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睡眠障碍与肌少症相关性的认识与思考

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【摘要】 肌少症是老年人群的临床常见病, 容易引起躯体功能障碍, 降低生活自理能力, 影响生活质量, 增加发生多种不良健康结局的风险。目前仍缺乏治疗肌少症的针对性药物, 早期识别肌少症并及时进行干预有助于防止其进一步发展。通过梳理文献, 发现睡眠障碍与肌少症具有较高的相关性, 昼夜节律、线粒体结构和功能、炎症因子、胰岛素共同影响着二者的发生、发展。从改善睡眠障碍的角度防治肌少症值得进一步探索, 褪黑素或许是治疗肌少症的潜在药物, 未来可加强相关临床及机制研究, 以助力肌少症的中药新药研发。

【关键词】 肌少症; 睡眠障碍; 失眠; 昼夜节律; 肠道菌群; 炎症因子; 褪黑素

Insights and reflections on correlation between sleep disorders and sarcopenia

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Abstract: Sarcopenia is a prevalent condition among the elderly, contributing to physical dysfunction, diminished ability to perform activities of daily living, reduced quality of life, and an increased risk of various adverse health outcomes. Currently, there is no targeted pharmacological treatment for sarcopenia. Early detection and timely intervention are critical in preventing its progression. A review of the literature reveals a significant correlation between sleep disorders and sarcopenia, with shared influencing factors including circadian rhythms, mitochondrial structure and function, inflammatory factors, and insulin. Treating sleep disorders as a potential strategy for the prevention and treatment of sarcopenia deserves further research. Melatonin may be a promising medication for the treatment of sarcopenia, and future clinical and mechanistic studies are needed to advance the development of novel traditional Chinese medicine-based medications for sarcopenia.

Keywords: sarcopenia; sleep disorders; insomnia; circadian rhythm; gut microbiota; inflammatory factors; melatonin

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肌少症亦称肌肉减少症, 是一种与增龄相关的肌肉量减少、肌肉力量下降和/或躯体功能减退的老年综合征^[1]。肌少症常导致患者虚弱、躯体功能障碍、行动困难、容易跌倒骨折、生活自理能力下降, 严重影响患者的生活质量, 并与多种不良健康结局的高风险相关, 如代谢紊乱、认知障碍、术后并发症、住院和死亡^[2-3]。据估计, 老年人肌少症全球患病率高达 10%~16%^[4]。作为增龄性疾病, 随着人口老龄化的发展, 肌少症的患病率会越来越高, 针对肌少症及其相关不良后果的防治将会成为全球卫生健康的巨大挑战。目前肌少症的发病机制尚不明确, 亦无针对性药物, 治疗仍以抗阻运动和营养支持为主。但肌少症患者肌力下降, 活动受限, 因此难以进行有效的运动锻炼^[5], 营养支持治疗的临床证据尚不充分。早期识别并及时干预有助于防止

肌少症的进一步发展,进而改善老年人的生活质量并降低发生相关不良后果的风险。近年来,老年人睡眠障碍的发生率明显升高,包括入睡困难、睡眠持续时间短、睡眠质量下降、白天嗜睡等,65 岁以上的老年人睡眠障碍的患病率超过 50%^[6]。随着年龄的增长,老年人睡眠时间、睡眠质量、睡眠结构均会发生改变^[7]。从增龄性疾病这一特征来看,肌少症与老年人睡眠障碍可能存在相关性,从改善老年人睡眠障碍这一角度入手,可能有利于肌少症的早期防治。

