如慢性高血糖、胰岛素抵抗、晚期糖基化终末产物(AGEs)积聚、慢性炎症状态等可通过多种分子机制激活泛素-蛋白酶体系统、抑制 mTOR 等合成信号通路,促进肌肉蛋白质分解、抑制合成,从而加速肌肉流失、导致肌少症的发生与发展。另一方面,肌少症本身由于骨骼肌质量与功能的下降,会进一步削弱葡萄糖的处置能力,加剧胰岛素抵抗,使得餐后血糖更易飙升且难以平稳,进一步放大血糖波动幅度,增加血糖控制的难度,形成恶性循环,增加糖尿病相关并发症的风险。鉴于肌肉质量与功能在血糖调节中的核心地位及其对 T2DM 患者预后的深远影响,系统探讨 T2DM 患者合并肌少症的临床特征、危险因素,并进一步探索通过营养、运动及药物干预改善肌肉健康以优化血糖管理的新策略,具有十分重要的临床意义。本综述旨在围绕 T2DM 与肌少症之间的双向关系及其对血糖稳定性的影响,总结最新研究进展,为临床防治提供理论依据与实践方向。

2. 2 型糖尿病肌少症的特点

2.1. 流行病学特征

国内外多项研究一致表明,T2DM 患者肌少症的发生率显著高于正常人群。一项纳入 6526 名受试者的荟萃分析显示,T2DM 患者发生肌少症风险显著高于非糖尿病患者($OR = 1.55$, 95% CI: 1.25~1.91, $p < 0.001$) [5]。Veronese 等研究进一步证实该风险,报告 T2DM 组肌少症患病率为 28.4%,显著高于对照组的 18.7% ($OR = 1.63$, 95% CI: 1.20~2.22, $p = 0.002$) [6]。中国研究也发现,T2DM 患者的肌少症患病率显著高于健康对照组(14.8% vs 11.2%, $p = 0.035$) [7]。这种高患病率与 T2DM 患者肌肉质量与力量加速流失密切相关[8]。老年 T2DM 群体中肌少症的负担尤为突出,例如新加坡社区中老年 T2DM 患者的患病率可

达 27.4% [9]。肌少症不仅显著增加 T2DM 患者功能障碍、跌倒及骨折风险, 还可能因肌肉这一关键代谢器官受损, 进一步加剧血糖控制难度及并发症发生风险。

2.2. 临床表现的复杂性

T2DM 合并肌少症在临床表现方面具有一定复杂性, 尤其在肌肉质量变化方面存在不一致的研究结果。尽管多数研究报道 T2DM 患者肌肉质量下降[8]。但近期的一项比较研究提示, 与血糖正常者相比, T2DM 患者虽肌肉质量未见显著差异, 但其肌肉力量及身体功能(如握力、步速等)却明显受损[5]。这一发现表明, 在 T2DM 患者中, 肌肉功能损害可独立于明显的肌肉质量减少而发生, 提示其可能作为肌少症的早期表现。潜在机制包括神经支配异常、肌纤维类型转换(如 II 型纤维减少)、线粒体功能障碍及肌肉内脂肪浸润等。此外, 肌肉质量评估方法(如未充分校正脂肪浸润)的局限性也可能导致对实际肌肉流失程度的低估。因此, 在临床筛查 T2DM 相关肌少症时, 除肌肉质量(建议采用经脂肪校正的评估指标, 如 DXA 所测四肢骨骼肌质量指数 ASMI)外, 应特别重视肌肉力量(如握力)和躯体功能(如步速、五次起坐试验)的评估。值得注意的是, 肌肉功能下降及线粒体功能障碍本身也会直接影响葡萄糖摄取与利用, 进而加重血糖波动。

2.3. 性别差异

T2DM 患者中肌少症的患病率存在显著的性别差异。部分研究提示男性患病风险更高[10]-[13], 也有研究报告女性患病风险显著升高(OR = 2.539, 95% CI: 1.475~4.371, $p < 0.05$) [14]。这一差异提示性激素水平、体成分分布以及生活方式等因素可能在 T2DM 相关肌少症的发生机制中发挥重要作用。

3. T2DM 肌少症的危险因素

T2DM 患者发生肌少症是多种因素共同作用的结果, 主要包括不可干预的固有因素、糖尿病相关的病理生理与并发症因素, 以及可干预的生活方式与治疗因素。识别这些危险因素, 尤其关注可干预因素, 对制定预防策略、改善肌少症和优化血糖控制具有重要意义。

