



糖尿病肌腱病变的发生机制及运动干预*

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摘要 糖尿病的长期持续可能并发慢性肌腱病变, 表现为肌腱结构与功能异常、愈合能力受损、生物力学特性下降等, 并加剧局部炎症、破坏胶原组分、引发血管病变及功能障碍, 包括周围神经病变等, 诱导肌腱病变的发生。适宜运动可减少晚期糖基化终末产物 (AGEs) 与特异性受体 (RAGE) 的结合, 降低肿瘤坏死因子- α (TNF- α) 等促炎因子表达, 上调白介素-10 (IL-10) 表达, 抑制肌腱炎症反应, 维持肌腱微环境稳态; 可提高胰岛素样生长因子-1 (IGF-1) 等促进胶原合成的因子释放, 稳定肌腱胶原合成, 维持肌腱结构完整; 可提高血管内皮生长因子 (VEGF) 等维持血管功能的蛋白质分泌, 促进肌腱血管生成, 改善肌腱营养供给; 可提高脑源性神经营养因子 (BDNF) 等神经相关因子的表达, 强化肌腱周围神经支配及营养支持, 增强肌腱神经控制效能, 进而减轻糖尿病肌腱相关病理改变。本文系统阐述了糖尿病肌腱病变的发生机制, 探讨运动干预的作用机制, 将为糖尿病患者制定精准运动干预及健身策略提供理论依据。

关键词 糖尿病, 肌腱病变, 发病机制, 运动干预**中图分类号** G804, R87**DOI:** 10.3724/j.pibb.2026.0196**CSTR:** 32369.14.pibb.20260196

糖尿病 (diabetes mellitus, DM) 是一种因遗传与环境因素相互作用, 导致胰岛素分泌缺陷或生物作用受损, 从而引发血糖持续升高的代谢疾病。在 DM 环境下, 机体会出现自由基产生增多、氧化应激以及炎症因子异常表达等变化, 引起微环境改变, 进而诱发一系列临床并发症, 而肌腱病变便是其中之一^[1]。据报道, 全球每年平均有 3 000 多万例不同程度肌腱损伤或肌腱病发生, 给社会带来巨大医疗负担^[2]。一项荟萃分析显示, DM 患者肌腱病变发生率达 90%, 且 2 型糖尿病 (type 2 diabetes mellitus, T2DM) 患者肌腱发生急性损伤概率是普通人的 5 倍, 这对患者活动造成极大风险^[3-4]。DM 肌腱病变的临床表现包括钙化、局部慢性疼痛、关节活动受限、肌腱损伤断裂风险增加及愈合能力降低, 好发于肩袖、跟腱、髌腱、手部屈肌腱等活动负荷较高的部位^[3]。在 DM 环境中, 晚期糖基化终末产物 (advanced glycation end-products, AGEs) 异常积累会抑制肌腱成纤维细胞线粒体功能与增殖能力, 影响肌腱功能与修复能力^[5]。同时, 肌腱来源干细胞 (tendon-derived stem cells, TDSCs) 也呈功能障碍并发生凋亡, 导致肌腱细胞分化及功

能异常^[6]。细胞外基质 (extracellular matrix, ECM) 稳态是维持肌腱结构与功能完整性的基础, 而 DM 引发的 ECM 损伤与微环境紊乱, 是导致肌腱功能障碍的关键病理机制^[7]。运动干预作为治疗 DM 的重要非药物手段, 在 DM 并发症 (含肌腱病变) 管理中亦有显著效力^[8]。据此, 本文系统论述 DM 肌腱病变的病理、生理机制及相关分子通路, 阐述运动对 DM 肌腱病变的作用、疗效及机制, 为 DM 患者防治肌腱病变及开发精准化运动干预策略或健身指导策略提供理论依据。

1 DM肌腱病变的病理变化

1.1 肌腱结构与组织学改变

正常肌腱中腱细胞呈细长或扁平状且数量稀

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疏,其胞体镶嵌于胶原纤维束之间,而胞质突起则沿胶原纤维长轴延伸,形成高度有序的细胞网络。相比之下,DM肌腱病变则表现出胶原纤维束排列紊乱、纹理走向异常、呈现锯齿状交错连接以及局部纤维隆起等畸形改变^[9]。腱细胞由TDSCs分化而来,但DM环境下高糖会诱导TDSCs向脂肪细胞或成骨细胞等非肌腱谱系分化,导致肌腱脂质堆积与钙化,引起胶原纤维排列紊乱,增加肌腱微撕裂风险^[10]。Chen等^[11]证实,DM会异常激活趋化因子CXC配体13(C-X-C motif chemokine ligand 13, CXCL13)-CXC基序趋化因子受体5(C-X-C chemokine receptor 5, CXCR5)轴,引起TDSCs成骨分化增强,使肌腱内部出现异位骨化,肌腱丧失弹性和伸展性。肌腱损伤后,损伤肌腱在愈合期间会出现成纤维细胞增殖、胶原蛋白合成增加、炎症因子表达下降等变化^[12]。但DM环境下,损伤肌腱面临成纤维细胞增殖能力下降及迁移能力减弱、胶原蛋白交联异常、持续慢性低度炎症微环境等改变,导致损伤肌腱处形成的瘢痕组织胶原含量减低、纤维排列紊乱,力学性能远逊于健康愈合的新生肌腱^[12-13]。以上结果表明,DM导致TDSCs分化异常、成纤维细胞增殖下降,从而引起胶原纤维形态改变,导致肌腱结构和组织学变化。

