

昼夜节律紊乱与工作相关肌肉骨骼疾患的研究进展

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摘要：

昼夜节律是人体内以 24 h 为周期的行为、生理和分子的周期变化。生物钟的紊乱不仅会影响个体的精神状态, 还与多种代谢系统疾病有关, 包括骨与肌肉的代谢调节。有研究发现, 工作相关肌肉骨骼疾患(WMSDs)除了受劳动负荷因素影响外, 还受轮班等昼夜节律因素调控。本文通过综述昼夜节律相关前因变量、结果变量与 WMSDs 的关系, 深入探讨两者共同的代谢标志物和作用机制, 系统阐述昼夜节律紊乱与 WMSDs 的内在联系。尽管现有研究已揭示昼夜节律紊乱对肌肉骨骼疾患的影响, 但两者关系的深入探索仍面临诸多混杂因素的挑战。未来应结合时间生物学, 整合主客观数据, 探讨环境-中间表型-疾病的作用路径, 更全面地揭示 WMSDs 发生的网络机制。

关键词：昼夜节律；工作相关肌肉骨骼疾患；生物钟；代谢；轮班

Research progress on correlation between circadian rhythm disturbance and work-related musculoskeletal disorders LAI Lichong, TAO Pinyue, FAN Dejing, LU Shuyu, PENG Jie, HUANG Huiqiao (The Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530005, China)

Abstract:

Circadian rhythm refers to the 24-hour periodic changes in behavior, physiology, and molecular processes in the human body. Disruptions to the circadian rhythm not only affect mental health but are also associated with various metabolic disorders, including the regulation of bone and muscle metabolism. Research has shown that work-related musculoskeletal disorders (WMSDs) are influenced not only by workload but also by circadian rhythm factors, such as shift work. This review examined the relationships between circadian rhythm-related antecedents, outcomes, and WMSDs, exploring their shared metabolic markers and mechanisms. It provided a systematic overview of the intrinsic connection between circadian rhythm disruptions and WMSDs. While current studies highlight the impact of circadian rhythm disturbances on musculoskeletal disorders, further investigation is required to address the confounding factors involved. Future research should integrate chronobiology with both subjective and objective data to explore the pathway from environmental factors to intermediate phenotypes to diseases, ultimately providing a more comprehensive understanding of the network mechanisms underlying WMSDs.

Keywords: circadian rhythm; work-related musculoskeletal disorder; circadian clock; metabolism; shift work

人体的昼夜节律系统根据生物钟对日常环境变化做出反应以优化行为, 中枢和外周生物钟都在调节肌肉骨骼系统和能量代谢之间的相互作用。工作相关肌肉骨骼疾患(work-related musculoskeletal disorders, WMSDs)是由工作和工作环境因素影响引起或加重身体结构如肌肉、关节、肌腱、韧带、神经、软骨、骨骼和局部血液循环系统等损伤^[1], 主要表现为骨关节和肌肉系统的疼痛及活动受限, 可引起非特异性腰痛、颈肩腕手综合征和腕管综合征, 严重者可导致机体慢性失能^[2]。患有 WMSDs 的工作者有较高的离职倾向、抑郁风险和较低的生活质量^[3-4], 也是病假、工作安全问题和工作质量下降的重要原因^[5]。有研究显示, 由于轮班工作会扰乱人体睡眠-觉醒周期, 其同样会增加 WMSDs 的发生风险,



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肌肉骨骼状态与轮班工作者生物节律的调节密切相关^[6]。并且 WMSDs 在制造业工人、消防员及医护人员等需要轮班的行业中有较高的发生率^[1, 7-8]。现有研究多聚焦于主要影响 WMSDs 发生的劳动负荷因素,如搬举重物和不良姿势等,较少探索生物钟与 WMSDs 之间的联系,本文对昼夜节律紊乱和 WMSDs 之间的关系进行综述,旨在分析两者之间的作用途径及潜在机制,为保障轮班工作者职业安全、促进其职业健康和提高疾病的防治水平提供科学依据。