3.1. 不可干预因素

年龄是肌少症最主要的危险因素, 肌少症患病率随年龄增长显著上升。流行病学数据显示, 在 T2DM 患者中, 65~69 岁、70~74 岁、75~80 岁和 80 岁以上年龄组的肌少症患病率分别为 17.4%、28.1%、52.4% 和 60% [13]。约 40% 的 80 岁以上 T2DM 患者合并肌少症[15]。T2DM 显著放大了年龄相关的肌肉质量与功能下降(即原发性肌少症), 其机制可能与慢性炎症、胰岛素抵抗、线粒体功能障碍、血管并发症及活动受限等因素协同作用有关。

3.2. 糖尿病相关的病理生理与并发症因素

3.2.1. 血糖稳态失衡

血糖稳态的长期失衡和短期波动被认为是驱动 T2DM 患者肌肉丢失和功能障碍的核心代谢病理生理机制之一。

1) 长期血糖控制:

糖化血红蛋白(HbA1c)与肌少症风险的关系尚存争议, 可能受人群特征和混杂因素影响。研究证实, HbA1c 升高与 T2DM 患者较低的下肢肌肉质量、较差的身体机能(如步速、平衡)以及更弱的膝伸肌力量显著相关[16], 肌少症发生率随 HbA1c 升高而增加, 尤其在偏瘦个体中更为显著[17]。但也有研究显示合并肌少症的男性患者 HbA1c 水平反而较低[18]。老年虚弱 T2DM 患者中较低 HbA1c 可能提示营养不良

和肌肉丢失, 而非血糖控制良好。这些矛盾提示 HbA1c 与肌少症的关系可能受人群特征和未控制混杂因素的影响。

2) 血糖波动:

血糖波动性增大是肌少症的重要危险因素。研究表明, 血糖在目标范围内时间(TIR)每降低 1%, 肌少症风险增加 3.7% (OR = 0.967, 95% CI: 0.941~0.995) [19]。血糖波动指标(如通过日内血糖平均波动幅度 LAGE 和血糖标准差 SDBG 评估)升高与男性患者低肌肉量显著相关[10], 其在女性中的作用尚需进一步研究。血糖波动通过诱导氧化应激、激活炎症通路、损害内皮功能和线粒体能量代谢, 干扰肌肉蛋白合成与分解平衡, 从而加剧肌肉流失和功能障碍。肌肉质量与功能下降又会削弱葡萄糖摄取与利用, 形成血糖波动与肌少症之间的恶性循环。

3.2.2. 糖尿病慢性并发症

1) 糖尿病周围神经病变(DPN):

DPN 是肌少症的独立危险因素, 可使风险增加 56.4% (OR = 1.564, $p = 0.048$)该关联在矫正年龄、高血压等混杂因素后仍存在[20]。神经病变严重程度与肌少症患病率呈正相关, 糖尿病患者中重度神经病变组肌少症患病率高达 58.4% [20]。神经支配受损导致肌肉失神经萎缩和肌力下降, Nomura 等研究还发现合并神经病变的 T2DM 患者膝关节伸展力量显著降低[21]。鉴于 DPN 与肌少症密切相关, 应对高风险人群(如合并足部畸形 DFD 者)进行早期筛查。

2) 糖尿病视网膜病变(DR):

肌肉质量减少及肌力低下与 DR 的进展显著相关, 特别是与增殖性视网膜病变(PDR)风险增加密切相关(肌少症: OR = 7.78, 95% CI: 1.52~39.81, $p = 0.014$; 肌力低下: OR = 6.25, 95% CI: 1.15~33.96, $p = 0.034$) [12], 这种关联提示微血管功能障碍可能是肌肉与视网膜病变的共同病理基础。

3.2.3. 内分泌功能紊乱

T2DM 患者普遍存在下丘脑 - 垂体 - 肾上腺(HPA)轴功能异常, 表现为皮质醇节律紊乱和夜间水平升高。这种异常的皮质醇暴露促进肌肉蛋白分解、抑制合成, 从而导致肌肉质量与力量下降[22] [23]。研究表明, 清晨基础皮质醇水平与骨骼肌质量指数(SMI)和肌肉密度(SMD)呈负相关, 是 T2DM 患者发生肌少症的独立危险因素[24]。HPA 轴失调不仅直接损害肌肉健康, 也加剧胰岛素抵抗和肝糖输出, 共同参与血糖稳态失衡。