1.2 生物力学性能改变

DM引起的AGEs过度增加可促进胶原分子之间的剪切转移,导致肌腱应变刚性改变,加大肌腱硬化风险,故在相同应力冲击下较正常肌腱更易出现损伤及结构变化^[14]。此外,AGEs可充填于肌腱空隙,并在肌腱之间堆积形成非酶交联结构,引起胶原纤维交联紊乱,加剧肌腱黏弹性下降,阻碍胶原纤维间滑动,最终导致肌腱功能受限^[15]。跟腱中AGEs积聚还会导致I型胶原组分减少,引起跟腱弹性减弱与杨氏模量降低,并使其抗张强度下降^[16]。临床上,DM患者跟腱常表现为长度缩短、横截面积减小、拉伸刚度增高,这些改变会导致跟腱功能受限,进而限制关节的活动范围^[17]。另一方面,由于跟腱增厚和刚性改变,DM患者步行时会出现垂直地面反作用力与净关节力矩动力学方向不一致的步态,导致踝关节杠杆平衡被打破,足部节段与踝关节活动度降低;这些改变引起下肢生物力学异常,表现为步速减慢、步幅缩短及站立相持续时间延长,进而造成跟腱持续性压力负荷,增加DM肌腱病变风险^[18]。这说明,DM可引起肌腱拉伸强度、拉伸刚度和黏弹性发生不同程度的变化,

从而导致肌腱生物力学性能下降和肌腱功能受限。

2 DM肌腱病变的发病机制

2.1 引发肌腱炎症反应

肌腱微环境稳态是维持肌腱细胞生理功能的基础。但DM所诱发的慢性高血糖会造成AGEs在肌腱ECM中异常蓄积,打破肌腱微环境稳态。高血糖环境下,AGEs通过与其特异性受体(receptor for advanced glycation end products, RAGE)结合,触发下游核因子- κ B(nuclear factor kappa-B, NF- κ B)信号通路激活,之后活化的NF- κ B作为炎症反应关键转录因子进入胞核,启动包括肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白介素(interleukin, IL)-1 β 和IL-6在内的一系列炎症因子表达,进而在肌腱中形成炎症循环,持续招募和激活免疫细胞,并进一步放大炎症反应^[1, 19]。另一方面,高糖环境下产生的代谢应激物还可引起核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3(nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3, NLRP3)炎症小体激活,促进IL-1 β 和IL-18成熟释放,加剧肌腱局部炎症与组织损伤^[20]。

此外,肌腱细胞促炎因子表达还受巨噬细胞极化状态的影响,DM微环境会显著干扰极化过程,影响肌腱内免疫细胞极化改变,造成M1型(促炎型)向M2型(抗炎/修复型)巨噬细胞转化受阻,引起肌腱炎症反应加剧^[21]。Ackerman等^[22]证实,DM会导致损伤肌腱中M1型巨噬细胞转化至M2型的时间延迟,表明DM会抑制肌腱中具有抗炎和促修复功能的M2型巨噬细胞极化,同时延长促炎的M1型巨噬细胞浸润时间。另有研究指出,DM病理环境下,糖脂毒性增强可导致促炎性脂肪因子脂肪酸结合蛋白4(fatty acid-binding protein 4, FABP4)表达增加,从而引起肌腱组织炎症反应,加剧肌腱病理改变^[6, 23]。因此,DM通过多种机制诱发肌腱组织炎症反应,造成肌腱损伤或增加肌腱病变风险。

2.2 改变肌腱胶原蛋白组分

胶原蛋白作为肌腱ECM重要组分,主要由I型胶原蛋白与III型胶原蛋白共同构成。在肌腱ECM中,I型胶原蛋白由2条 α 1(I)链和1条 α 2(I)链构成,占成熟肌腱胶原含量的90%以上,具有高度的抗张强度和刚性,是肌腱承受高机械负荷及力传递的基础骨架。III型胶原蛋白则由3条 α 1(III)链构

成, 在成熟肌腱中胶原含量低于10%, 且胶原纤维直径较细, 力学强度较低但弹性较高^[24]。在新生肌腱形成初期, III型胶原蛋白作为主要的新生基质成分主导纤维网络的构建, 但随着组织结构逐步成熟, 其表达逐渐下调, 由I型胶原蛋白替代, 进而赋予新生肌腱良好的抗张强度及生物力学特性, 故I型胶原蛋白与III型胶原蛋白比例可作为衡量胶原蛋白组织特性的重要标志^[25]。但DM环境下, 肌腱胶原蛋白组分会发生改变, 表现为I型胶原蛋白减少、III型胶原蛋白增多^[26]。

临床水平上, DM患者因肌腱中I型胶原蛋白减少、纤维化和代谢功能障碍相关通路的富集, 从而易发生肌腱损伤^[27]。细胞水平上, 高葡萄糖浓度(25 mmol/L)培养下大鼠跟腱成纤维细胞72 h后死亡率增加3倍, 且成纤维细胞胶原蛋白合成速率下降^[28]。另外, 高血糖还能通过影响TDSCs分化进程, 干扰胶原蛋白的分泌, 改变肌腱组分。碱性螺旋-环-螺旋转录因子(scleraxis, Scx)是一种重要的基本螺旋-环-螺旋(basic helix-loop-helix, bHLH)样转录因子, 可通过靶向调控I型胶原蛋白alpha 1链(collagen type I alpha 1 chain gene, *Col1a1*)、I型胶原蛋白alpha 2链(collagen type I alpha 2 chain gene, *Col2a1*)及腱调蛋白(tenomodulin, *Tnmd*)等肌腱标志物基因表达, 进而在肌腱发育、稳态维持及损伤修复中发挥重要作用^[29]。但高血糖却可影响肌腱细胞生长因子的表达, 进而干扰胶原分子生成。Wu等^[30]报道, 高糖经腺苷酸激活蛋白激酶(AMP-activated protein kinase, AMPK)/早期生长反应因子1(early growth responsive gene-1, *Egr1*)通路引起肌腱细胞下游Scx、转化生长因子- β (transforming growth factor- β , TGF- β 1)、*Col1a1*、*Col1a2*和双糖链(biglycan, *Bgn*)表达下降, 进而导致肌腱胶原蛋白合成减少和肌腱稳态失衡。体内研究亦证实, DM能显著抑制损伤跟腱胶原合成能力。Yang等^[31]对大鼠跟腱断裂处分别注射低、高剂量D-核糖, 以模拟AGEs对跟腱损伤修复影响, 发现高剂量D-核糖会导致损伤跟腱I型胶原蛋白含量降低。DM不仅影响损伤跟腱I型胶原蛋白合成, 还会干扰III型胶原蛋白形成。Ahmed等^[32]以跟腱横断手术模拟跟腱断裂, 发现修复期DM损伤跟腱I型与III型胶原mRNA表达分别降低35%和55%, 而在愈合期, 普通损伤跟腱I型胶原增加率较健康跟腱达96%, DM损伤跟腱则无显著增加, 而III型胶原

