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糖尿病慢性骨骼肌损害发病机制的研究进展

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摘　要

骨骼肌是胰岛素刺激下葡萄糖摄取的核心代谢组织，负责人体高达85%的葡萄糖代谢，同时又是胰岛素抵抗的主要部位。当机体长期处于高血糖时，肌肉会受到一定程度的损害，称为肌病，而肌肉的损害反过来又会加重胰岛素的抵抗，如此形成恶性循环。糖尿病患者骨骼肌损害隐匿，易被忽视，但却对葡萄糖代谢有着重要影响，本文就糖尿病骨骼肌损害发病机制的研究进展进行综述，为糖尿病患者血糖控制及预防相关并发症提供依据。

关键词

糖尿病，骨骼肌，肌病

Study Progress on the Pathogenesis of Skeletal Muscle Damage in the Diabetes Mellitus

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Abstract

Skeletal muscle is the core metabolic tissue of glucose uptake stimulated by insulin, which is re-

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sponsible for up to 85% of glucose metabolism in the human body, and is also the main part of insulin resistance. When the body is in hyperglycemia for a long time, muscle will be damaged to a certain extent, which is called myopathy, and muscle damage in turn will aggravate insulin resistance, thus forming a vicious circle. Skeletal muscle damage in patients is hidden and easy to be ignored, but it has an important impact on glucose metabolism. This paper reviews progress on the pathogenesis of skeletal muscle damage in the diabetes mellitus, so as to provide basis for blood glucose control and prevention of related complications in patients with diabetes.

Keywords

Diabetes Mellitus, Skeletal Muscle, Myopathy

1. 引言

糖尿病(diabetes mellitus, DM)是一种以高血糖为主要特征的慢性进展性疾病[1]，已成为严重的全球性的健康问题[2]，其慢性并发症有糖尿病肾病、糖尿病视网膜病变、糖尿病神经病变、糖尿病下肢动脉病变和糖尿病肌病等，是影响患者生存质量和致死、致残的重要原因[3]。其中糖尿病肌病是指无法保持肌肉的质量和功能[4]，起病隐匿，可累及心肌、平滑肌、骨骼肌，造成患者肌疲劳、肌无力，甚至肌萎缩，严重者可并发肌梗死、肌炎、肌脓肿等。目前，糖尿病骨骼肌病变日益受到临床关注，其在 1 型糖尿病(T1DM)和 2 型糖尿病(T2DM)患者中均可发生[5] [6]，尤其是病程长且血糖控制不佳的患者，最初常表现为肌肉疼痛或无力，随后可出现局部皮肤肿胀，甚至出现肿块[7]，本文对其发病机制的最新研究进展进行综述。

2. 代谢因素

众所周知，糖尿病是以慢性高血糖为特征的代谢性疾病，长期的碳水化合物、脂肪以及蛋白质等代谢紊乱可引起糖尿病患者多系统损害，其中包括骨骼肌病变。

2.1. 蛋白质代谢异常

肌肉蛋白质合成和分解之间的平衡控制骨骼肌的质量。糖尿病患者骨骼肌质量的降低与蛋白质的合成减少或分解增加有关[8]。FoxOs 是叉头盒(Fox)蛋白家族中广泛表达的转录因子，在肌肉中，FoxO 蛋白的主要功能是激活 E3 泛素连接酶 MuRF1 和 MAFbx (两种肌萎缩蛋白)的转录，FoxO3 的激活是介导肌肉蛋白质分解的关键途径。Lee 等[9]研究结果表明，高血糖会导致肌管中酵母线粒体逃逸 1 样 ATP 酶(Yme1L)减少或缺失，一方面激活 AMPK 和 FoxO3a，下调 Akt 信号通路，减少肌肉蛋白质的生成及促进蛋白质的分解，另一方面增加肌肉生长抑制素的表达，抑制 IGF-1/PI3K/Akt 途径，促进肌纤维的分解，最终导致肌肉萎缩。而 Brocca 等[10] [11]研究发现 FoxO 的缺失既影响蛋白质的水解，又影响蛋白质的合成。

泛素－蛋白酶体系统(ubiquitin-proteasome system, UPS)负责大多数细胞内蛋白质的分解，这一过程涉及蛋白质泛素化以及蛋白酶体降解。Reddy 等[12]利用大鼠模型证明了糖尿病状态下肌肉中存在 UPS 活性增加，使蛋白质分解增多，导致骨骼肌消瘦或萎缩。UPS 还介导肌原纤维分解，Cohen 等[13]提出钙蛋白酶-1 通过催化结蛋白丝解聚促进肌原纤维的分解和肌肉的萎缩，而结蛋白丝的丢失广泛出现在糖尿病肌肉中。

