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钠－葡萄糖共转运蛋白2抑制剂治疗多囊卵巢综合征研究进展

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摘　要

多囊卵巢综合征是无排卵性不孕最常见的原因，其发病机制主要与胰岛素抵抗、高雄激素血症以及肥胖相关。目前尚无根治多囊卵巢综合征的治疗手段，以对症治疗为主，通过减重和药物干预可以改善患者代谢及生殖结局，常用的药物有二甲双胍和避孕药。钠－葡萄糖共转运蛋白2抑制剂是一种新型降糖药物，具有减重、降糖、改善胰岛素抵抗、抗炎等作用，可使多囊卵巢综合征患者获益，相关的临床实验也逐渐增多，取得了可观的疗效，本文总结了钠－葡萄糖共转运蛋白2抑制剂的治疗多囊卵巢综合征可能的作用机制及最新进展，旨在为临床用药提供参考。

关键词

多囊卵巢综合征，钠－葡萄糖共转运蛋白2抑制剂，胰岛素抵抗，高雄激素血症

Research Progress of Sodium-Glucose Cotransporter 2 Inhibitor in the Treatment of Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome is the most common cause of anovulatory infertility, and its pathogenesis is mainly related to insulin resistance, hyperandrogenemia and obesity. At present, there is no radical treatment for polycystic ovary syndrome, mainly symptomatic treatment, weight loss and drug intervention can improve patients' metabolism and reproductive outcome, and the commonly used drugs are metformin and contraceptive. Sodium-glucose cotransporter 2 inhibitor is a new type of hypoglycemic drug, which may benefit patients with polycystic ovary syndrome by reducing weight, reducing blood glucose, improving insulin resistance and anti-inflammation, and the related clinical trials are gradually increasing. Considerable efficacy has been achieved. This paper summarizes the possible mechanism and latest progress of sodium-glucose cotransporter 2 inhibitors in the treatment of polycystic ovary syndrome, aiming to provide reference for clinical medication.

Keywords

Polycystic Ovary Syndrome, Sodium-Glucose Cotransporter 2 Inhibitor, Insulin Resistance, Hyperandrogenemia

1. 引言

近年来，我国劳动年龄人口数量减少，老龄化程度进一步加深，使经济和社会可持续发展受到一定影响。实施三孩生育政策及配套支持措施，有利于缓解人口老龄化，保持合理的劳动力结构和数量。但是近几年的调查发现中国人口出生率和人口增速不升反降。除去社会经济发展因素、育龄妇女持续减少、生育观念变化等多方面因素影响外，出生率的降低和生殖力降低存在密切关系。生殖力又称可育性、生育力，是指女性、男性或夫妇双方能够生育活产婴儿的生理能力[1]。低生殖能力通常是指任何形式的生育能力下降，并且长时间不怀孕。在中国，女性不孕症患病率亦呈上升趋势：1988 年在全国范围内进行的一项大规模调查显示，育龄妇女 2 年不孕症患病率为 6.7%；2010 年至 2011 年，一项包括 25,270 对夫妇的基于人群的研究发现总体不孕症患病率为 15.5%；到 2019 年，在河南省进行的一项调查显示女性不孕症患病率已上升至 24.58% [2]。因此，缓解影响生殖力的危险因素及有效治疗影响生殖力的相关疾病势在必行。无排卵性不孕最常见的原因是多囊卵巢综合征(polycystic ovary syndrome, PCOS) [3]。PCOS 是一种异质性疾病，主要表现为高雄激素血症、排卵功能障碍、卵巢多囊样改变，表型的流行程度根据生命阶段、基因型、种族和环境因素(包括生活方式和体重)而有很大差异[4]。根据不同的诊断标准，多囊卵巢综合征在育龄期女性中发病率占 7%~13%，且有显著增加的趋势[5] [6] [7]。

2. PCOS 发病机制

2.1. 高雄激素血症

目前 PCOS 的发病原因尚未完全阐明，可能与遗传、环境、种族等因素有关[8] [9]。最近的研究发现，多囊卵巢综合征的核心病因和主要内分泌特征是高雄激素血症(Hyperandrogenism, HA)和胰岛素抵抗

