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糖皮质激素诱发类固醇肌病的研究现状

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摘　要

糖皮质激素作为一种抗炎及免疫抑制剂，是各种自身免疫性疾病的重要药物。但如果使用不当或在少数敏感个体中使用，则可诱发类固醇肌病(steroid myopathy, SM)。糖皮质激素过量是导致肌肉萎缩的关键因素，近年来研究者越来越关注糖皮质激素对肌肉的影响，加大了对SM发病机制及诊断的研究，促进对整个类固醇肌病的了解。下列对该病整体认识进行综述如下。

关键词

类固醇肌病，糖皮质激素，肌病

Research Status of Glucocorticoid Inducing Steroid Myopathy

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Abstract

Glucocorticoid, as an anti-inflammatory and immunosuppressant, is an important drug for various autoimmune diseases. However, if it is used improperly or in a small number of sensitive individuals, it can induce steroid myopathy (SM). Excessive glucocorticoid is a key factor leading to muscle atrophy. In recent years, researchers have paid more and more attention to the influence of glucocorticoid on muscle, increasing the research on the pathogenesis and diagnosis of SM, and

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promoting the understanding of the whole steroid myopathy. The overall understanding of the disease is summarized below.

Keywords

Steroid Myopathy, Glucocorticoid, Myopathy

1. 引言

糖皮质激素(glucocorticoid, GC)具有强大的抗炎和免疫抑制功能，是一种常用的抗炎药物，临床广泛用于炎症及自身免疫性疾病，如肾病、哮喘、系统性红斑狼疮、类风湿关节炎和各种血管炎等。糖皮质激素使用得当，常常疗效明显，甚至可以治疗各种肌病，包括炎症性肌病和由于离心运动引起的肌肉损害，但长期使用、使用不当或在少数敏感个体中使用，糖皮质激素可诱发类固醇肌病(steroid myopathy, SM) [1]。其发生率 2.4%~21%，甚至更多，它是 GC 应用的不良反应之一，也是药物诱发肌病中最常见的类型之一。

类固醇肌病是一种非炎症性毒性肌病，是由 Cushing (1932)首次提出，可由内源性或外源性皮质类固醇激素增多所致[2]。内源性见于库欣综合征(Cushing's syndrome)，内源性糖皮质激素过量导致患者近端肌肉萎缩和无力[3]，外源性见于使用糖皮质类固醇激素(glucocorticoid, GC)诱发的肌病，亦称 GC 性肌病。其发生率 2.4%~21%，甚至更多，特别是老年人、癌症患者、身体不活动患者、负氮平衡患者等多见[4] [5]，主要表现为疲劳、虚弱、肌痛、肌肉萎缩和肌无力，对姿势肌肉的影响大于非姿势肌肉，对肢体近端的影响大于远端肌肉，并且库欣综合征体征明显，满月脸，水牛背，向心性肥胖，皮肤变薄伴有红斑。并且以含氟糖皮质激素(地塞米松、倍氯米松、曲安西龙等)较非氟性制剂(如泼尼松等)更易诱发[6]。近年来研究者越来越关注糖皮质激素对肌肉的影响，加大了对类固醇肌病发病机制及诊断的研究，促进对整个类固醇肌病的了解。下列对该病相关知识进行综述如下。

2. 发病机制

根据患者起病情况分为急性及慢性两种[7]。

1) 急性类固醇肌病

急性类固醇肌病的确切机制尚不清楚，但可能对肌肉收缩和能源生产产生直接影响有关。类固醇具有许多非基因组效应[8]。其病理特征是选择性的粗肌丝缺失。Mozaffar 等[9]在啮齿类动物中通过肌动蛋白(actin protein)和肌球蛋白重链(myosin heavy filament, MyHC)浓度监测及 MyHC 和 Actin mRNA 分析，发现 Actin 浓度没有明显变化，而选择性的 MyHC 缺失，从而导神经内致严重的肌萎缩。另外，Hanson 等[10]研究发现在短期内单独应用大剂量糖皮质激素后可以出现横纹肌溶解，提示糖皮质激素能够导致肌膜的损害。