1 睡眠障碍是肌少症的危险因素

睡眠在维持肌肉质量方面起着重要作用^[8]。睡眠障碍与肌少症的发生有明显的相关性,睡眠持续时间过短或过长、低睡眠质量、睡眠不规律都会增加肌少症的患病风险。

流行病学调查^[9]显示,慢性肝病合并肌少症患者存在失眠的概率高达 69.8%,显著高于非肌少症患者。有学者^[10]观察发现,绝经后女性睡眠持续时间是活动能力和肌肉力量的独立预测因子,睡眠时间>9 h 的女性肌肉质量、肌肉力量和活动能力均明显下降,这可能与长时间睡眠减少日常活动时间有关。Kwon 等^[11]的研究支持了这一观点,该研究显示,与 7 h 睡眠相比,睡眠时间>9 h 的人群患肌少症的风险明显增加,亚组分析发现这类人群缺少规律的体育运动。有研究^[12]对 45 岁以上的人群进行了为期 4 年的随访,结果显示与每晚睡眠 6~8 h 的参与者相比,睡眠时间较短(每晚<6 h)的参与者 4 年内发生肌少症的风险增加 53%,控制潜在混杂因素后其相关性依然显著,而长时间睡眠(每晚>8 h)与肌少症无明显相关性。睡眠不足导致肌少症,可能与白天疲倦和注意力不集中导致身体活动减少有关^[13]。另有研究^[14-15]发现,睡眠持续时间与肌肉减少症患病率之间存在 U 型关系,睡眠时间较短和较长的老年人均表现出更高的肌少症患病率。因此,最佳睡眠时间建议维持在 6~8 h。

除了睡眠持续时间以外,睡眠质量和规律的睡眠习惯也与肌少症的发生有关。匹兹堡睡眠质量指数(PSQI)是临床评价睡眠质量的常用工具,PSQI 评分越高代表睡眠质量越差。研究^[8,16]表明,在调整年龄、身体活动、胰岛素抵抗稳态模型和睾酮等混杂因素后,高 PSQI 评分与较差的肌肉质量相关。Yu 等^[17]调查了 1 620 名年龄在 47~59 岁的人群,发现晚睡晚起的“夜晚型”睡眠与男性肌少症患病风险增加有关。与非轮班工人相比,作息时间不规律的轮班工人患肌少症的风险更高^[18]。睡眠剥夺会使肌肉质量减少、肌肉组织萎缩^[19],进而对运动表现和运动后恢复产生负面影响^[20]。与睡眠相关的疾病也与更高的肌少症患病率相

关,与无阻塞性睡眠呼吸暂停(OSA)的老年人相比,OSA 患者的肌少症患病风险增加 2 倍^[21]。

这些研究表明,睡眠障碍是肌少症的危险因素,良好的睡眠可能有利于预防肌少症的发展。

2 睡眠障碍与肌少症在发病机制上存在相关性

2.1 昼夜节律

昼夜节律可影响骨骼肌的结构和功能,在肌肉代谢中起着至关重要的作用^[22]。昼夜节律基因表达数量会随着年龄的增长而减少,因此老年人更容易发生睡眠障碍^[23]。昼夜节律紊乱会加速衰老,衰老又会导致昼夜节律紊乱,二者相互影响^[24]。睡眠可以调节机体生长激素、皮质醇、睾酮、胰岛素样生长因子 1 和胰岛素水平,介导多种蛋白质合成和降解途径来重建肌肉纤维、力量和功能^[25-26]。

研究^[27]发现,长期恒定的光照会破坏小鼠的睡眠节律,从而导致其骨骼肌功能下降、骨量减少。生物钟基因 *Bmal 1* 和 *Clock* 是产生昼夜节律分子振荡器的关键组成部分,*Bmal 1* 基因敲除小鼠昼夜节律行为受损,寿命缩短并表现出过早衰老表型,包括肌少症、骨质疏松和器官萎缩等^[28]。*Bmal 1* 和 *Clock* 基因的直接靶点成肌分化蛋白(MyoD)是肌生成的主要调节因子,MyoD 表达降低会导致骨骼肌功能下降和结构改变,线粒体亦会出现以呼吸功能下降、肿胀和嵴破坏为特征的改变^[29]。*Clock* 基因突变会改变小鼠的睡眠结构,缩短睡眠时间^[30];*Bmal 1* 基因敲除小鼠正常活动/休息节律(睡眠/觉醒节律)混乱,骨骼肌功能和质量下降,肌肉纤维萎缩和胶原蛋白含量增加,线粒体结构破坏^[31]。以上研究表明,睡眠障碍与肌少症在昼夜节律基因表达层面上存在关联。

2.2 肠道菌群

肠道微生物有助于分解食物,合成氨基酸,提供营养支持,其组成和结构对骨骼肌质量及功能具有重要影响^[32-33]。研究^[34]表明,老年肌少症患者的肠道菌群结构会发生变化,与非肌少症比较,肌少症患者的示波螺旋藻和瘤胃球菌微生物类群的丰度增加,巴尼塞拉科和白藜科的丰度则降低。使用抗生素抑制小鼠的肠道菌群后,小鼠表现出骨骼肌萎缩,血清胆碱减少、胰岛素样生长因子 1 表达降低,与骨骼肌生长和线粒体功能相关的基因转录减少,移植正常小鼠的肠道菌群后可以逆转上述改变,补充短链脂肪酸也有助于修复骨骼肌损伤^[35]。