3.3. 可干预的生活方式与治疗因素

3.3.1. 营养不良

营养状况差显著增加肌少症风险[25]。能量摄入每增加 1 单位, 肌少症风险降低 14% (OR = 0.86; 95% CI: 0.78~0.95; $p = 0.001$) [26]。蛋白质摄入不足和维生素 D 缺乏也会损害肌肉蛋白合成[27]。除了蛋白质总量的摄入, 优质蛋白质(富含亮氨酸)及其在各餐中的均匀分布对最大化刺激肌肉合成尤为重要。

3.3.2. 体力活动缺乏

肌少症患者普遍活动水平较低[11] [13]。每日步行超过 5400 步可降低 70%的肌少症风险[11]。抗阻运动是增加肌肉质量和力量最有效的方式, 结合有氧运动可同时改善肌肉健康和胰岛素敏感性。

3.3.3. 药物影响

不同降糖药物对肌肉代谢有不同影响。有的降糖药物如二甲双胍对肌少症有保护作用, 但像 SGLT2 抑制剂可能导致体重下降和肌肉减少, 因此在临床选择降糖药物时, 应综合评估其对肌肉健康的潜在影响, 优先考虑对肌肉中性或有益的药物, 并在必要时加强营养和运动干预。

4. T2DM 肌肉与血糖稳定性的关系概述及相关研究

4.1. 骨骼肌在血糖稳态中的核心作用

骨骼肌是胰岛素介导的葡萄糖摄取和处置的主要组织, 约占全身葡萄糖利用的 70%~80%, 其质量与功能状态对维持血糖稳态具有关键作用。大量流行病学研究表明, 较高的肌肉质量与更好的血糖调节能力及更低的 T2DM 发病风险显著相关。常用的肌肉质量评估指标包括肌肉质量指数(MMI, 即总骨骼肌质量与体重之比)和四肢骨骼肌质量(ASM)。Srikanthan 等基于第三次全国健康和营养检查调查(NHANES III)的横断面研究发现, 较高的 MMI 与较低的胰岛素抵抗及糖尿病前期患病率相关[28]。一项韩国中青年队列研究进一步证实, MMI 与 T2DM 风险呈显著负相关[29], 且肌肉质量与葡萄糖利用水平也呈负相关[30]。值得注意的是, 肌肉质量的保护作用存在性别和肥胖状态的修饰效应。低肌肉质量与血糖波动的负向关联在男性 T2DM 患者中尤为突出[10] [31], Tatsukawa 等的研究也报道, ASM 与 T2DM 风险的负相关性仅在正常体重男性中显著, 在女性或超重/肥胖男性中未观察到显著关联[32], 提示男性患者肌肉流失更易导致葡萄糖处置能力下降和加剧血糖波动。在老年人群(≥ 70 岁)中, 肌肉与脂肪组织的代谢交互更为复杂。研究显示, MMI (四肢骨骼肌质量指数)和 FMI (躯干脂肪质量指数)均为该年龄段男性 T2DM 发生的独立危险因素[33], 突显了老年群体中体成分与糖代谢关系的特殊性。

4.2. 肌少症对 T2DM 及血糖稳定性的反作用：恶性循环的形成

肌少症(以低肌肉质量为特征)不仅是 T2DM 的结果, 更是加剧其病理进程和血糖管理难度的重要因素, 形成双向恶性循环: 低肌肉质量减少了胰岛素介导葡萄糖处置场所, 导致全身葡萄糖处理能力下降[34], 伴随肌肉减少的肌间脂肪(IMAT)和肌内脂肪(IMCL)的异常堆积, 成为促炎因子(如趋化因子)的来源, 进一步加剧局部胰岛素抵抗和肌肉功能障碍[35]。骨骼肌的进行性减少导致胰岛素介导的葡萄糖摄取和处置能力持续下降, 加重全身胰岛素抵抗和血糖异常[34]。一项针对韩国 >65 岁男性 T2DM 患者的研究发现, 较低的下肢肌肉质量和较差的身体表现与血糖控制不佳显著相关[36]。

4.3. 肌少症与血糖波动的关联：动态平衡的破坏

除长期血糖指标(如 HbA1c)外, 血糖波动本身也与肌少症状态显著相关[37]。具体而言, 血糖在目标范围内时间(TIR)与四肢骨骼肌质量指数(ASMI)及握力呈显著正相关; 相反, 血糖高于目标范围时间/幅度(TAR/MG)则与 ASMI 和握力呈负相关[19]。这表明良好的血糖稳定性(尤其是高 TIR)可能通过减轻氧化应激和 AGEs 积累, 保护肌肉蛋白质合成通路[38], 有望打破肌少症与高血糖之间的恶性循环。