1 WMSDs 的昼夜节律紊乱相关前因变量

1.1 睡眠节律

研究表明,长时间的轮班工作(>9 h)是 WMSDs 重要的预测因素^[9],并且轮班工作年限与 WMSDs 呈剂量-反应关系,轮班作业时长每增加 5 年,下肢 WMSDs 患病风险增加 4%^[10]。同时高频的夜班增加了多部位疼痛的风险^[11]。与固定白班相比,轮班工作与任何一个部位的慢性肌肉骨骼疼痛发生率之间存在显著关联,并且轮班工作可通过 C 反应蛋白(c-reactive protein, CRP)与慢性肌肉骨骼疼痛间接相关。在睡眠节律研究中,睡眠障碍、失眠、肌肉骨骼疾患存在高度共病^[12],睡眠时间长短与肌肉骨骼疼痛之间存在“U 型”关系,睡眠≤5 h 或≥9 h 的人多部位肌肉骨骼疼痛的发生率明显高于睡眠 7 h 的人^[13];与睡眠时间<5.5 h 的参与者相比,睡眠时间延长的参与者骨密度有所增加,拐点在 6.5~9 h 之间^[14]。同时有研究发现,睡眠开始时间和睡眠质量都对颈部和上背部疼痛的发展有显著影响^[15]。与没有失眠的参与者相比,患有中度至重度失眠的参与者的钙含量较低,并且抑郁情绪和焦虑情绪介导了失眠症状对肌肉骨骼疼痛的影响^[16-17]。此外,有熬夜习惯且缺乏运动的工作者 WMSDs 的发生风险显著增加,其中规律的体育锻炼可提高身体对肌肉的敏感性和协调性,并且加快人脑反应速度,有效地延缓因年龄增加而致的肌肉骨骼力量减弱^[18]。在昼夜节律时型的研究中,芬兰出生队列 15 年的数据显示,夜晚型患者在基线和随访时发生多部位肌肉骨骼疼痛的概率是清晨型患者的 2.5 倍。与清晨型相比,夜晚型在 31~46 岁之间更有可能经历多部位的肌肉骨骼疼痛^[19];同时,一项纳入 4 257 名参与者的纵向研究显示,夜晚型比清晨型对肌肉骨骼疼痛更敏感,相关生活质量更低^[20]。

1.2 社会环境

持续光照会破坏机体中枢及外周生物钟系统,导

致昼夜节律紊乱。骨骼肌通过增加线粒体数量和体积来满足能量需求,而昼夜节律紊乱可损害骨骼肌线粒体数量及结构,导致运动耐力受损^[21],所以光照的调节对骨骼肌肉节律有重要影响。有研究提出,可以将光作为治疗一系列肌肉骨骼疾患疼痛和炎症的替代药物^[22]。同时在工作条件中,工作控制感和工作间休息与肌肉骨骼疾患密切相关。在 7 年的随访研究中,高等和中等工作时间控制的员工因肌肉骨骼疾患缺勤的风险降低,尤其是年龄较大的工人从更高水平的工作时间控制中受益^[23]。有研究显示,在社会心理学因素中,休息时间不充足对肌肉骨骼疾患的影响最大,并且与人体工效学存在协同交互作用^[24]。控制潜在混杂因素后发现,休息时间充足、自主选择工作间休息、工作气温变化不大、加班少是 WMSDs 的保护因素^[25]。规律与舒适的社会工作环境对肌肉骨骼健康的调节十分重要。在轮班护理人员的调查中发现,基于压力的工作与家庭冲突能预测腰椎和颈椎疼痛,减少医疗环境中的压力可以作为护理人员肌肉骨骼疾患预防方法的核心组成部分^[26]。

1.3 饮食策略

在饮食行为中,禁食对肌肉特异性节律基因表现出抑制作用,导致肌肉时钟重置^[27]。而饮食模式和时机对肌肉骨骼节律也存在重要影响,在间歇性禁食中,长达 6 个月的限时饮食方案实现适度减重(减轻基线体重的 5%)时,有一定的保护性骨骼效果,而 5:2 饮食(以 7 d 为 1 个饮食周期,其中 2 d 实施严格的能量限制,即摄入所消耗能量的 25%,剩余 5 d 正常进食)、隔日禁食与骨骼健康结局的关系有待进一步探究^[28]。有研究表明改变能量摄入的时间分布,将能量摄入限制在 08:00—16:00,可改善全身胰岛素敏感性,增加骨骼肌对葡萄糖和支链氨基酸的摄取^[29]。多项研究显示,限时饮食和生酮饮食可以改善慢性肌肉骨骼疾患患者的生活质量^[30]。同时高热量饮食后的短期禁食可以改善体积骨密度、骨微结构和胫骨远端的强度,从而促进骨骼健康^[31],这些均为肌肉骨骼疾患的饮食指导提供参考。众所周知,咖啡因会影响人体的昼夜节律,研究表明与不喝咖啡组相比,有喝咖啡习惯的参与者膝关节骨性关节炎发生率升高,其中每天摄入≥7 杯咖啡是不喝咖啡的 3.81 倍,再次支持了昼夜节律与肌肉骨骼疾患的关系。