2) 慢性类固醇肌病

a) **肌肉纤维**

骨骼肌萎缩的属性是肌肉纤维的尺寸减小。糖皮质激素诱导的肌肉萎缩影响快速收缩糖酵解肌纤维(II 型肌纤维)。主要是 IIb 纤维受到影响，而较少或没有观察到的影响 1 型(氧化)纤维[11]。IIb 型纤维的

活动频率低于 IIa 型或 I 型纤维，正常活动模式的差异可能导致 IIb 型纤维更大的类固醇诱导萎缩[12]。

b) **抗蛋白质合成代谢作用**

① 糖皮质激素可破坏氨基酸平衡，阻碍氨基酸向肌细胞内转运而抑制蛋白合成；② 糖皮质激素通过降低翻译起始因子(eIF)水平，干扰 mRNA 翻译，阻碍 II 型肌纤维蛋白合成[13]；③ 糖皮质激素可以下调肌细胞表达的胰岛素、胰岛素生长因子(insulinlike growth factors, IGF-1)及氨基酸(尤其是亮氨酸)，从而阻碍肌卫星细胞向肌纤维分化；④ 糖皮质激素水平增高损伤垂体－性腺轴功能，导致睾酮水平的相对减少，使雄激素受体在肌细胞的表达下调，使肌肉蛋白的合成下降；GC 的萎缩效应可能受到性别的影响，而这种性别差异可能是由睾酮水平的差异所介导的。⑤ 糖皮质激素可造成 Myostatin 肌肉抑制素表达上调，Myogenin 肌细胞生成素表达下调，从而抑制肌肉蛋白的合成和肌细胞的生成[7]。

c) **促蛋白分解代谢作用**

糖皮质激素对肌肉蛋白水解的分解代谢作用是主要细胞蛋白水解系统激活的结果[14]包括泛素－蛋白酶体系统(ubiquitin-proteasomsystem, UPS)、溶酶体系统、钙依赖蛋白酶系统(Ca^{2+}/calpain 钙调蛋白)及碱性肌原纤维蛋白酶途，其中以泛素－蛋白酶体系统及碱性肌原纤维蛋白酶途径最为敏感[14] [15]。

d) **致线粒体功能异常的作用**

SM 患者线粒体的钙负荷、氧化能力和膜电位受损。肌细胞由于长期暴露于糖皮质激素导致线粒体基因表达损伤和钙、细胞色素 C 的释放，从而使细胞功能降低。DU 等[16]研究发现，糖皮质激素受体不仅对核基因转录发挥明显的基因效应，而且能够转移进入线粒体，调节线粒体膜的渗透性，从而影响氧化磷酸化、细胞存活和凋亡的线粒体基因的表达。

e) **肌膜兴奋性的改变**

SM 患者可出现肌膜渗透性的改变。RICH 等[17]通过对 SM 患者肌纤维动作电位、刺激频率及波幅的监测，观察到肌膜兴奋性下降，考虑糖皮质激素与电压依赖性 Na^{+}通道的失活致膜电位变化有关。

f) **局部因素**

糖皮质激素也可以通过改变生长因子的产生来引起肌肉萎缩，这些生长因子控制着肌肉的局部发育。它们抑制肌肉产生 IGF-1。胰岛素样生长因子-1 通过增加蛋白质合成和肌肉生成，同时减少蛋白水解和细胞凋亡来刺激肌肉的发育[18] [19]。糖皮质激素也刺激肌肉产生肌肉生长抑制素。肌肉生长抑制素通过下调卫星细胞的增殖、分化和蛋白质合成来抑制肌肉组织的发育。由于这些原因，肌肉 IGF-1 减少和肌肉生长抑制素增加在糖皮质激素诱导的肌肉萎缩中起关键作用[11]。

3. 临床表现

对于任何患有新发疲劳或持续肌肉无力的患者，都需要高度怀疑类固醇肌病，这与皮质类固醇治疗后的剂量或时间无关[20]，既可发生于治疗初始，也可发生于维持治疗阶段，可表现为急性和慢性两种形式[21]。