睡眠时间与肠道微生物的多样性呈正相关,睡眠不足会改变肠道微生物的多样性^[36]。肠道微生物群及其代谢物表现出昼夜节律性,睡眠碎片化和睡眠时间不足都与肠道菌群失调有关,睡眠不足相关的代谢紊乱可能是通过特定肠道细菌的过度生长来介导的,响应睡眠不足而生长的细菌物种的最终产物能够诱发疲

劳,降低身体活动能力^[37]。研究^[38]发现,睡眠剥夺小鼠的肠道菌群结构发生改变,肠道内短链脂肪酸水平明显减少。作息不规律的轮班工人肠道瘤胃球菌的丰度增加^[39],这与肌少症患者的肠道菌群表现相似。来自动物研究的证据也支持这一关联^[40]。可见睡眠障碍与肌少症存在着相似的肠道菌群改变。

2.3 线粒体 线粒体因衰老或损伤导致的功能障碍与肌少症的发生密切相关^[41-42]。线粒体结构损伤容易导致活性氧产生过多,加剧机体的氧化应激反应,供能效应下降^[43]。线粒体结构改变,膜通透性升高,内容物外漏,会导致运动神经元和肌纤维死亡^[44]。线粒体还可介导细胞凋亡,激活泛素-蛋白酶体系统,加速肌肉蛋白降解,诱发肌少症^[45]。致命性家族性失眠患者的脑组织中,与线粒体呼吸链相关基因和蛋白质的表达明显降低^[46]。睡眠剥夺会导致线粒体数量减少,电子传递链受损,活性氧产生过多,导致其结构损伤和功能障碍,并进一步诱导细胞凋亡^[47-50]。

2.4 炎症因子 炎症因子可抑制蛋白质合成,加速蛋白质降解,甚至直接作用于骨骼肌细胞,加速其凋亡^[51]。肌少症患者的血清炎症因子水平显著高于正常人群,炎症因子水平与肌少症患者的肌肉力量呈负相关^[52]。血清C反应蛋白(CRP)、白细胞介素(IL)-6与肿瘤坏死因子- α (TNF- α)水平升高均可能导致肌肉质量及力量下降,进而引发肌少症^[53-54]。睡眠剥夺会导致健康成年人血清IL-6和CRP水平升高^[55-56]。研究^[38]发现,睡眠剥夺小鼠血清TNF- α 水平升高。Patel等^[57]研究发现,基于自我报告的习惯性睡眠持续时间与CRP、IL-6水平呈线性正相关,睡眠时间 >7.6 h时,每增加1 h,CRP水平增加8%、IL-6增加7%;通过多导睡眠图监测的睡眠持续时间则与TNF- α 水平呈线性负相关,睡眠时间 <6.2 h时,每减少1 h,TNF- α 水平增加8%。

2.5 胰岛素 胰岛素抵抗、糖尿病被认为是老年人肌肉质量和肌肉功能丧失的主要危险因素^[58]。高糖状态会过度激活泛素-蛋白酶体系统,从而加速蛋白质分解,导致肌肉萎缩^[59]。胰岛素治疗可以促进葡萄糖与氨基酸向骨骼肌转运,使蛋白质合成增加、降解减少,进而抑制2型糖尿病患者的肌肉质量下降^[60-61]。Ayas等^[62]对70 026名女性进行了长达10年的随访,结果显示睡眠时间与糖尿病发病呈U型关系,睡眠时间 ≤ 5 h,糖尿病风险增加57%,睡眠时间 ≥ 9 h,糖尿病风险增加47%。

3 抗失眠治疗可能对肌少症有效

3.1 褪黑素 褪黑素是一种与昼夜节律调节有关的激素,老年人睡眠障碍及肌少症的发病可能与衰老过程中褪黑素的流失有关^[63]。研究^[64]发现,与正常老年人

相比,老年肌少症患者的血浆褪黑素水平明显降低,受试者工作特征(ROC)曲线分析结果显示,血浆褪黑素水平预测肌少症的曲线下面积(AUC)为0.715($P<0.01$),最佳界值为3.2 ng/L,敏感度为76.7%,特异度为68.3%,褪黑素水平与四肢骨骼肌指数(ASMI)呈正相关,褪黑素水平升高,肌少症的风险减少,由此提出血浆褪黑素可作为肌少症的潜在生物标志物。