1.4 生理激素

褪黑激素是调节生物昼夜节律的内源性吲哚胺类物质,可以模拟 DNA 羟甲基化酶 Tet1 的抑制能力,

增强成年骨骼干细胞的软骨形成能力^[32]。有研究发现,褪黑素可以通过与膜或细胞内受体相互作用,促进自噬流量,清除自由基,抑制促炎因子的释放,阻断凋亡途径,维持椎间盘的结构完整性,增强不同类型椎间盘细胞的抗应激能力和基质合成代谢^[33]。同时褪黑素的抗氧化作用不仅可以对抗骨质疏松,还可以治疗肌肉骨骼疾患^[34]。慢性昼夜节律失调会显著降低皮质醇水平,虽然适量的皮质醇对于应对压力是必要的,但长期过量的皮质醇会抑制蛋白质合成,促进肌肉分解;同时皮质醇日间变异性高的肌肉骨骼疾患患者身体功能较低,更容易发生疼痛灾难^[35]。生长激素可通过胰岛素样生长因子-1(insulin-like growth factor 1, IGF-1)这一主效应影响肌肉的生长与修复,同时也与软骨细胞代谢功能障碍和肥大变化有关,生长激素缺乏症患者股骨颈、股骨干、全髌、腰椎骨密度均显著降低^[36]。甲状腺激素水平对肌肉力量和耐力有直接影响,可以调节许多关键的生长因子信号通路,包括 IGF-1、甲状腺激素相关蛋白、成纤维细胞生长因子,从而影响骨骼生长^[37]。同时,性激素作为与昼夜节律密切相关的激素,可通过生物钟的调节在慢性疼痛中发挥一定作用,成为潜在的治疗途径^[38]。

2 WMSDs 的昼夜节律紊乱相关结果变量

肌肉骨骼节律或功能的异常反过来也会影响昼夜节律的相关后果。有研究表明,补充肌酸可以增加大脑肌酸储备,有助于增强健康人群的记忆能力,尤其是在老年人或代谢压力时期(即睡眠剥夺)^[39-40]。而患有慢性肌肉骨骼疼痛的老年人经常患有认知障碍和下肢身体功能减退,且疼痛程度与步态表现能显著预测整体认知功能^[41-42]。在慢性炎症条件下,肌肉表型和功能的变化会通过炎症因子的表达和分泌、昼夜节律异常而引起免疫功能障碍并加速代谢疾病的恶性循环^[43]。在社会心理影响中,临床骨关节炎常存在于腕关节、膝关节和手部的 2 个或 3 个部位,限制了患者的活动,增加了社交时差与社会隔离的风险,同时社会隔离在较差的步行时间、认知障碍和抑郁间发挥调节作用^[44]。并且在调整了年龄变量后,自我评定健康状况不佳、患有肌肉骨骼疾患的人群发生社会隔离的风险更大^[45]。

3 WMSDs 与昼夜节律紊乱共同的生物标志物

3.1 疼痛相关生物标志物

WMSDs 的疼痛多为慢性疼痛。有研究表明,在局

部慢性肌肉疼痛中,乳酸水平会升高,是潜在的生物标志物^[46]。同时,乳酸能够直接调节蛋白质功能以控制细胞周期和增殖的生化机制^[47],还可以通过调节血糖和日间运动活动节律来治疗重度抑郁症^[48]。神经肽 Y 是中枢神经系统中含量最丰富、分布最广的神经肽之一,涉及广泛的生理功能,如昼夜节律和记忆^[49]。而神经肽 Y 可以诱导脂肪组织的脂肪分解,导致前成骨细胞分化为成骨细胞和骨形成,骨组织交感神经张力被调低以促进成骨细胞的成骨活动^[50]。