5. 通过改善肌肉健康优化血糖稳定性

多项临床研究证据支持, 针对肌肉质量与功能进行干预, 是打破 T2DM 患者高血糖与肌少症间恶性循环、实现血糖稳定的关键策略。主要干预途径包括如下内容。

5.1. 运动干预：以抗阻训练为核心

抗阻训练(RT)可通过增加肌肉量、增强肌力、提升 GLUT4 表达与糖原合成酶活性等机制, 显著改善胰岛素敏感性和葡萄糖摄取[39]。RT 可有效降低 HbA1c [40], 部分研究也显示其降低空腹血糖的效果[41]。对于体重正常($BMI < 25 \text{ kg/m}^2$)的 T2DM 患者, 单独进行 RT 在改善 HbA1c 水平方面可能优于单独有氧训练, 其效果与四肢骨骼肌肌量增加相关, 且肌量为 HbA1c 下降的独立预测因子[42]。肥胖($BMI \geq 25 \text{ kg/m}^2$)的 T2DM 患者, 有氧训练与 RT 组合方式在降低 HbA1c 水平方面效果最优[43] [44]。对于老年患者, RT 可显著增强肌力、骨密度及血糖指标(HbA1c, FBG, HOMA-IR)。握力等肌力指标与更优血糖代谢

和更低 T2DM 风险相关[45]。

5.2. 营养干预：多元策略协同

补充亮氨酸或富含亮氨酸的蛋白质(每日 1.2~6 g)可改善肌力、瘦体重和活动能力[46] [47]。观察性研究进一步表明, 遵循地中海饮食及增加水果蔬菜的摄入量与身体机能改善、肌肉萎缩和衰弱风险降低有关[48]。膳食纤维的摄入不仅有助于改善血糖控制、降低高胰岛素血症和调节血脂[49], 较高膳食纤维摄入量还与更大的瘦体重、较低的脂肪含量及较低的肌少症患病率相关[50] [51], 尤其在女性中, 膳食纤维摄入与骨骼肌质量百分比呈正相关[52]。此外, 微量元素如硒和镁也可能对老年人的肌力和骨骼健康具有积极作用[48] [53], 但它们在 2 型糖尿病(T2DM)相关肌少症中的具体作用机制及效果, 仍需更多研究进一步阐明。

5.3. 药物治疗：关注体成分影响

部分降糖药物在控糖的同时对体成分具有潜在益处: GLP-1 受体激动剂(GLP-1 RA)与 SGLT2 抑制剂(SGLT2i): 可减少内脏脂肪和肝脏脂肪沉积。二甲双胍: 改善外周组织的胰岛素敏感性, 可能通过促进葡萄糖/钙摄取及抗炎抗氧化机制对肌量与肌力产生积极影响[13] [54]-[57]。噻唑烷二酮类(如吡格列酮): 可通过调节肌细胞内脂代谢提升能量利用效率[58]。对于老年患者在使用 GLP-1 RA 可能导致食欲下降和肌肉流失, 需个体化评估; SGLT2i 低血糖风险低, 但需注意其促肌肉合成效应在老年群体中可能减弱。

6. 结论与展望

本文系统综述了 T2DM 与肌少症在流行病学、临床表现及危险因素等方面的关联, 并总结了通过改善肌肉质量与功能以优化血糖稳定性的策略。主要结论如下: 现有证据表明, T2DM 与肌少症之间存在双向恶性循环。高血糖及血糖波动促进肌肉流失和功能减退; 而肌少症又反过来削弱葡萄糖摄取与利用能力, 加剧血糖控制难度。在干预方面, 多项研究支持采取综合性策略, 包括以抗阻训练为核心的运动疗法、注重优质蛋白和合理膳食模式的营养支持、选用对体成分有积极影响或中性作用的降糖药物。展望未来, 研究应进一步深入揭示 T2DM 肌少症的分子机制, 尤其关注性别特异性通路和老年人群中肌肉、脂肪与血糖调控的交互作用。临床实践需致力于制定个体化干预方案, 整合肌肉功能评估与影像学等多模态工具, 并积极探索新型降糖药物、特定营养配方和运动处方对肌肉代谢的长期效应。通过打破肌少症与高血糖之间的恶性循环, 将为 T2DM 患者提供更为全面、有效的管理手段, 最终改善其生活质量和长期预后。

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