mRNA表达普通损伤跟腱为5倍, DM损伤跟腱仅3倍, 表明DM可改变损伤跟腱愈合进程中胶原蛋白结构组分。另外, 基质金属蛋白酶2(matrix metalloproteinase, MMP-2)与组织金属蛋白酶抑制物2(tissue inhibitor of metalloproteinase 2, TIMP2)可负性影响肌腱胶原组分, 导致损伤肌腱重塑异常。在高糖环境下, 跟腱组织MMP-2与TIMP2表达均升高, 并伴I型胶原蛋白表达下降及III型胶原蛋白表达增加^[33]。这说明, DM可造成肌腱胶原蛋白比例失衡, 致使肌腱组织结构改变, 进而可能引发肌腱病变或肌腱损伤。

2.3 促进肌腱血管病变

肌腱外ECM形成与成纤维细胞增殖分化依赖于肌腱血管提供的营养物质与氧气, 但高糖环境会引起血管内皮功能障碍、基底膜增厚、毛细血管密度下降及组织缺氧等改变, 从而引起DM微血管并发症, 导致肌腱结构完整性破坏、生物力学性能改变及再生修复能力减弱^[34]。而DM患者AGEs含量增加可能是引起微血管并发症的重要因素。Kato等^[35]研究发现, DM患者血清AGEs水平与血管并发症的恶化程度呈正相关。此外, DM患者肌腱毛细血管基底膜较正常血管厚, 这会引发局部毛细血管血流灌注障碍, 造成肌腱组织处缺氧及营养障碍, 引发肌腱组织代谢紊乱, 最终导致肌腱损伤及愈合延迟^[36]。该病理特征在动物实验中亦被证实。Xu等^[37]发现, T2DM大鼠肩袖血管生成Bonar评分在2、4、8及12周时间点均显著高于非T2DM对照组, 并呈现随病程延长而递增的变化特征。Hotta等^[38]进一步对大鼠肌腱毛细血管的微血管通透性和超微结构进行评估, 发现DM大鼠肌腱毛细血管中红细胞间隙宽度较对照组减少20%, 且单位周长的细胞间隙数量与宽度分别增加2.2倍及下降30%, 揭示了DM导致毛细血管腔狭窄及红细胞通过受阻的病理特征。这可能与高糖环境抑制血管生成相关因子表达有关。DM环境下高糖会引起TDSCs血管内皮生长因子(vascularendothelial growth factor, VEGF)表达下降, 外泌体miR-181b-5p显著上调, 进而靶向抑制核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)/血红素氧合酶1(heme oxygenase-1, HO-1)通路, 加剧内皮细胞氧化损伤及早衰, 从而诱发肌腱血管源性病变^[39]。此外, DM还能抑制VEGF生物合成, 进而减少新生血管生成。例如, DM肌腱损伤后VEGF及胸腺素 β 4(thymosin β 4, T β 4)

mRNA及蛋白质表达显著下调,进而引起新生血管生成受阻,这可能是DM导致肌腱病变且损伤愈合延迟的原因^[40]。

同时,DM还能通过激活VEGF上游转录抑制因子进而导致其表达下调。据报道,DM肌腱损伤小鼠中核心转录共激活因子Yes相关蛋白(yes-associated protein, YAP)/转录联合激活因子(transcriptional activator with PDZ-binding motif, TAZ)持续核转位,引起下游靶基因结缔组织生长因子(connective tissue growth factor, CTGF)与半胱氨酸丰富血管生成诱导因子61(cysteine-rich angiogenic inducer 61, CYR61)表达上调,这不仅能加剧肌腱纤维化,还能进一步通过miR-130a-3p转录抑制VEGFR1表达,进而影响VEGF合成,间接扰乱血管生成^[6]。Liu等^[41]同样发现,高糖诱导的TDSCs因线粒体活性氧类(reactive oxygen species, ROS)过载,激活AMPK/哺乳动物雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1, mTORC1)轴,导致低氧诱导因子-1 α (hypoxia-inducible factor 1- α , HIF-1 α)翻译后修饰异常,引起其在核内堆积,不能有效结合VEGF启动子区低氧反应元件(hypoxia response element, HRE)序列,造成VEGF合成阻滞,致使肌腱血管生成障碍。这表明,DM可通过降低血管生成相关因子表达,造成新生血管生成减少,导致肌腱营养与代谢受阻,增加肌腱病变风险。

2.4 诱导肌腱周围神经病变

神经系统通过支配邻近肌肉的运动神经、分布于周围皮肤的感觉神经,以及位于腱鞘区域的本体感觉神经末梢协同调节肌腱功能。然而,DM环境下肌腱周围神经会发生病变,进而影响肌腱功能。临床层面,感觉神经纤维损伤会导致患者本体感觉功能减退,表现为运动控制精度下降及步态异常,致使肌腱处于异常力学负荷状态,增加肌腱病变风险^[42]。这一神经损伤不仅加剧疾病发生,还直接影响肌腱修复进程。Xu等^[43]聚焦骨与肌腱损伤修复过程中的神经调控机制,发现肌腱处感觉神经与交感神经的动态平衡,是肌腱修复过程中调节炎症、血管生成和形成瘢痕组织的关键,故合理神经分布是维持肌腱健康状态的基础。因此,神经系统的完整性对于防治肌腱病变至关重要。而作为对神经系统发挥营养作用的神经因子,是维持神经系统完整性的基础。研究表明,肌腱微环境中富含的神经生长因子(nerve growth factor, NGF)、脑源性

