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成人退行性脊柱侧凸的病因学研究进展

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摘　要

成人退行性脊柱侧凸(adult degenerative scoliosis, ADS)是伴随脊柱结构退变出现的进行性三维畸形，其发病率随着老龄化的加剧显著上升，已成为中老年人群慢性腰背痛、神经功能障碍及生活质量下降的重要病因。近年来，ADS的病因学研究逐步从单一退变机制转向多维度交互作用模型的探索，但退变与侧凸的因果关系、遗传－环境因素的权重及研究方法学的局限性等问题仍存争议。本文系统综述ADS的病因学研究进展，重点剖析：1) 脊柱退变的核心病理机制，包括椎间盘蛋白多糖流失、关节突关节退变及骨质疏松的协同作用；2) 多维度病因学证据，如遗传易感基因及代谢综合征的独立影响；3) 病因学假说的核心争议，包括“退变先行”与“侧凸导致退变”的循证分歧。现有研究表明，ADS的发生发展是遗传易感性、局部退变、生物力学失衡及全身代谢异常共同作用的动态过程，其中椎间盘非对称退变可能通过“应力集中－炎症激活－骨重塑异常”反馈环路驱动畸形进展。然而，现有研究多局限于横断面分析或低仿真模型，难以揭示病因的时序性与空间特异性。未来需依托纵向队列、多组学整合及人工智能辅助分析，构建“分子－影像－力学”跨尺度病因网络，以明确关键靶点并指导早期干预。本文强调多学科交叉研究的重要性，为ADS的精准分型与个体化防治提供理论依据。

关键词

成人退行性脊柱侧凸，生物力学，基因组学，综述

Research Progress of Etiology of Adult Degenerative Scoliosis

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Abstract

Adult degenerative scoliosis (ADS) is a progressive three-dimensional malformation accompanied by the degeneration of spinal structure. Its incidence rate has increased significantly with aging and has become an important cause of chronic low back pain, neurological dysfunction and declining quality of life in middle-aged and elderly people. In recent years, the etiology research of ADS has gradually shifted from a single degeneration mechanism to exploring multidimensional interaction models. However, there is still controversy over the causal relationship between degeneration and scoliosis, the weight of genetic-environmental factors, and the limitations of research methodology. This article provides a systematic review of the etiology research progress of ADS, with a focus on analyzing: 1) The core pathological mechanisms of spinal degeneration, including the synergistic effects of intervertebral disc proteoglycan loss, facet joint degeneration, and osteoporosis; 2) Multidimensional etiological evidence, such as the independent effects of genetic susceptibility genes and metabolic syndrome; 3) The core controversy of the etiological hypothesis includes the evidence-based divergence between "degeneration first" and "scoliosis leading to degeneration". Existing research indicates that the occurrence and development of ADS is a dynamic process of genetic susceptibility, local degeneration, biomechanical imbalance, and systemic metabolic abnormalities. Among them, asymmetric degeneration of intervertebral discs may be driven by a feedback loop of "stress concentration-inflammation activation-bone remodeling abnormalities" to promote the progression of deformities. However, existing research is mostly limited to cross-sectional analysis or low simulation models, making it difficult to reveal the temporal and spatial specificity of the etiology. In the future, it is necessary to rely on longitudinal queues, multi-omics integration, and artificial intelligence-assisted analysis to construct a "molecular-imaging-mechanics" cross-scale etiological network, in order to identify key targets and guide early intervention. This article emphasizes the importance of interdisciplinary research, providing a theoretical basis for the precise classification and individualized prevention and treatment of ADS.