3.2 炎症生物标志物

研究表明,昼夜节律紊乱会引发更高水平的全身炎症,加剧慢性炎症和代谢性疾病的风险,使 24 h 血清白细胞介素-6(interleukin-6, IL-6)、CRP 和肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)等炎症标志物水平增加 3%~29%^[51]。在昼夜节律的表现中,唾液 IL-6 水平在觉醒时达到峰值,从早上到中午逐渐下降,在入睡前再次达到峰值,且随着睡眠时间的延长,血清 IL-6 水平升高^[52]。同时,昼夜节律失调使 24 h 高敏 CRP 增加 11%^[53],睡眠不足 ≥ 2 h 的青少年血清 CRP 水平显著高于无睡眠不足的青少年^[54]。炎症标志物不仅可以反映昼夜节律的规律性,还可以反映肌肉骨骼疾患的具体情况,作为动态监测工具,反映治疗的有效性。有研究显示,WMSDs 严重程度与 CRP 存在强相关,而 TNF- α 、IL-6 参与骨吸收和形成的代谢过程,与 WMSDs 的患病数量相关^[55]。

4 WMSDs 与昼夜节律紊乱的机制探究

4.1 生物钟在肌肉骨骼细胞表达的基因中断

研究表明,生理活动过程与光/暗周期的一致性可为生物体提供生存优势,有助于调节哺乳动物体内的多种稳态过程,包括肌肉骨骼的稳定^[56]。Perrin 等^[57]对股外侧肌活检标本进行了全基因组转录组分析,发现鉴定的 5000 个前 mRNA 中有显著的昼夜节律振荡,约占人类肌肉中表达的总基因的 50%,对成熟 mRNA 的进一步分析确定了超过 1000 个 mRNA 表现出昼夜节律模式,当基因表达中断,骨骼肌健康防线将降低。

4.2 细胞应激反应

昼夜节律基因如 *PER2* 可以通过影响细胞内蛋白质的稳定性和细胞周期的调控来响应不同类型的细胞应激,包括基因毒应激、代谢应激和炎症应激,导致肌肉骨骼的细胞功能障碍和组织退化^[58]。有研究显示,当轮班工作者的夜班次数增多,会产生不平衡的氧化应激反应,导致早期生物衰老,即氧化/甲基化 DNA 碱

基和白细胞端粒长度(leucocyte telomere length, LTL)升高,影响肌肉和骨骼的健康,增加 WMSDs 的风险^[59]。

4.3 代谢和能量平衡失调

昼夜节律紊乱可能导致代谢途径的编码基因表达异常,进而影响能量代谢和物质利用,昼夜节律也随着葡萄糖、蛋白质和脂肪摄入量的变化而变化^[60]。代谢和能量平衡的失调可能使肌肉和骨骼组织得不到充分的营养支持,降低其修复和再生能力,从而增加 WMSDs 的风险^[61]。

4.4 睡眠-疲劳机制

昼夜节律紊乱常导致睡眠障碍,包括入睡困难、睡眠质量下降和白天嗜睡等,进一步导致疲劳和注意力不集中等问题^[62],同时由于疲劳和注意力不集中,工人可能更容易采取不良的工作姿势或忽视正确的操作规范,不良的工作姿势和习惯会增加肌肉和骨骼的负担,导致 WMSDs 的发生^[63]。

5 结论与展望

WMSDs 与昼夜节律密切相关,肌肉骨骼的昼夜节律研究可为维持肌肉质量和功能的内在机制提供重要见解^[64]。目前,越来越多的证据表明,昼夜节律紊乱对肌肉骨骼疾患的发生、发展具有重要作用,但研究多聚焦于特定行业或人群,昼夜节律与 WMSDs 的评估方法尚未统一,且多来源于自我报告,两者之间的关系存在较多混杂因素。在未来的研究中,应基于基础研究及广泛的流行病学分析,结合时间生物学与主客观数据,将昼夜节律与 WMSDs 的发生发展系统地联系起来,探讨环境-中间表型-疾病的作用路径,更全面地阐述发生 WMSDs 的网络机制。

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