神经营养因子(brain-derived neurotrophic factor, BDNF)等神经因子,可为肌腱周缘神经提供营养支持,保障其调控肌腱运动功能的正常发挥^[44-45]。

但DM会导致神经营养因子表达下降,进而影响肌腱周围神经传递与营养功能。Ahmed等^[46]研究发现,在T2DM大鼠跟腱损伤模型中,无论是损伤侧还是非损伤侧,其跟腱NGF表达均下降,而BDNF表达则无明显变化。NGF表达受阻将影响周围神经轴突的结构重塑,导致轴突长度缩短及神经支配障碍,进而损害DM肌腱本体感觉反馈及肌腱的运动调控。此外,DM导致的神经因子匮乏,会阻碍肌腱处周围神经自我更新进程,一方面削弱神经对肌腱的支配能力,另一方面减少对神经元的营养支持,最终干扰新生胶原合成代谢及肌腱组织再生修复^[1]。另外,感觉神经末梢释放的降钙素基因相关肽(calcitonin gene-related peptide, CGRP)与P物质(substance P, SP)神经肽作为关键信号分子,在肌腱中具有促进局部血管生成、抑制炎症反应、刺激胶原蛋白合成及调节成纤维细胞活性的功能,这对于维持肌腱稳态至关重要^[47]。但DM环境下这些神经肽物质的分泌减少,从而造成肌腱周围神经传递与营养异常,引起周围神经功能障碍,最终影响肌腱胶原纤维新生与本体感觉能力^[42]。因此,DM通过下调神经因子及相关神经活性物质表达,阻碍周围神经信号传导,诱发肌腱周围神经病变,削弱运动神经支配,增加肌腱损伤或肌腱病变风险(图1)。

3 运动干预对DM肌腱病变的疗效与机制

3.1 运动通过降低炎症反应改善肌腱ECM稳态

肌腱炎症可打破ECM稳态,造成肌腱病变发生及损伤肌腱愈合延迟。而DM环境下,由于肌腱ECM中AGEs与RAGE结合,导致炎症反应加剧,并最终打破肌腱ECM稳态,引发肌腱细胞代谢异常,造成肌腱病变发生^[1]。运动干预可以通过增强胰岛素敏感性,维持血糖稳态,有效减少AGEs与RAGE结合,降低肌腱炎症反应,进而抑制AGEs与胶原蛋白的交联进程,维持肌腱弹性并重塑肌腱ECM稳态^[48]。有氧运动能系统性和局部性降低肌腱病模型中的血清及肌腱炎症水平,改善肌腱ECM稳态。研究证明,4周游泳训练可显著降低I型胶原酶诱发的跟腱病大鼠血清TNF- α 、IL-1 β 表达,提高抗炎因子IL-10表达,有效缓解跟腱病大鼠系统炎症^[49]。而Smith等^[50]采用高重复高力

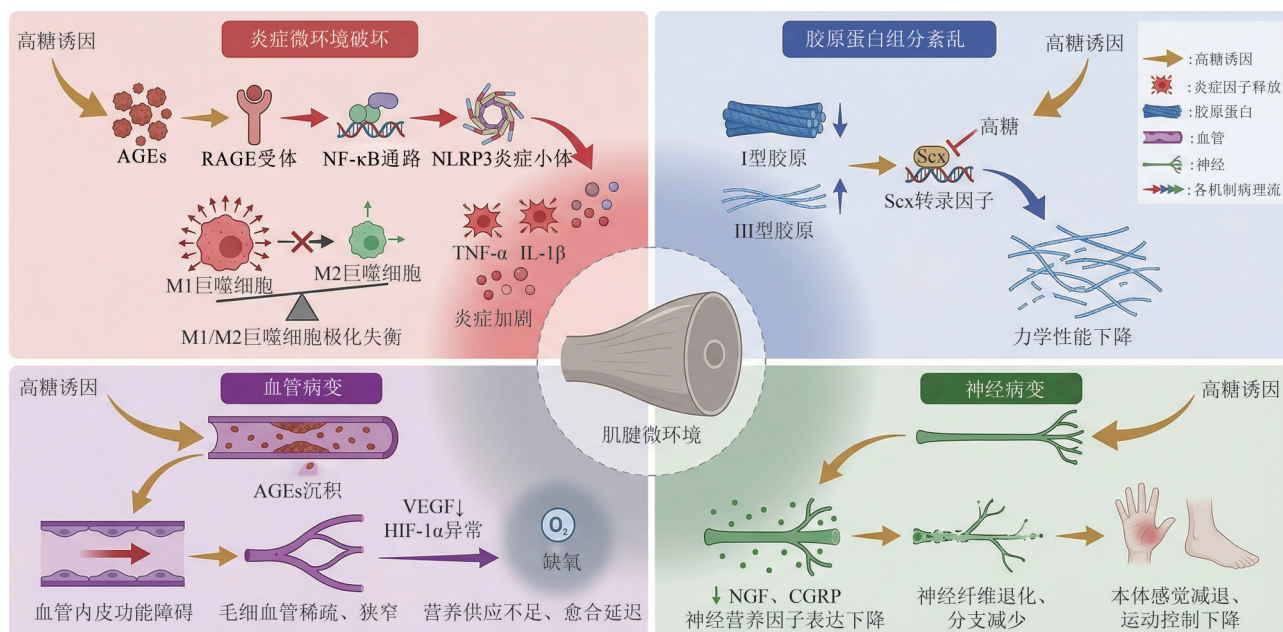


Fig. 1 Diagram of the pathogenesis of diabetic tendinopathy

图1 DM肌腱病变的发病机制

DM诱导AGEs积累,引起肌腱炎症反应加剧,并引发胶原组分改变、血管病变、神经病变,最终诱发DM肌腱病变发生。AGEs:晚期糖基化终末产物;RAGE:特异性受体;NF-κB:核因子-κB;NLRP3:核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3;TNF-α:肿瘤坏死因子-α;IL-1β:白介素-1β;M1:促炎型巨噬细胞;M2:抗炎/修复型巨噬细胞;Scx:碱性螺旋-环-螺旋转录因子;VEGF:血管内皮生长因子;HIF-1α:低氧诱导因子-1α;NGF:神经生长因子;CGRP:降钙素基因相关肽。