Keywords

Adult Degenerative Scoliosis, Biomechanics, Genomics, Review

1. 引言

成人退行性脊柱侧凸(adult degenerative scoliosis, ADS)是指骨骼发育成熟后，由于椎间盘及小关节等脊柱结构的非对称性退行性改变，导致出现 Cobb 角大于 10˚的脊柱侧凸畸形。全球范围内 ADS 的发病率随着年龄的增长而显著增加，有研究表明[1]，这种病变多发生在 60 岁以上人群，60 岁以上人群中 ADS 的发病率约为 13.3%~68%，常累及胸腰段和腰椎，其中发达国家的发病率较高，女性发病率高于男性。ADS 最常见的症状为腰背部疼痛[2]，此种疼痛多为机械性疼痛，平卧时疼痛减轻，久坐、长时间行走或劳累后疼痛加重。此外，患者还可能出现晨僵，即经过一夜睡眠后，脊柱僵硬，活动受限，稍加活动后僵硬感会减轻，但随着进一步活动，腰痛症状又会反复出现。其下肢症状包括主要包括根性疼痛、间歇性跛行与肌肉无力[3]。由于脊柱侧凸导致椎管狭窄或神经根受压，刺激神经根，部分患者所出现的下肢放射性疼痛可放射至小腿，甚至足部。且由于脊柱侧凸同时影响神经的血液供应，引起神经缺血缺氧，部分患者在行走一段距离后，会出现下肢疼痛、麻木、无力等症状，需要停下来休息片刻后才能继续行走。同时，部分患者可能会出现下肢肌肉无力，尤其是在长时间行走或劳累后，腿部会感觉发软，甚至无法

支撑身体的重量。随着病情的进展，在一些严重的情况下，脊柱侧凸可能会压迫脊髓或神经根，导致神经功能障碍，如感觉异常、运动障碍、大小便功能障碍等。近年来，成人退行性脊柱侧凸的病因学研究逐渐增多[4]，涉及椎间盘、小关节、骨质疏松、肌肉韧带退变、遗传因素、生物力学改变以及炎症因子等多个方面，但其发生发展机制尚不明晰，目前尚难以明确各因素之间的主次关系，以及它们在不同个体中如何相互作用。通过深入研究各种因素的作用机制，有助于发现高风险人群，并更精准地制定治疗策略，使得早期干预成为可能，延缓疾病进展，减轻患者的痛苦和经济负担，本文章对成人退行性脊柱侧凸病因学研究进展进行综述。

2. 生物力学因素

2.1. 椎间盘退变

有研究表明，椎间盘退变是 ADS 发生的始动环节[5]。随着年龄的增长，椎间盘中的蛋白聚糖水平降低，渗透压下降，核细胞密度减少，导致椎间盘的结构完整性受损[6]。这种退变使得椎间盘退变通常是由椎间盘中分解代谢和合成代谢过程之间出现不平衡。导致椎间盘膨出和髓核和水分的损失，随后造成椎间盘高度下降。另外，血髓核屏障被破坏导致髓核细胞暴露于免疫系统，最终造成外基质的破坏和椎间盘结构完整性的丧失[7]。在这种情况下，异常血管生成已被确定为椎间盘退变进展中的一个关键事件。Koerner 等人发现，退行性脊柱侧凸患者的后纤维环样本显示血管生成素和血小板衍生生长因子(PDGF)-B 的表达增加，作为多种反应的转录调节因子，PDGF-B 已被证明调节血管发育这一促血管生成因子使内皮细胞向组织深处迁移，最终导致新血管的形成[8]。

2.2. 关节突关节退变

Park 等人利用有限元分析发现关节突关节的退变是 DAS 发生和进展的关键因素之一[9]。关节突关节退变的早期表现为软骨磨损，随着软骨的逐渐退化，关节表面变得粗糙不平，导致关节接触应力分布不均。这种不均匀的应力分布会进一步刺激软骨下骨，引发骨赘形成。骨赘的出现不仅会限制关节的活动范围，还可能进一步改变关节的力学特性，当软骨磨损和骨赘形成时，关节面的匹配度被破坏，关节囊和韧带的张力也会发生变化，从而导致关节失稳[10]。在腰椎中，关节突关节的退变尤为显著，因为其承载的应力较大。关节突关节的软骨下骨硬化和骨赘形成会改变关节的正常形态和功能，导致关节的机械阻挡作用减弱，进而影响脊柱的稳定性。关节失稳会进一步引发脊柱的不对称应力分布，导致椎体侧方滑移和旋转畸形，最终形成脊柱侧凸[11]。

2.3. 椎旁肌功能退化

椎旁肌是维持脊柱稳定的重要结构，其功能退化主要表现为肌肉萎缩、脂肪浸润、肌纤维类型改变和力量下降[12]。随着年龄的增长，椎旁肌的脂肪浸润增加，肌肉横截面积(CSA)减小，导致肌肉力量下降，进而影响脊柱的稳定性。根据 Hueter-Volkmann 定律[13]，椎旁肌功能退化会导致脊柱两侧的负荷分布不均，这种不平衡会加剧脊柱的侧凸。Zhou 等人[14]通过对 50 名患者进行 3D 重建测量 PSM 的肌肉体积(MV)和脂肪渗透(FI)，并通过 X 线检查评估脊柱参数，比较了凸面(CV)和凸面(CC)的值。结果显示，ADS 患者脊柱两侧 PSM 的 MV 和 FI 存在显着差异。同时，ADS 的 PSM 在脊柱不同节段表现出不同程度的退行性变，并与 Cobb 角呈正相关。