机体中存在一种葡萄糖－丙氨酸代谢循环，将葡萄糖与蛋白质代谢联系起来。Okun 等[14]研究发现破坏肝脏丙氨酸代谢后的糖尿病小鼠骨骼肌质量增加 13%，肱三头肌质量增加 9%，胫骨前肌质量增加 10%，表明在 T2DM 的高血糖状态下，肝脏丙氨酸代谢活性增强，导致骨骼肌中丙氨酸代谢减弱，蛋白质合成减少或分解增多，出现肌肉无力或萎缩。

Sirtuins (SIRT)是一种蛋白质烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD)依赖性脱乙酰酶，由 7 种亚型(SIRT1-7)组成，调节肌肉的生长发育。Surinlert 等[15]利用体外实验发现，糖尿病的高血糖状态通过调节 SIRTs 基因的表达来诱导成肌细胞的细胞周期停滞或凋亡以及蛋白质分解，导致肌生成障碍和肌肉萎缩。

2.2. 脂质代谢异常

糖尿病患者骨骼肌纤维内和纤维间都存在大量的脂肪沉积[16]，这种异常的脂质积聚会促进成肌细胞向脂肪细胞转化，从而影响骨骼肌的再生，导致肌肉减少、退化和不良重塑以及肌力降低[17] [18] [19]。

血小板衍生生长因子(platelet-derived growth factor, PDGF)是一种关键的纤维－脂肪祖细胞(fibro-adipogenic progenitor, FAP)调节因子，Farup 等[20]实验发现 T2DM 患者的骨骼肌中出现 PDGF 驱动 FAPs 亚群转化，从而导致骨骼肌纤维脂肪变性，使得骨骼肌代谢和收缩功能受损。Gumucio 等[21] [22]通过骨骼肌损伤模型也证明了肌肉的脂质病理性积聚可以导致骨骼肌的纤维化，而糖尿病患者肌肉中便存在这种病理性积聚。

2.3. 线粒体功能障碍

线粒体与骨骼肌的质量和功能密切相关[23]。线粒体在骨骼肌蛋白质合成与分解代谢信号通路中扮演重要角色，决定着蛋白质的质量。肌肉收缩的能量由 ATP 提供，而 ATP 在线粒体中产生，当线粒体功能障碍时，肌肉能量供给不足，骨骼肌即可出现相应的改变及功能受损。

骨骼肌由不同类型的肌纤维组成，主要包括快纤维和慢纤维两种类型。慢纤维存在于收缩缓慢的肌肉中，主要由有氧能量机制(如氧化磷酸化)提供能量，线粒体含量较高；快纤维依靠糖酵解机制快速爆发能量，线粒体含量较低。糖尿病状态下的骨骼肌纤维类型分布会发生改变，以满足能量需求[24]。一些研究报告表明，与健康对照组相比，T2DM 患者表现出从慢纤维到快纤维的类型转变[25]。Monaco 等[26]研究结果表明，T1DM 患者肌纤维内反复出现的细胞内高血糖会导致线粒体功能降低，肌肉表现出力量生产减少、疲劳增加、肌肉干细胞丢失，以及对糖酵解代谢依赖更大，并且伴随纤维类型组成的变化。两种不同类型链脲佐菌素糖尿病小鼠模型实验发现糖尿病骨骼肌病变与线粒体功能相关基因表达下调有关[27]。

2.4. 晚期糖基化终末产物(Advanced Glycation End Products, AGEs)形成

高血糖会导致参与各种细胞过程的蛋白质和酶的糖基化。葡萄糖自动氧化产生的内源性代谢物甲基乙二醛(methylglyoxal, MG)、乙二醛和 3-脱氧葡萄糖苷(3-deosyglucose, 3-DG)是反应性糖基化试剂，可还原糖产生 AGEs [28]。非酶的糖基化始于席夫碱的形成，然后转化为中间产物，最后转化为 AGEs 并逐渐积累。Chiu 等人[29]实验发现糖尿病状态下 AGEs 通过腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)下调蛋白激酶 B(Akt)信号通路诱导肌生成障碍或肌萎缩。Mori 等[30] [31]研究发现 2 型糖尿病患者肌纤维中 AGEs 累积到一定程度便会交叉连接肌肉胶原蛋白，使肌肉硬化，降低肌肉收缩的张力。

2.5. 氧化应激

糖尿病患者长期的高代谢状态可提高细胞内活性氧(reactive oxygen species, ROS)的负荷，ROS 产生

过多以及抗氧化防御降低引起的氧化应激导致骨骼肌肌原纤维蛋白含量减少，进而导致肌肉质量减少，最终导致骨骼肌收缩能力和力量生成降低[32]。Sanchez-Duarte 等[33]通过实验发现尼可地尔可以改善糖尿病大鼠骨骼肌的氧化应激状态从而预防糖尿病骨骼肌损害。

2.6. 炎症反应

局部或全身炎症通过改变肌肉组织中的分子结构以调节肌肉质量或力量[34]。纤溶酶原激活物抑制物-1 (plasminogen activator inhibitor, PAI-1)是一种促炎标记物，有研究发现 PAI-1 在 1 型和 2 型糖尿病以及未经胰岛素治疗的糖尿病动物模型中均表达升高，PAI-1 的升高破坏骨骼肌的细胞外基质(extracellular matrix, ECM)重塑，导致肌肉的修复和再生障碍[35]。