度伸手和拉杆训练增加肌腱负荷以构建肌腱病模型,亦发现6周跑台锻炼可降低大鼠血清促炎因子IL-1β、TNF-α水平,升高抗炎因子皮质醇、IL-10水平,并减轻肌腱炎症程度。此外,Irani等^[51]研究发现,损伤跟腱大鼠在进行低强度跑台训练后,其损伤跟腱处丙二醛(malondialdehyde,MDA)浓度降低,TNF-α表达下调,氧化应激及炎症反应缓解,跟腱损伤修复能力提高。同样,Gundogdu等^[52]在胶原酶诱导的大鼠跟腱病模型中发现,8周跑台运动(5 d/周,30 min/d)可显著提高跟腱组织总抗氧化能力(total antioxidant capacity,T-AOC),降低促炎因子IL-1β、TNF-α表达,改善跟腱氧化损伤和炎症。上述研究表明,适宜强度有氧运动可减轻肌腱炎症反应,维持肌腱ECM稳态。

适度机械负荷亦可抑制肌腱微环境中促炎因子表达,改善ECM稳态;但过高机械负荷不仅不能降低肌腱炎症水平,反而导致促炎因子增加,从而加剧肌腱炎症和ECM稳态失衡。据报道,8%以上大强度拉伸会上调肌腱成纤维细胞IL-1β刺激的环氧加氧酶-2(cyclooxygenase-2,COX-2)、MMP-1表达,促进炎症标志物前列腺素E2(prostaglandin

E2,PGE2)产生,但4%小强度拉伸则显著抑制上述反应,减少肌腱成纤维细胞内炎症反应^[53]。这表明,适宜机械负荷通过抑制肌腱炎症来改善肌腱ECM稳态,为肌腱损伤患者及DM肌腱病变患者精准制定干预方案提供了重要依据。

3.2 运动促进胶原合成改善肌腱病变

肌腱主要由I型胶原蛋白与III型胶原蛋白构成,其合成受磷脂酰肌醇3激酶(phosphoinositide3-kinase,PI3K)/蛋白激酶B(protein kinase B,Akt)通路控制^[54]。激活PI3K/Akt通路可增加I型胶原蛋白表达,促进肌腱损伤修复^[55]。DM诱发肌腱病变的机制可能与PI3K/Akt通路抑制引起的肌腱I型胶原蛋白合成下降有关^[26,56]。而运动可通过促进胰岛素样生长因子-1(insulin-like growth factor 1,IGF-1)表达,进而激活PI3K/Akt通路,提高肌腱I型胶原蛋白合成^[57]。此外,DM会上调MMPs与TIMPs表达,减少肌腱Scx、Mohawk基因(Mkx)和Tnmd产生,导致肌腱胶原蛋白合成障碍,引起肌腱退变^[30,58]。但运动可降低MMPs与TIMPs表达,维持肌腱胶原平衡,改善ECM结构与功能^[59]。同时,运动还能上

调 *Scx*、*Mkx* 和 *Tnmd* 等肌腱特异性标志物表达, 促进肌腱细胞定向分化与胶原蛋白合成, 防止肌腱钙化发生^[60]。

尽管不同方式的运动均能通过促进胶原蛋白合成来抑制肌腱病变, 但所涉机制却不相同。有氧运动通过重塑肌腱细胞微环境稳态与施加轻度机械张力刺激, 进而促进胶原蛋白合成, 维持肌腱生理功能及促进损伤肌腱修复。*deOliveira* 等^[61] 研究证实, 3 周渐进有氧训练能显著上调 DM 跟腱损伤模型大鼠跟腱 I 型胶原表达, 而 III 型胶原、MMP-3、MMP-13 等蛋白质表达却无显著改变。这说明, 有氧运动能有效促进成熟 I 型胶原合成, 优化胶原比例, 促进损伤肌腱结构重塑与功能恢复, 抑制 DM 肌腱胶原蛋白比例失调及加速 DM 损伤肌腱新生。抗阻训练可通过机械负荷直接作用于肌腱细胞, 激活丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) /胞外信号调节激酶 (extracellular signal-regulated kinase, ERK) 和 PI3K/Akt 等胶原合成级联反应, 促进腱细胞基因表达和 ECM 重塑, 抑制肌腱病变发生及增强损伤肌腱修复, 阻止 DM 引起的肌腱病理性胶原组分改变^[62-63]。高强度间歇训练 (high-intensity interval training, HIIT) 是一种通过短时间高强度运动与低强度间歇交替进行来改善机体代谢的锻炼方式。据报道, HIIT 可上调跟腱中腱蛋白 XB (tenascin XB, *TNXB*)、骨桥蛋白 (osteopontin, *OPN*) 和 *TGF-β1* 基因表达, 促进跟腱胶原蛋白合成^[64]。HIIT 还能提高肌腱 *IGF-1Ea* 基因表达, 促进骨骼肌生成 IGF-1, 并激活 PI3K/Akt 通路, 加速跟腱 I 型胶原蛋白形成^[65]。以上研究证实, 不同方式运动能通过多种机制促进肌腱胶原蛋白合成, 进而抑制 DM 肌腱病变。