3. 遗传与分子生物学因素

3.1. 遗传标志物

椎间盘的退行性改变已经被证实存在一定的遗传性因素[15]，但是 ADS 是否具有遗传性诱因尚未证

明。检测成人退行性脊柱侧弯以及疾病进展的遗传标记领域日益增多。雌激素受体基因已被证明与骨和关节软骨疾病相关，是开发退行性脊柱侧弯遗传标记的目标[16]。Park 等人收集了 404 名患者的血液样本以分析雌激素受体基因的基因型频率，特别关注 PvuII和 XbaI多态性[17]。与对照组相比，退行性腰椎侧凸患者 PvuII多态性存在显着差异(p = 0.0287)。另外，Akesson 等人通过队列研究发现腰椎退行性病变的女性 PTH2R SNP rs897083 等位基因过度表达(p = 0.0021) [18]。且 PTH2R 基因的变异可能导致已知导致 ADS 的脊柱年龄相关退行性表现[19]。除上述探讨的最大样本量的研究的遗传标记外，也存在一些较小的研究，Zhu 等人利用生物信息学分析得出 10 个具有一定特异性的 ADS 相关的中枢基因：ELANE、LTF、DEFA1B、SLC2A4、DEFA1、FAXDC、LCN2、CTSB、FDFT1 和 AURKA [20]，这些研究虽得出了部分基因与成人退行性脊柱侧凸之间的相关性，但缺乏实验，仍需细胞实验及动物模型的进一步验证。

3.2. 血清标志物

近年来，蛋白质组学和基因组学技术的发展为血清标志物的研究提供了有力支持。Hosogane 等人发现，KS、II型胶原裂解(C2C)和II型前胶原 C-前肽(CPII)在退行性腰椎侧凸队列中显著高于对照组[21]。另外，Lee 等研究发现，IL-6-572 G/C 表达多态性在退行性腰椎侧凸患者中存在显著差异(p = 0.0168) [22]。Zheng 等人发现，miR-143 减少和 COX-2 表达上调与退行性脊柱侧凸的进展有关[23]。Hwang 等人发现，作为编码II型胶原蛋白的 α-1 链的基因，COL 2A 1 与退行性腰椎侧凸显著相关[24]。此外，Eguchi 等人发现，退变性腰椎侧凸患者血清戊糖苷水平显著升高[25]，并与冠状面和矢状面畸形的严重程度相关[26]。上述研究发现的差异大多是基于横断面研究，这些标志物有可能是疾病的继发改变，而非发病的始动因素，难以确定其在 ADS 发病中的因果关系，关于 ADS 和疾病进展的标志物仍有待进行系统性研究。

4. 其他因素

4.1. 激素水平与骨代谢异常

因退行性脊柱侧凸患者常为中老年人，且这些患者大多数合并有骨质疏松症，X 线片常见骨质疏松型椎体压缩性骨折[27]，故在早期有学者认为 ADS 的发生可能与骨质疏松有关[28]。但有部分学者则对上述观点存在质疑。就病因学而言，骨质疏松与 ADS 之间没有明显的相关性，即骨质疏松的患者椎体稳定性较差极易加重脊柱侧凸的进展，因而骨密度的降低是退行性脊柱侧凸的促进因素而非始动因素[29]。国内亦有研究发现，ADS 患者脊柱的侧凸程度与骨质疏松程度无明显相关性，骨质疏松症是退行性脊柱侧凸发病的加重因素[30]。因此，骨质疏松可能与 ADS 的进展相关而并非始动因素。同理，绝经后女性的雌激素水平显著降低，雌激素对骨骼的保护作用减弱，导致骨质疏松和骨质减少，增加骨折风险，同时也可能加重脊柱的退行性变化[31]。这也是 ADS 患者女性发病率高于男性的原因之一。此外，甲状旁腺激素(PTH)主要调节钙和磷的代谢，维持血钙水平的稳定。PTH 水平的异常可能导致骨质疏松和骨质减少，引起椎体压缩性骨折，破坏脊柱生物力学平衡，从而加剧脊柱的退行性变化[32]。