1) 急性 SM 也称为急性四肢瘫痪性肌病(acute quadriplegic myopathy)、重病性肌病(critical illness myopathy)或重症监护性肌病(critical care myopathy) [13]，系类固醇使用后于急性期出现的一组肌病综合征。急性多表现为近端和远端肌肉群迅速进行性衰弱[22]。临床上出现广泛肌无力及横纹肌溶解，伴有肌痛，严重者可发生呼吸肌受累。有些患者表现为严重肌萎缩、迟缓性四肢瘫、腱反射减弱或消失，而感觉系统及颅神经多不受累[10]。

2) 慢性类固醇肌病主要表现为疲劳、虚弱、肌痛、肌肉萎缩和肌无力，对姿势肌肉的影响大于非姿势肌肉，对肢体近端的影响大于远端肌肉。骨盆束肌比手臂受累更严重；颅神经支配的肌肉和括约肌没有受损，远端肌肉很少受到影响[16] [21]。而且库欣综合征体征明显，满月脸，水牛背，向心性肥胖，皮

肤变薄伴有红斑。并且肌肉无力多表现为潜伏地发展，进展缓慢，通常无痛或轻度疼痛。多在使用剂量为 40~60 mg/天的泼尼松或等效药物至少 1 个月导致一定程度的肌肉无力以及使用非氟尿苷糖皮质激素，特别是甲基强的松龙时，会引起急性肌肉无力痛苦综合症[23]。

SM 易感人群主要为老年人、肿瘤患者和激素治疗前存在营养不良、长期活动差、卧床及负氮平衡患者[4]。多在脓毒血症、恶病质、饥饿、代谢性酸中毒、严重胰岛素缺乏等病理情况时发生，患者以肌肉萎缩为重要临床特征。

4. 诊断检查

4.1. 肌肉力量评估

大多数医生通过手动肌肉测试评估类固醇肌病患者的肌肉损伤，其中半定量评估包括肌肉强度主观给予等级：最低等级表示没有收缩性，最高等级表示正常运动[24] [25]。一种替代半定量力量评估的方法是直接量化等长肌肉力量[26]。虽然等长活动在日常生活中很少见，但等长强度的测量是简单、有效、可靠的，并且与功能能力有很强的预测关系[24] [26]。尽管不仅是肌肉，而且神经机制可能是类固醇肌病患者肌肉无力的基础[27]，但我们认为系统地将测力仪纳入患者的常规检查可用于诊断和监测肌病过程。

4.2. 针吸活组织检查

急性 SM 主要为 I、II 型肌纤维弥漫性损害，而慢性 SM 主要为 II 型肌纤维选择性萎缩。具有特征性的病理改变是 II 型纤维选择性萎缩，以 IIB 型纤维萎缩最为突出，部分纤维呈“小角化”改变[28]。这一病理学改变被广泛研究，但一些研究表明，I 型纤维在严重类固醇肌病中也显示大小和脂滴减少，而纤维萎缩的恢复通常发生在激素紊乱或糖皮质激素停药后，并且在其他条件下 II 型肌纤维选择性萎缩，比如衰老、神经病变等。并且这一检查是有创的检查且木有研究表明这一检查与疾病严重程度直接存在相关性。

4.3. 血尿中肌肉相关酶

血清中肌肉相关酶如肌酸激酶、乳酸脱氢酶、肌红蛋白和醛糖等水平正常状态下是正常的，敏感性低，对肌酸激酶和肌红蛋白的分析灵敏度分别为 3 U/l 和 21 ng/ml。然而，在急性期，肌酸激酶和醛糖水平可能相对升高[23]，尿中的 3-甲基组氨酸(3 MH)也升高。尿肌酸水平升高常先于临床肌病症状，与肌无力严重程度相关，可用于临床监测肌病的发生和发展[29]。目前还没有可用于临床和研究环境的可靠(尿液或循环)生物标志物来识别类固醇肌病，跟踪其随时间的进展，并监测其对干预措施的反应。

4.4. 肌电图

肌电图急性坏死性 SM 主要表现为大量异常自发电活动，并可见潜伏期短、波幅低、时程短的多相运动单位波。慢性 SM 中，常规的肌电检查方法只有少部分可见低波幅、短时程的运动单位波[8]。但是，同样的电生理异常也可以观察到其他几个生理(即固定)或病理内分泌(即，衰老，药物使用，神经肌肉紊乱)条件下，肌肉纤维减少或增加。