(Insulin resistance, IR) [10]。PCOS 患者有高雄激素血症和/或高雄激素表现者占 60%~80%，有不同程度的胰岛素抵者占 50%~70% [11] [12]。在卵巢卵膜细胞及肾上腺皮质网状带的细胞中，胆固醇经过一系列酶促反应，转化为脱氢表雄酮(DHEA)和雄烯二酮[13]。研究表明，高雄激素血症可引起促黄体生成素分泌增加、下丘脑垂体性腺轴紊乱、排卵障碍，从而导致不孕，且雄激素过多影响脂肪组织重新分布，促进内脏脂肪积累，引起棕色脂肪组织功能障碍、肝脏组织变性，损害瘦素的减肥特性、增加肥胖几率，从而加重胰岛素抵抗[14]。雄激素作用于中枢和多种外周组织，通过不同机制驱动 PCOS 的发生发展。

2.2. 胰岛素抵抗

除高雄激素血症以外，PCOS 发病的另一重要机制是胰岛素抵抗。胰岛素抵抗被定义为胰岛素介导葡萄糖摄取、葡萄糖产生和/或脂肪分解等代谢作用的能力下降，导致需要增加胰岛素量来实现正常的代谢作用。不同组织对胰岛素的敏感性反应各不相同，这使得 PCOS 女性的胰岛素抵抗定义变得复杂[12]。IR 导致胰岛 β 细胞代偿性分泌更多胰岛素，从而引起高胰岛素血症，血液中高水平胰岛素通过 MAPK 通路刺激 GnRH 基因转录，增加 LH 脉冲分泌，从而显著增加卵巢雄激素合成[15]。高胰岛素血症导致高雄激素血症的另一个可能的机制是抑制肝脏产生性激素结合球蛋白(SHBG)，由于睾酮与 SHBG 高度结合，血清 SHBG 浓度的降低将增加循环睾酮的组织可用性[16]。有证据表明，高胰岛素血症虽然不是解释低/无排卵的唯一因素，但可能确实有助于多囊卵巢综合征的窦卵泡功能障碍和无排卵机制，使用二甲双胍等胰岛素增敏剂可改善月经周期和慢性无排卵症状[17] [18]。

2.3. 肥胖

肥胖在 PCOS 发病机制中发挥的作用也不可小觑。多囊卵巢综合征患者肥胖的可能性几乎是非多囊卵巢综合征的女性的三倍，患病率因种族、地区和文化而异，从 38%到 88%不等[19] [20]。肥胖，尤其是在肥胖和非肥胖多囊卵巢综合征女性中常见的内脏脂肪，会放大和恶化多囊卵巢综合征的所有代谢和生殖结果[21]。与正常体重妇女相比，肥胖患者更容易出现月经少和无排卵症状，卵母细胞质量更差，体外受精等生育治疗的成功率降更低，且身体质量指数(BMI)越大，不孕时间越长[22]。在临床上，即使是适度的体重减轻(~5%)也会导致多囊卵巢综合征患者的生殖、高雄激素和代谢特征有意义的改善，这突出了肥胖和多囊卵巢综合征之间的生物学联系[23]。

2.4. 炎症与氧化应激

此外，氧化应激与炎症在 PCOS 的发病机制中也占有一席之地。PCOS 女性血清中氧化应激标志物水平升高，氧化应激过程中产生的活性氧会破坏蛋白质、脂质和 DNA，从而导致组织损伤[24]。氧化应激增加的后遗症是产生促炎细胞因子，诱导 IR 和高雄激素血症，并增加心血管疾病的机会[25]。PCOS 患者细胞间黏附分子(ICAM)-1、肿瘤坏死因子(TNF)-α、单核细胞趋化蛋白(MCP)-1、C 反应蛋白(CRP)、IL-8 等，这表明体内有炎症[26]。炎症与肥胖、心血管疾病、胰岛素抵抗和糖尿病相关，这些是 PCOS 的代谢方面[27]。