3.3 运动促进血管生成维护肌腱血管功能

血管相关生长因子可改善血管内皮结构与功能, 保障肌腱组织营养与氧气的充分供应。在 DM 环境下, 血管相关生长因子 (如 VEGF) 表达会受到抑制, 从而诱发滋养肌腱的血管病变, 表现为基底膜增厚、血流受阻, 导致肌腱组织缺氧和代谢紊乱, 最终引发肌腱病变或延缓受损肌腱愈合进程^[36, 39]。但多种不同方式的运动均可通过调节血管相关生长因子, 改善血管内皮结构与功能, 进而对肌腱血管产生积极效应。

离心运动能积极影响受伤肌腱愈合过程和血管化, 表现为 VEGF 基因表达在损伤后第 1 天迅速升高并随后下降, 同时血管生成素 1 (angiopoietin 1,

Ang1) 表达也显著升高, 而 *Ang1* 能促进血管稳定性, 进一步增强肌腱血管生成及减少瘢痕形成, 达到降低肌腱血管损害的目的^[66]。拉伸运动能促进 *TGF-β1* 和 *HIF-1α* 信号激活, 刺激肌腱细胞表达并释放血管生成样蛋白 4 (angiopoietin-like 4, *ANGPTL4*), 更新肌腱血管^[67]。阻力运动通过上调跟腱结缔组织生长因子 (connective tissue growth factor, *CTGF*)、VEGF 和核心蛋白聚糖 (decorin, *DCN*) 表达, 进而抑制肌腱血管钙化进程, 维持肌腱血管生理功能^[68]。此外, 运动与按摩协同作用还可提高肌腱 VEGF-A、成纤维细胞生长因子 2 (fibroblast growth factor-2, *FGF-2*) 和白细胞分化抗原 34 (cluster of differentiation 34, *CD34*) 等血管生成标志物表达, 从而增强肌腱血管生成能力, 抑制 DM 对肌腱血管生成因子的抑制作用^[69]。上述研究证明, 运动通过促进血管生成因子分泌并维持血管稳定性, 对肌腱血管重塑产生积极作用, 从而改善 DM 肌腱血供环境并抑制肌腱病变。

3.4 运动调节相关神经因子强化肌腱周围神经支配

神经因子 BDNF、NGF、SP 能够营养及支持周围神经, 从而增强对肌腱的支配能力。但 DM 可导致 BDNF、NGF、SP 下降, 从而引起肌腱周围神经营养障碍与信息传输速率减缓, 最终抑制肌腱正常生理功能^[42, 46]。运动则能显著上调肌腱中相关神经因子水平, 进而改善肌腱周围神经支配。

研究表明, 身体活动可使跟腱病患者血清 BDNF 升高, 且循环 BDNF 能被跟腱组织摄取利用, 进而发挥神经营养效应, 支持局部周围神经功能^[70]。另据报道, 健康成人接受总负荷量相同的不同强度运动干预后, 血清 NGF 水平显著升高, 且该效应与运动强度呈正相关, NGF 水平在低、中及高强度跑台运动后分别升高 12%、19% 和 23%^[71-72]。运动后 NGF 与 BDNF 同时上调, 使二者协同发挥神经营养作用, 从而在 DM 跟腱组织中维持神经营养平衡, 并对 DM 环境所引起的跟腱血管损伤修复提供营养基础^[46]。另有研究采用石膏固定与运动干预两种方式处理损伤跟腱, 发现在断裂后第 8 和第 17 天, 运动组大鼠 BDNF 和碱性成纤维细胞生长因子 (basic fibroblast growth factor, *bFGF*) 基因表达均显著升高, 并认为运动可通过提高损伤跟腱中神经因子表达, 改善周围神经支配, 促进肌腱愈合^[73]。此外, 主动运动亦可促进

脑衰反应调节蛋白2 (collapsin response mediator protein 2, CRMP-2) 表达, 参与神经突的伸长和再生过程。在大鼠跟腱损伤模型中, 主动运动大鼠跟腱CRMP-2表达显著上调, 表明主动运动可通过加速局部神经突再生和神经修复促进损伤跟腱愈合^[74]。此外, 运动还能增加肌腱中SP表达, 从而提高周围神经对肌腱的支配效率。但SP过度增加会与受体神经激肽1受体 (neurokinin 1 receptor, NK-1R) 结合而引起肌腱疼痛^[75]。例如, 在兔跟腱病模型中, 不同过载机械负荷均能上调跟腱SP

水平, 但在第1周轻载荷时SP增加先于肌腱病发生, 而在第3周与第6周进行过度载荷运动时, 肌腱病发生与SP增加同步出现, 表明肌腱周围神经复原进程中, 适当的运动负荷强度可以促进肌腱神经病变的改善, 但过度负荷反而会加重肌腱病变^[76]。以上研究表明, 运动能通过调节BDNF、NGF、SP等相关神经因子参与神经营养过程, 强化对肌腱支配能力及肌腱细胞更新能力, 增强机体修复肌腱周围神经损伤, 进而改善DM肌腱病变 (图2)。