4.5. 双能 X 线吸收仪和生物电阻抗分析

双能X线吸收仪(DXA)衍生的瘦体重和生物电阻抗分析(BIA)衍生的肌肉质量估计值被广泛用于临床研究和营养状况和肌肉减少症的常规评估[30] [31]。DXA 装置的基本测量输出参数包括全身和区域骨密度、瘦软组织质量和脂肪质量的测量[31]。当交变电位施加到身体上时，BIA 测量阻抗。阻抗测量用于通过预测方程估计总体水分，无脂肪质量，肌肉质量[32]和阑尾肌质量[33]。全身及附件规范数据肌肉质量

适用于不同的种群[34] [35] [36] [37]。此外，这些方法在健康受试者和患者身体成分评估的可靠性已有文献[1] [30] [34] [35] [37]。总的来说，使用 DXA 或 BIA 衍生的指数来鉴定肌肉萎缩是有实用的临床目的，但他们不是非常准确。这是因为肌肉萎缩不是一个统一的条件，因为它影响体位肌肉比非体位肌肉更多。

4.6. 影像学技术

Khaleeli 等[38]在库欣综合征患者中通过 X 射线计算机断层成像(CT)研究显示，干预前后大腿和小腿肌肉横截面积增加。在最近的一项研究中，Miller 等[39]评估了皮质醇增多症和健康对照患者的 CT 扫描，前者的横截面积和腰肌密度低于后者。此外，他们发现腰大肌密度和尿游离皮质醇之间存在显著的负相关。然而使用 CT 评估肌肉大小(即肌肉横截面积)和结构(即肌肉密度)是复杂的高成本和不必要的辐射暴露。另一个工具是用于诊断和随访炎性肌病的磁共振成像(MRI) [7] [40]内分泌以及肌肉减少症研究，它不仅能够研究肌肉大小，而且能够研究肌肉脂肪浸润[41]。评估肌肉脂肪化的磁共振脂肪测量技术主要包括视觉评估分级法、T2 mapping、Dixon 技术及 MRS 等，MRI 脂肪评估测量技术是一种无创性的检查方法，但还存在几点不足：1) 成像时间长，后处理繁琐；2) 目前尚无公认的最优化测量方式；3) MRI 脂肪评估测量技术还处于研究阶段，还未被广泛应用到临床工作中。并且到目前为止，还没有研究进行调查的有用性磁共振成像诊断和监测类固醇肌病。尽管如此，不论作为科研项目还是临床检查项目，MRI 脂肪测量技术在评估患者病情、指导临床选择治疗方案、评估临床治疗效果方面都有着十分乐观的应用前景。测量肌肉大小的另一种技术是超声检查，定量超声是在二维超声图像中提取结构性参数，如羽状角(pennation angle, PA)、肌纤维长度(fascicle length, FL)、肌肉厚度(muscle thickness, MT)、肌肉横截面积(cross sectional area, CSA)和横断面厚宽比(thickness width ratio, TWR)等，以显示肌肉的状态变化，并以此评估肌肉活动时的状态变化，所以超声测量厚度是估计躯干和肢体肌肉功能和力量的有效、可靠方法[42]。

4.7. 剪切波弹性成像(SWE)

SWE 评估组织的刚度，这是由发生在肌肉疾病的组织病理学变化改变。虽然不能免疫技术问题，肌肉 SWE 表现出良好的重复性[43]。因此，SWE 有可能解剖肌炎和类固醇肌病的不同组织病理学肌肉变化[44]。

虚弱和肌痛的症状往往被错误地认为是原发病的一部分。事实上，没有一个单一的测试是这种情况的诊断[45] [46]增加了及时识别的困难。不同的调查可用于诊断和监测类固醇肌病，而目前没有工具可用于预测和预后的肌病过程。鉴于现有的证据表明肌肉质量和力量的定量评估对于检测和跟踪不同疾病中肌肉萎缩和无力的进展是有用的，相关研究表明这些测量也应该系统地纳入类固醇肌病患者的常规检查。而且通过综合评估肌肉质量，力量(通过等长测力法)和性能(通过一项或多项以下评估：通常的步态速度测量，6 分钟步行测试，楼梯爬高功率测试) [47] [48]也可以应用于类固醇肌病患者的常规检查。