3. PCOS 治疗现状

多囊卵巢综合征不仅给患者的身心健康带来不利影响，也导致了巨大的医疗保健相关经济负担[28]。然而，用于该病的治疗策略仍然有限，目前仍以对症治疗为主，包括改善饮食、减重、促排卵、改善胰岛素抵抗、降低雄激素水平等治疗[29] [30] [31] [32]。改善生活方式是多囊卵巢综合征患者治疗的基石，贯穿治疗全过程甚至患者的一生。2019 年，一篇纳入了 15 项随机对照试验(RCT)和 498 名参与者的报告称，与最小干预或常规护理相比，生活方式干预可显著降低体重和体重指数，并改善高雄激素血症和胰

岛素抵抗[33]。但临床实践表明，对于一些肥胖多囊卵巢综合征患者，改善生活方式是无效的。虽然减肥药物如奥利司他及减重手术也被推荐用于治疗肥胖多囊卵巢综合征，但奥利司他引起吸收不良及胆汁淤积的副作用限制了该药物的使用，减肥手术引起的创伤及一些不可逆转的副作用也影响了其应用。对于患有 PCOS 的成年女性，常用口服避孕药来治疗雄激素分泌过多和/或月经周期不规律，但避孕药会对血脂有不利影响，增加静脉血栓形成和心血管事件的风险[34] [35]。在临床上，降糖药物如二甲双胍、吡格列酮、利拉鲁肽等也被用于治疗多囊卵巢综合征，但是在改善月经周期、促排卵、改善高雄激素血症、提高生殖能力等方面收益有限[36] [37] [38]。因此，寻找更加有效的 PCOS 代谢和生殖功能改善药物具有非常重要的意义。

4. 钠－葡萄糖共转运体-2 治疗 PCOS 可能的作用机制

钠－葡萄糖共转运体-2 (sodium glucose cotransporter 2, SGLT-2)抑制剂是一类新型口服降糖药物，通过阻断近端肾小管 S1 和 S2 段表达的的 SGLT2 受体，抑制葡萄糖和钠离子的重吸收，降低肾糖阈，从而发挥降糖作用，这种作用机制与胰岛素无关，不会增加低血糖的风险[39] [40]。目前全球共有 6 种 SGLT-2 抑制剂，因为降糖外的显著的心肾获益而获得全球很多指南的推荐。在解读 sglt2 抑制剂的众多作用机制中，我们发现其部分机制可能会对 PCOS 患者的代谢包括胰岛素抵抗、体重、炎症等具有明显改善作用，甚至会进而因为代谢和胰岛素敏感性的改善带来月经周期或者排卵功能的改善。

首先，早期研究发现，SGLT2 在成年雄性啮齿类动物中的表达存在性别差异，雄激素在调节小鼠 SGLT2 表达方面具有主要作用，雌性小鼠在使用睾酮治疗后 SGLT2 上升到雄性小鼠水平[41]；2021 年发表的一项研究显示，给予 4 周龄雌性 Sprague Dawley 大鼠双氢睾酮(DHT)治疗 90 d 后，SGLT2、SGLT4 和 GLUT2 的表达上调，这也为干预 PCOS 患者干 SGLT-2 的活性提供了相应的基础，当然这不是必需的基础，因为在某些根本没有 SGLT-2 表达的器官，依然在使用恩格列净等药物中产生了获益[42]。

第二，sglt2 抑制剂有明确的体重减轻作用。SGLT2 抑制剂抑制葡萄糖和钠离子在近端肾小管重吸收，使葡萄糖、钠离子随尿液流出，减轻水钠潴留，每天排出约 60~80 克葡萄糖，热量丢失约 240~320 卡路里，底物利用从碳水化合物转移到脂质和酮类，进而引起脂肪分解和脂肪氧化增强，降低体脂含量，最终引起体重减轻[43]。卡格列净通过改善脂肪细胞和脂肪组织中的脂肪酸氧化和线粒体功能来预防 hfd 诱导的肥胖和肥胖相关的代谢紊乱，这种能量耗散作用可能由 PPARα 介[44]。在小鼠模型中，达格列净被证明干扰能量代谢，激活腺苷酸活化的蛋白激酶，促进乙酰辅酶 A 羧化酶磷酸化，抑制脂肪酸合成，促进脂质分解。临床研究发现，Sglt2 抑制剂不仅可以减轻糖尿病患者的体重，罹患 PCOS 的肥胖妇女也有体重受益，达格列净、恩格列净、卡格列净及利格列净均可减轻超重和肥胖 PCOS 的体重、腰围、臀围、基础代谢率等[45] [46] [47]。