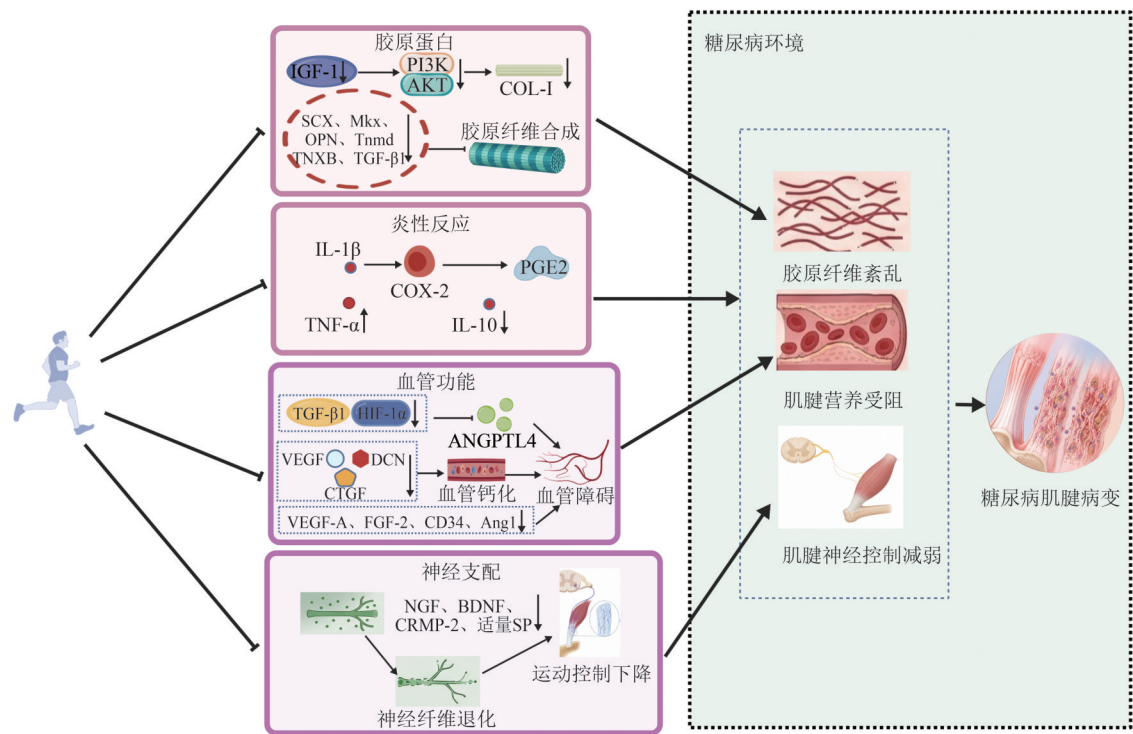


Fig. 2 The mechanism by which exercise improves diabetic tendinopathy
图2 运动改善DM肌腱病变机制示意图

运动可以通过抑制肌腱炎症反应、稳定肌腱胶原合成、优化胶原比例、促进肌腱血管生成、强化肌腱周围神经支配及营养支持, 从而抑制DM肌腱相关病理改变。“→”表示促进作用, “-”表示抑制作用。AGEs: 晚期糖基化终末产物; RAGE: 晚期糖基化终末产物受体; TNF-α: 肿瘤坏死因子-α; IL: 白介素; COX-2: 环氧加氧酶-2; PGE2: 前列腺素E2; IGF-1: 胰岛素样生长因子-1; PI3K: 磷脂酰肌醇3激酶; Akt: 蛋白激酶B; Scx: 碱性螺旋-环-螺旋转录因子; Mxx: Mohawk基因; Tnmd: Tenomodulin; TGF-β1: 转化生长因子-β; TNXB: 生腱蛋白XB; OPN: 骨桥蛋白; BDNF: 脑源性神经营养因子; CRMP-2: 脑衰反应调节蛋白2; NGF: 神经生长因子; SP: P物质; VEGF: 血管内皮生长因子; Ang1: 血管生成素1; HIF-1α: 低氧诱导因子-1α; ANGPTL4: 血管生成样蛋白4; CTGF: 结缔组织生长因子; DCN: 核心蛋白聚糖; VEGF-A: 血管内皮生长因子-A; FGF-2: 成纤维细胞生长因子2; CD34: 白细胞分化抗原34。

4 总结与展望

综上所述, DM作为一种以高血糖为典型特征的代谢性疾病, 可通过增强肌腱炎症反应、引起肌腱胶原组分失衡、诱发肌腱血管病变及生成功能障

碍、诱导肌腱周围神经病变等关键病理机制, 引发肌腱结构功能紊乱、生物力学性能下降、愈合及修复能力受损, 导致肌腱病变发生。适宜运动可降低肌腱炎症反应、稳定肌腱胶原合成、促进肌腱血管生成及功能改善、强化肌腱周围神经支配及营养支

持, 最终实现抑制DM肌腱相关病理改变的目的。

但目前尚存在一些亟待解决的关键问题。a. 应注重从不同运动方式的角度探讨其对DM肌腱病变的干预疗效及机制。b. DM肌腱病变早期诊断标志物有待丰富完善, 未来应利用多组学技术对AGEs亚型、miRNA谱、胶原代谢产物等进行分析。c. 应重视探究运动过度或负荷过载对DM肌腱病变的负面效应及机制。对上述问题的解决, 将有助于进一步揭示运动干预对DM肌腱病变的作用及疗效机制, 进而为DM患者制定精准化运动干预策略及健身指导策略提供理论依据。