4.2. 代谢综合征与脊柱退变加速

代谢综合征(metabolic syndrome)是一组复杂的代谢紊乱疾病，包括肥胖、糖尿病、高血压和脂代谢异常等[33]。近年来，越来越多的证据表明代谢综合征与脊柱退变加速之间存在显著关联[34] [35]。较高的 BMI，特别是超重或肥胖，与椎间盘退变的风险有关[36]。体重的增加会导致脊柱的机械负荷显著增加，这种额外的负荷会加速椎间盘的磨损和退变。而肥胖引起的全身性炎症反应可进一步加剧椎间盘的退变。Jin 等人[37]通过双样本孟德尔随机化分析得出二型糖尿病患者发生椎间盘退变的风险比非二型糖尿病患者高 6.9% (OR: 1.069; 95% CI: 1.026~1.115; p = 0.002)。值得一提的是，代谢综合征中的疾病与成人退行

性脊柱侧凸并无直接的因果关系，而是通过多种机制相互作用，加速成人退行性脊柱侧凸的发展[38]。

5. 病因学假说的争议与挑战

成人退行性脊柱侧凸的病因学研究中，“退变先行”与“侧凸导致退变”的因果关系之争是核心争议之一。这一争议的本质在于明确脊柱结构异常与退行性改变之间的时序性和驱动关系，对临床干预策略(如早期矫正手术或保守治疗)具有重要的指导意义。“退变先行”假说[39]认为：椎间盘、关节突关节等结构的原发性退变是侧凸发生的始动因素。即椎间盘退变导致脊柱节段稳定性下降，引发不对称应力分布，进而通过“椎体–椎间盘–肌肉”反馈环路加剧冠状面失衡[40]。一项包含 78 名 ADS 患者的影像学研究证实：ADS 患者的凸侧椎间盘退变程度常较凹侧更严重[41]。反对者指出，部分 ADS 患者早期即存在轻度脊柱排列异常(如先天性半椎体或青少年期残留侧凸)，此类结构性畸形可通过长期异常载荷加速退变进程[42]。但现有证据的可靠性仍受限于研究方法学的固有缺陷。目前常用的 ADS 动物模型多为大鼠非对称椎间盘压缩模型，四足动物的脊柱载荷分布(以轴向压力为主)与人类直立姿态下的力学环境(剪切力占比高)存在本质差异。即使通过手术诱导侧凸，其畸形模式与人类 ADS 也不完全匹配。而小鼠基因编辑模型多表现为广泛性脊柱退变而非局灶性侧凸，无法揭示生物力学与分子网络的区域特异性交互作用。另外，多数研究依赖横断面数据或回顾性影像学分析，难以确定退变与侧凸的时序关系。例如，椎间隙狭窄与侧凸角度的相关性可能同时反映因果关系(退变导致侧凸)或结果(侧凸加速退变)。

6. 小结与展望

本文章对成人退行性脊柱侧凸的病因学研究进展进行综述，在疾病的发生发展过程中，年龄相关性椎间盘脱水、骨质疏松等引发脊柱刚度下降，微小畸形(如旋转或侧方滑移)在动态载荷下逐渐累积；异常脊柱排列导致局部应力集中，进一步激活破骨细胞和促炎因子释放，加速椎体骨重塑及椎间盘退变；椎旁肌代偿性肥大与脂肪浸润加剧脊柱失稳，最终进入“退变促进畸形，畸形加重退变”的不可逆阶段。作为一种退行性疾病，ADS 病程缓慢且病因复杂，疾病后期治疗代价过大，故应在早期尽快明确其病因，即有针对性消除其进展因素。但是，当前 ADS 的病因学研究仍处于“碎片化证据”向“系统理论”过渡的阶段。争议性假说的并存凸显了疾病机制的复杂性，而方法学局限则要求研究者创新技术路线。在改进现有 ADS 动物模型的同时，加入影像学、组织学及生物力学等多维度手段对模型进行验证，进一步改进动物模型，以更好地模拟人类 ADS 的病理机制，为相关研究提供更可靠的实验助力。未来需通过跨学科协作，在精细化模型构建和高证据等级临床研究的基础上，逐步揭示退变与畸形的动态交互规律，为个体化防治提供理论支撑。

致　谢

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