第三，sglt2 抑制剂可以改善胰岛素抵抗，增加骨骼肌等靶器官的胰岛素敏感性。在 Zucker 糖尿病肥胖大鼠身上进行的实验发现，卡格列净使 ZDF 大鼠的基础和餐后高血糖恢复正常，通过消除糖毒性改善了肝脏受损的葡萄糖效能和肌肉的胰岛素敏感性，从而恢复了 ZDF 大鼠的代谢灵活性[48]。恩格列净可降低小鼠空腹胰岛素水平和 HOMA-IR，改善葡萄糖耐量和胰岛素敏感性[49]。Sglt2 抑制剂在临床上的治疗 T2DM 的效果也证实了从动物实验中得出的结论。服用达格列净治疗 5 周后，T2DM 患者代谢发生类似热量限制的重大调整，脂肪氧化增加，肝脏和脂肪胰岛素敏感性改善，24 小时能量代谢改善[50]。

第四，SGLT-2 抑制剂可减轻炎症、抑制氧化应激。在卡格列净治疗 2 型糖尿病肾病的实验中，肿瘤坏死因子受体(TNFR) 1、白介素(IL)-6、基质金属蛋白酶(MMP) 7 和纤连蛋白(FN) 1 的减少表明，卡格列净有助于逆转与炎症、细胞外基质转换和纤维化相关的分子过程[51]。恩格列净可以消除高糖状态下肾小管细胞产生的超氧化物，通过抑制线粒体活性氧(ROS)生成、MMP 和 ATP 生成，减少高糖诱导的细胞凋

亡，改善线粒体功能，保护肾小管周围毛细血管免受高糖介导的损伤[52]。在一项包含 35 例 T2DM 合并冠状动脉疾病患者的小规模随机对照试验中，每日服用达格列净 5 mg，总疗程 6 个月，可显著降低血浆 TNF-α [53]。SGLT2 抑制剂可以使血液循环中的炎症标志物减少，这一点也在啮齿动物身上得到了验证，2022 年的一项荟萃分析表明，使用 SGLT2 抑制剂治疗导致 IL-6、CRP、TNF-α、和 MCP-1 水平降低[54]。

第五，晚期糖基化终产物(AGEs 在 PCOS 病理生理机制中发挥的作用日益受到重视。AGEs 是过量的糖与蛋白质结合的产物，通过人体内合成和高热量食物摄入 2 种途径[55]。PCOS 患者中 AGEs 水平升高，循环中的 AGEs 在不同组织中沉积，通过活性氧形成而引起细胞损伤；AGEs 受体(RAGE)是促炎受体，PCOS 患者卵巢 AGEs 受体表达升高，从而改变 PCOS 女性的甾体生成和卵泡生成，因此这表明 AGEs 与 PCOS 患者的高雄激素血症与胰岛素抵抗有关[25]。Sglt2 抑制剂，如恩格列净，降低 AGEs 的作用在保护心脏肾脏等器官保护作用中得到了体现[56]。

5. 结论

近年来，sglt2 抑制剂用于治疗超重肥胖 PCOS 患者的研究逐渐增多。与二甲双胍疗效相似，sglt2 抑制剂在改善患者体重、腰围、臀围、腰臀比和增加胰岛素敏感性方面取得了可观的疗效。然而，在改善性激素水平方面，各种 sglt2 抑制剂的治疗效果各不相同，未取得一致的研究结论。另外，由于用药时间普遍较短，既往进行的临床试验未详细评估生殖结局[45] [46] [47] [57] [58] [59]。目前关于 sglt2 抑制剂在 PCOS 患者中的安全性和有效性的原始研究较少、样本量小，用药时间较短，需要更多治疗时间更长的试验来评估补充 SGLT-2 抑制剂对 PCOS 患者的长期影响。

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