5. 诊断与鉴别诊断

类固醇肌病的诊断通常比较困难，尤其需要与炎性肌病鉴别，临床体征、实验室检查和电生理检查大多时候可能并没有特异性提示作用[49]。由于慢性类固醇肌病发病缓慢且隐匿，我们不易察觉到，所以当患者有长期使用糖皮质激素史及短期大量使用糖皮质激素史时，并出现肌肉无力现象时要高度注意肌病。下面我们重点关注一下慢性类固醇肌病与炎性肌病的鉴别诊断[22]。1) 肌肉无力发生的时间：慢性类固醇肌病多见于糖皮质激素治疗后 ≥1 个月，而炎性肌病多发生于疾病活动期。2) 库欣综合征：慢性类固醇肌病多有，而炎性肌病有或无。3) 肌酶水平：慢性类固醇肌病正常或轻度升高，而炎性肌病多升高。4) 糖皮质激素剂量(减少/停止)：慢性类固醇肌病表现为 3~4 周内病情改善，而炎性肌病症状加重。5) 尿肌酸：慢性类固醇肌病通常升高，糖皮质激素停用后降低，而炎性肌病通常升高，糖皮质激素停用

后增高。6) 神经肌电图：慢性类固醇肌病常正常，或小振幅多相动作电位不伴有针刺自发活动，而炎性肌病小振幅高频多相动作电位，针刺自发活动和纤颤。7) 肌肉组织活检：慢性类固醇肌病 IIB 型肌纤维萎缩，而炎性肌病肌内或血管周围炎性浸润(多发性肌炎)和束周萎缩(皮肌炎)。8) 磁共振：慢性类固醇肌病无研究，而炎性肌病疾病早期：T2 加权相对对称的近端肌肉水肿样改变，可为弥漫性或局灶性；慢性疾病：脂肪沉积的区域相对对称的 T1 和 T2 加权高信号。

6. 治疗与预后

糖皮质激素作为一种抗炎及免疫抑制剂，是广泛用于治疗各种自身免疫性疾病的重要药物。所以对于外源性类固醇肌病的治疗及管理主要是：减少糖皮质激素剂量、隔日给药方案、避免含氟糖皮激素、补充优质蛋白[28]。另外，一定程度的有氧运动和阻力运动可能对糖皮质激素所致类固醇肌病患者的肌肉萎缩有缓解作用，可通过口服阿法骨化醇，补充谷氨酰胺、丙氨酰谷氨酰胺等方式预防糖皮质激素引起的肌肉萎缩[7] [50]。

6.1. 生长因子

通过增加胰岛素生长因子(IGF-1)及抑制生物抑制可防止糖皮质激素诱导的肌肉萎缩。肌肉 IGF-I 过表达[51]或 Mstn 缺失[52]可防止 GC 诱导的肌肉萎缩。因此，IGF-I 刺激或 Mstn 阻滞可能有益于各种肌病，例如由高剂量 GC 引起的肌病。最近，Ghrelin，一种主要由胃产生的循环激素，也被证明可以抑制 GC 诱导的骨骼肌萎缩。

6.2. 雄激素

有研究表明[53] [54] [55]使用雄激素如睾酮，nandrolone (一种最小芳香化类似物)或选择性雄激素受体调节剂(SARM)可以防止由 GC 引起的动物和人的肌肉质量和力量下降。睾酮与许多其他合成代谢刺激一样，能够刺激肌肉 IGF-I 表达。与 IGF-I 相似，睾酮可以降低由肌管内气相色谱引起的蛋白质降解和 Atrogenes 的诱导[56] [57] [58] [59]。此外，睾酮阻止参与 GC 分解代谢作用的几个基因如 REDD1，FOXO1，p85 something 和 IRS-1 的肌肉表达的变化[60]。最后，睾酮阻断 GC 诱导的 Akt 和其他参与蛋白质合成的蛋白质如 S6K1 和 GSK3 的去磷酸[57]。因此，睾酮似乎可以逆转 GC 的大部分分解代谢作用。