2.7. 铁缺乏

骨骼肌中铁含量约 10%~15%，其在骨骼肌的能量代谢方面起着至关重要的作用。铁缺乏时，线粒体内嵴膜的密度降低，导致线粒体氧化效率低下。另外，缺铁还会影响氧磷含量，进而影响氧的传递等，这些因素致使骨骼肌氧化能力下降，产生功能障碍[36]。

3. 血管因素

骨骼肌代谢需要的氧和底物由血液输送，血管数量减少或形态改变以及血管内皮细胞功能障碍等都可影响骨骼肌的生长发育。

3.1. 毛细血管改变

高血糖会改变毛细血管床，降低毛细血管扩散能力，破坏骨骼肌的血流动力学调节。T1DM 动物模型骨骼肌表现出毛细血管与纤维比率下降、血管生成失调以及血管基底膜增厚[37]。

3.2. C5b-9 微血管沉积

C5b-9 又称为末端补体复合物(terminal complement complex, TCC)或膜攻击复合物(membrane attack complex, MAC)，是一种补体衍生物，肌内膜毛细血管 C5b-9 沉积通常与微血管硬化有关。Paul 等[38]通过对糖尿病患者的肌肉进行活检，发现超过 90%的患者肌肉中存在 C5b-9 的微血管沉积。

3.3. 内皮细胞功能改变

血管内皮细胞产生的 DLL4 (Delta-like grand 4, Delta 样配体 4)是一种血管调节因子，Notch 信号通路是调节机体细胞增殖、分化的重要途径。内皮 DLL4-肌肉 Notch2 轴是一种调节肌肉分解代谢信号的中央上游机制。Fujimaki 等[39]研究发现在糖尿病患者肌肉中，微血管内皮细胞释放 DLL4 增加，然后激活肌肉 Notch2，使肌肉分解代谢增加，导致肌肉质量的降低。

4. 钙的释放与转运异常

横纹肌的肌浆网(sarcoreticulum, SR)膜中，ryanodine (一种离子通道)受体(RyR)负责细胞内 Ca^{2+}的释放[40]，从而触发肌肉收缩。糖尿病患者的肌肉细胞在静息条件下，过量的 SR Ca^{2+}通过 RyR“泄漏”，导致肌肉的收缩能力下降[41] [42]。肌浆网钙 ATP 酶(sarco (endo) plasmic reticulum calcium ATPase, SERCA)负责肌肉中 Ca^{2+}的转运，Oldfield 等[43]发现糖尿病小鼠骨骼肌中出现 SERCA 活性的紊乱及受损，导致骨骼肌功能障碍。

5. 其他

Miller 等[44]在实验中发现，糖尿病患者的骨骼肌中腺嘌呤核苷酸(ADN: ATP, ADP, AMP)特征性减

少，表明核苷酸降解的增加导致骨骼肌功能下降和萎缩。Nutter 等人[45]发现在慢性高血糖症小鼠的腓肠肌中存在五个影响肌肉生长、代谢和收缩的基因错误拼接，提出了信使 RNA 选择性剪接可能是糖尿病骨骼肌病变的原因之一。还有一些研究发现糖尿病小鼠肌肉质量的减少伴随着一些如肌生长抑制素等萎缩信号通路的上调[46]。近年来，异常自噬已被证实是诱导骨骼肌损伤的一个重要因素。Yang 等[47]利用糖尿病小鼠实验得出脂质沉积、炎症反应以及氧化应激的增强会增加骨骼肌的自噬水平，从而加剧肌病。糖尿病患者尿中会出现丙烯醛复合物的增加，Chen 等[48]利用动物实验证明丙烯醛通过 Akt 信号通路抑制肌生成，诱导肌肉萎缩并延缓肌肉再生，表明丙烯醛可能是糖尿病肌病的危险因素。脂联素在骨骼肌的代谢和分化中起着关键性作用[49]，Coleman 等[37]提出 T1DM 状态下脂联素的稳态调节发生了改变，进而导致骨骼肌力量受损、代谢能力改变及再生能力降低等。与神经干细胞相似，肌肉中同样存在骨骼肌干细胞(或称卫星细胞)，糖尿病肌肉中存在卫星细胞功能障碍，使肌肉结构、功能和代谢变化，进而导致肌肉无力，肌肉萎缩等[50]。

6. 总结

糖尿病患者骨骼肌损害临床表现隐匿但并非少见，其可能机制有蛋白质与脂质代谢异常、线粒体功能障碍、血管因素以及钙代谢紊乱等。由于骨骼肌在葡萄糖代谢中具有重要地位，深入研究糖尿病骨骼肌病变这一并发症显得尤为重要，目前对于其机制的研究大多数仍停留在体外及动物研究水平，这些因素如何相互关联以及在多大程度上发挥作用还有待进一步阐明。

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