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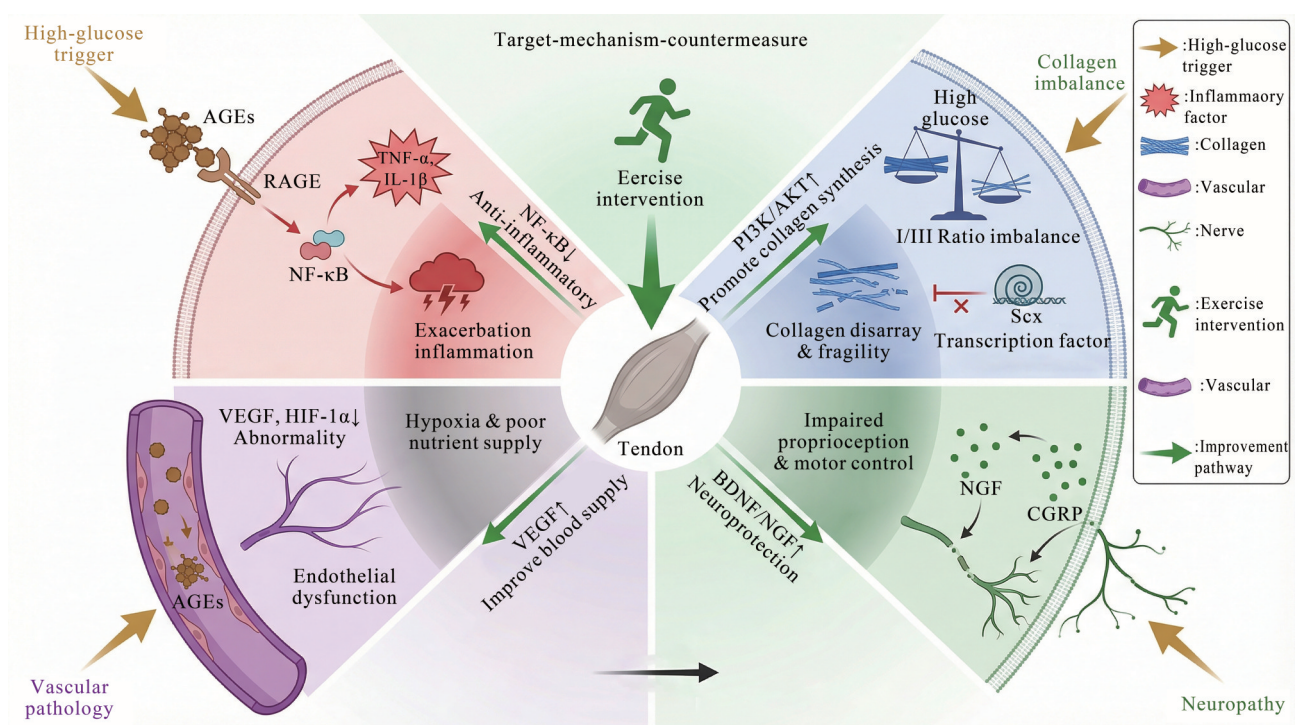
Mechanisms of Diabetic Tendinopathy and Exercise Intervention*

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Graphical abstract



Abstract Diabetic tendinopathy is a common and disabling musculoskeletal complication of diabetes, clinically characterized by tendon thickening, pain, impaired healing capacity and compromised biomechanical performance, collectively undermining joint function and quality of life. Its pathogenesis is multifactorial. On the one hand, chronic hyperglycaemia promotes the abnormal accumulation of advanced glycation end products (AGEs) within tendon collagen, leading to non-enzymatic crosslinking and engagement of the receptor for AGEs (RAGE), which in turn triggers inflammasome activation and sustains inflammatory responses. On the other hand, the diabetic milieu disrupts collagen metabolic homeostasis, impairs microvascular function and induces peripheral neuropathy; together, these alterations drive extracellular matrix degeneration and weaken the

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mechanical properties of tendon. Exercise, as a non-pharmacological intervention, can ameliorate these pathological changes through multiple integrated mechanisms. First, exercise attenuates tendon inflammation and restores microenvironmental homeostasis. Regular physical activity reduces AGE-RAGE signalling, thereby suppressing downstream expression of tumour necrosis factor (TNF) and interleukin-1 β (IL-1 β), while upregulating the anti-inflammatory cytokine interleukin-10 (IL-10). This shift from a pro-inflammatory to a pro-resolving milieu not only restrains chronic inflammation but may also limit excessive inflammasome activation in tenocytes and tissue-resident immune cells. Second, exercise enhances local expression of insulin-like growth factor 1 (IGF-1), thereby activating the phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt) signalling pathway. This axis stimulates tenocyte proliferation, augments synthesis of type I collagen — the principal load-bearing component of tendon — and thereby promotes tissue repair, preserves tensile strength and supports matrix synthesis and structural integrity. In addition, exercise improves blood supply and nutrient delivery to tendon by increasing the expression of vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF) and the small leucine-rich proteoglycan decorin (DCN), thereby enhancing capillary growth, coordinating collagen fibrillogenesis and actively suppressing pathological vascular calcification. Exercise also increases the expression of angiopoietin-like 4 (ANGPTL4), fibroblast growth factor 2 (FGF-2) and CD34. Through the concerted actions of these factors, exercise promotes angiogenesis, restores the microvascular network and ensures adequate oxygen and nutrient supply to relatively ischaemic tendon tissue. Finally, exercise elevates levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), supporting neuronal survival, axonal growth and the function of sensory and sympathetic nerve endings within tendon, thereby exerting neurotrophic and neuromodulatory effects and improving tendon innervation and neuromuscular control. Moreover, exercise upregulates collapsin response mediator protein 2 (CRMP-2), a molecule involved in axonal guidance and regeneration, and moderately increases the activity of substance P (SP), thereby helping to regulate neurogenic inflammation, pain perception and trophic support for tenocytes. Drawing together current evidence, this review systematically summarizes the mechanisms underlying diabetic tendinopathy and examines the mechanistic basis of exercise intervention, with the aim of providing a theoretical framework for the development of precise exercise strategies for affected individuals. However, several key issues remain unresolved: the therapeutic efficacy and mechanistic specificity of different exercise modalities in diabetic tendinopathy have yet to be defined, and early diagnostic biomarkers remain insufficiently characterized. Future studies should apply multi-omics approaches to profile AGE subtypes, miRNA signatures and collagen metabolic products, and should also clarify the adverse effects and underlying mechanisms of excessive exercise or mechanical overloading in diabetic tendinopathy. Such efforts will further elucidate the therapeutic effects and mechanisms of exercise in diabetic tendinopathy and provide a stronger basis for precision exercise prescription and fitness guidance in patients with diabetes.

Key words diabetes, tendinopathy, pathogenesis, exercise intervention

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