6.3. 营养素

支链氨基酸，Yammoto 等[60]发现，支链氨基酸(BCAAs)，特别是亮氨酸，通过抑制 UPS 和自噬途径(LC3-I 向 LC3-II 的转化受到抑制)，防止地塞米松所诱发的大鼠比目鱼肌肉萎缩，表明 BCAA 减少地塞米松诱导的蛋白质破坏，抑制肌肉萎缩。

谷氨酰胺作为必需氨基酸，Hickson 等发现谷氨酰胺能防止类固醇诱发的肌肉萎缩，并且谷氨酸的糖皮质激素诱发的肌肉生长抑制素的高表达，而循环中 IGF-I 的水平不受影响[61] [62] [63]，表明谷氨酰胺抑制生长抑制素表达防止肌肉萎缩。

多不饱和脂肪酸(Ω-3 脂肪酸如二十二碳六烯酸(DHA)、二十碳五烯酸(EPA)、A-亚麻酸(ALA)、牛磺酸)。ω-3 脂肪酸的补充提高了混合肌肉蛋白质合成和骨骼肌质量和大小的比例[64] [65] [66]，DHA 通过抑制蛋白酶体活性和延缓肌肉蛋白质降解来防止肌肉萎缩[67]，研究发现诱导有相关研究表明[68] [69]牛磺酸运输基因表达也可以防止肌肉萎缩。

维生素族，维生素 E 通过减轻地塞米松诱导的氧化应激作用来防止肌肉萎缩[70]。维生素 D 通过抑制 FoxO1 转录活性以及 C2C12 成肌细胞中减少 FoxO1 靶萎缩基因(包括阿托金-1 和组织蛋白酶 L)的表达，来预防肌肉减少症或抑制肌肉萎[71] [72] [73]。维生素 A (维甲酸 RA)的这些作用可能诱导骨骼肌细胞

11β-HSD1 mRNA 表达和活性的抑制，从而抑制 GR 转录激活和降低糖皮质激素敏感性[74]。维生素 C 通过泛素连接酶的 mRNA 表达水平明显升高来抑制肌肉萎缩[75]。

矿物质(萝卜硫素)，地塞米松处理显着激活蛋白水解并上调肌肉特异性泛素 E3 连接酶标志物如阿特菌素-1/MAFbx 和肌肉生长抑制素的 mRNA 表达。此外，地塞米松治疗抑制肌生成调节因子 MyoD 的蛋白质合成，肌管直径和 mRNA 表达，而补充萝卜硫素可逆转这些特征[76]。

6.4. 肌酸

肌酸可以减轻肌肉重量减轻和腓肠肌萎缩[77] [78]，增加肌肉质量。肌酸增加 IGF-I 表达作用于肌肉细胞[79]。综上肌酸也有抗肌肉萎缩功能。

6.5. 盐酸克伦特罗

是一种 β_2 肾上腺素受体激动剂，过去用于增加牲畜肌肉重量。有关研究表明可以通过激活 Akt/mTOR 途径或间接地通过增加 IGF-I 表达和通过下调 Mstn 表达直接发挥其对肌肉的抗分解代谢作[80] [81] [82] [83]，从而拮抗 GC 诱发的骨骼肌肉萎缩。

6.6. 体育锻炼

有证据[84] [85]表明，适度的体育锻炼，尤其是有氧运动和耐力训练能防止和减轻激素引起的肌肉萎缩和无力。

6.7. 11-羟基类固醇脱氢酶 1 型(11-HSD1)

11β-HSD1z 增加了可的松对蛋白质降解以及对人和小鼠骨骼肌管中 Atrogin-1 和 MuRF-1 表达的影响[86]。因此，抑制 11-HSD1 可能是防止病理状况下肌肉萎缩的一个重要途。

6.8. 新药研究

RU486 是一种选择性 GC 受体拮抗剂，有关研究[87]提示其对 GC 诱发的肌肉萎缩具有潜在治疗作用。类固醇米非司酮(RU-486)，其主要效力是抗孕激素的，使得其作为 GC 拮抗剂的效用有限。

7. 结论

总之，糖皮质激素引起的类固醇肌病会引起肌肉的改变，对于发病机制及临床表现大家已经有了整体的认识和了解，但是在诊断和治疗上还有很大的空间，需要我们进行深入的研究和认识。

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