褪黑素通常被当成安眠药使用,用于改善睡眠问题^[65],近年来越来越多的研究发现其在肌少症治疗方面的巨大潜力。褪黑素具有良好的抗炎、抗氧化、清除自由基、保护线粒体结构和功能的作用^[24],并可逆转与年龄相关的神经肌肉传递功能障碍^[66-67],改善*Bmal 1*基因敲除小鼠的肌少症相关症状^[31]。此外,褪黑素还可以减少细胞凋亡,保护卫星细胞,减轻氧化应激反应,甚至促进肌肉再生^[68-71]。还有研究^[72]发现,褪黑素可改善由睡眠限制导致的肠道微生物群昼夜节律紊乱。

综上,褪黑素治疗肌少症具有一定的可行性。但有学者^[73]提出低剂量褪黑素可能不足以对肌少症产生有益影响,需要进一步研究二者的量效关系。

3.2 γ -氨基丁酸(GABA) GABA是人体中枢神经系统的主要抑制性神经递质,具有缓解焦虑、失眠,延缓衰老等功效^[74]。GABA能神经元广泛分布于中枢神经系统中,参与睡眠-觉醒调控过程,其水平降低与失眠的发生密切相关^[75]。与年轻小鼠相比,老年小鼠腓肠肌GABA含量明显降低^[76]。口服GABA可以改善睡眠障碍受试者的睡眠质量^[77]。与单纯营养支持联合抗阻运动相比,补充GABA可以明显增加健康志愿者的肌肉质量^[78]。

3.3 中药 具有安眠作用的中药治疗肌少症具有一定疗效。《灵枢·营卫生会》载:“老者之气血衰,其肌肉枯,气道涩,五脏之气相搏,其营气衰少而卫气内伐,故昼不精,夜不瞑。”其提示老年人肌肉衰减与睡眠/觉醒紊乱可能存在相关性,气血衰少、营卫不调可能是肌肉衰减合并睡眠障碍的主要病机。补中益气汤能显著提高失眠患者的睡眠及生活质量,并调节患者的肠道菌群^[79-81]。该方还可以有效改善老年肌少症患者的肌肉质量、肌肉力量,进而提升身体活动功能和日常生活能力,其机制可能与降低血清炎症因子IL-6、TNF- α 水平有关^[82-84]。刘继业等^[85]使用自拟增肌颗粒(由党参30 g、黄芪20 g、白术15 g、牛膝15 g、杜仲15 g、甘草10 g、当归20 g、熟地黄15 g、黄精15 g、黑芝麻10 g、狗脊10 g、香附10 g组成)治疗肌少症,经治疗患者骨骼肌质量指数、握力、步速均显著提升,失眠症状改善,血清CRP、IL-6水平降低。酸枣仁是治疗失眠的常用中药,酸枣仁提取物能明显降低失眠模型大鼠血清IL-2、

IL-6、IL-1 β 、TNF- α 水平,增加线粒体数量,改善线粒体功能^[86-89]。

3.4 运动 运动是治疗肌少症的重要方法,也是治疗失眠的常用方法。定期锻炼可以影响昼夜节律基因的表达,改善昼夜节律紊乱^[90-91]。通过耐力运动训练可以恢复 *Clock* 基因突变小鼠骨骼肌中线粒体含量和运动耐量^[92],提示运动可以预防昼夜节律紊乱引起的肌肉功能障碍。有学者^[93]推测,运动对肌少症有效可能与其能够改善骨骼肌昼夜节律有关。

4 小结

睡眠障碍是肌少症的危险因素,睡眠障碍与肌少症在发病机制上存在相关性,昼夜节律、线粒体结构和功能、炎症因子、胰岛素共同影响着睡眠障碍与肌少症的发生、发展。睡眠障碍与肌少症的发生均与增龄相关,而褪黑素水平随着年龄的增长而降低。褪黑素具有改善睡眠、调节昼夜节律、抗炎、抗氧化、清除自由基、保护线粒体结构和功能、改善神经肌肉接头功能障碍、保护卫星细胞、调节肠道菌群等作用,是治疗肌少症极具潜力的药物,具有良好的应用前景。从改善睡眠障碍的角度防治肌少症值得进一步探索,中医药在调节睡眠方面具有不可替代的优势,未来可加强相关临床及机制研究,以助力肌少症的中药新药研发。

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