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多囊卵巢综合征与代谢综合征各组分关系的研究进展

王亚倩，张媛媛*，付春雷

延安大学医学院，陕西 延安

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摘　要

多囊卵巢综合征(Polycystic ovary syndrome, PCOS)是育龄期女性常见的妇科生殖内分泌疾病，严重影响女性的生殖健康。近年来，PCOS的发病率逐年上升，这一趋势引起了国内外学者的广泛关注。PCOS患者常与肥胖、胰岛素抵抗、高脂血症等代谢综合征(Metabolic syndrome, MetS)各组分密切相关，PCOS合并MetS一种或多种组分常常加重病情的发展。本文就PCOS与MetS各组分的相关调查研究进行综述。

关键词

多囊卵巢综合征，代谢综合征，肥胖，高血压

Research Progress on the Relationship between Polycystic Ovary Syndrome and Metabolic Syndrome Components

Yaqian Wang, Yuanyuan Zhang*, Chunlei Fu

Medical College of Yan'an University, Yan'an Shaanxi

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Abstract

Polycystic ovary syndrome (PCOS) is a common gynecological endocrine disorder in women of childbearing age, significantly affecting women's reproductive health. In recent years, the incidence of PCOS has been increasing annually, a trend that has attracted widespread attention from

*通讯作者。

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domestic and foreign scholars. PCOS patients are often closely associated with components of metabolic syndrome (MetS) such as obesity, insulin resistance, and dyslipidemia. The presence of one or more components of MetS in PCOS patients often exacerbates the progression of the disease. This article provides a review of the research on the relationship between PCOS and the various components of MetS.

Keywords

Polycystic Ovary Syndrome, Metabolic Syndrome, Obesity, Hypertension

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1. 引言

多囊卵巢综合征(Polycystic ovary syndrome, PCOS)是一种复杂的妇科生殖内分泌疾病，严重影响患者的身心健康，其发病率高达 5%~18% [1]。PCOS 的发生、发展通常与肥胖、胰岛素抵抗(Insulin resistance, IR)显著相关，而这种机体代谢紊乱是导致 PCOS 女性生活质量下降的最主要原因[2]。PCOS 的病因复杂，临床表现也存在高度异质性。2023 年出版的 PCOS 评估和管理国际循证指南推荐使用 2018 年《国际循证指南》标准诊断 PCOS，该标准建立在 2003 年鹿特丹共识的基础上，诊断需要排除相关疾病后存在以下两种情况：① 临床和(或)生化高雄激素血症；② 排卵障碍；③ 超声提示卵巢多囊样改变[3]。

代谢综合征(Metabolic syndrome, MetS)又称胰岛素抵抗综合征，是以肥胖、血脂代谢紊乱、高血糖及高血压等特征聚集发病的一组临床症候群，可导致一些列心血管疾病的发生及发展[4] [5]。近年来，全世界患 MetS 的人数显著增加[6] [7] [8] [9] [10]。一项具有全国代表性的横断面研究[11]发现，中国 20 岁及以上居民 MetS 的患病率为 31.1%，女性的患病率显著高于男性(32.3% vs 30.0%)。世界卫生组织于 1998 年正式给出了“代谢综合征”的概念，随后各国政府和专业机构根据各国的人种、人群差异制定了用于当地的诊断标准并持续更新[12]，根据目前我国人群 MetS 的流行病学资料分析结果，于 2020 年出版了中国 2 型糖尿病的防治指南，该指南进一步修订了 MetS 各组分的量化指标。具体的诊断标准为：1) 腹型肥胖：腰围男性 ≥ 90 cm，女性 ≥ 85 cm；2) 高血糖：空腹血糖 ≥ 6.1 mmol/L 或糖负荷后 2 h 血糖 ≥ 7.8 mmol/L 和(或)已确诊为糖尿病并治疗者；3) 高血压：血压 ≥ 130/85 mmHg (1 mmHg = 0.133 kPa)和(或)已确认为高血压并治疗者；4) 空腹三酰甘油(TG) ≥ 1.70 mmol/L；5) 空腹 HDL-C < 1.04 mmol/L。以上具备 3 项或更多项即可诊断[5]。

2. PCOS 与 MetS 的相关性

大量研究表明，PCOS 患者患 MetS 的风险明显增加[12]-[20]。Apridonidze T 等人[21]研究发现，PCOS 女性中，MetS 的患病率为 43%，比一般人群中年龄匹配的女性高出近 2 倍。Marcondes JA 等人[22] [23]发现，与没有 MetS 的 PCOS 女性相比，同时患有 MetS 的女性更肥胖、更年长，且 MetS 的患病率随年龄和体质量指数(body mass index, BMI)增加而增加，提示 PCOS 与 MetS 两种不同的疾病之间密切相关。

PCOS 患者机体的代谢紊乱包括体脂增多、血脂紊乱、葡萄糖耐量异常、IR 以及高血压等[24]。研究表明，脂肪组织具有能量储存作用，可参与机体内分泌、炎症调节等，肥胖人群发生心脑血管疾病、排卵障碍的风险较高，可促进 PCOS 的进展[25]。MetS 的危险因素包括糖尿病、妊娠期糖尿病病史、肥胖、

IR 和 PCOS [26]。蒲丹兰等人[27]认为，IR 可能是 MetS 和 PCOS 之间的一个重要纽带。此外，一些脂肪因子，如瘦素、胰岛素样生长因子-1 和脂联素，也与 MetS 和 PCOS 相关。这些发现突显了 IR 和脂肪因子在这两种疾病发病机制中的重要性。也有研究表明，患有 PCOS 伴 MetS 的患者生育力下降，且妊娠并发症风险增加[28] [29] [30]。因此，有必要对 MetS 各组分与 PCOS 之间的发病关联、发展、治疗等方面进行深入研究和探讨。

3. PCOS 与 MetS 各组分的相关性

3.1. PCOS 与腹型肥胖

有研究表明，肥胖是 PCOS 的独立危险因素。评估肥胖的常用指标包括腰围、臀围、BMI 等[31]。据统计，高达 38%到 88%的 PCOS 女性被确诊为超重或肥胖[32]，特别是在 PCOS 患者中常见的腹型肥胖，会恶化 PCOS 引起的所有代谢和生殖问题[33]。Jurczewska J 等人[34]研究发现，在 PCOS 患者中，与腹部肥胖指数正常的女性相比，内脏脂肪组织量更多的女性患 IR 的概率更高。虽然 PCOS 与肥胖的相关机理目前尚不清楚，但许多专家都指出可能与基因及环境等因素相关，并涉及了神经系统内分泌及免疫功能的复杂调节。Anagnostis P 等人[35]认为，肥胖会影响子宫内膜胚胎植入和其他生殖功能，进而可能导致受孕延迟、流产率增加等。Ahmed B 等人[36]认为脂肪组织增多且功能失调，导致巨噬细胞聚集并极化为促炎状态。过量的脂肪组织释放出游离脂肪酸(FFA)、活性氧(ROS)和促炎细胞因子。过量的 FFA 进入肝脏、肌肉和胰腺等非脂肪器官的细胞内，以异位脂肪的形式沉积，产生脂毒性，继而导致细胞器失调，而失调的细胞器会释放过量的 ROS 和促炎因子，引起全身炎症。全身慢性低度炎症又会阻碍胰岛素的正常作用，破坏葡萄糖的稳态，最终导致机体内分泌失调。另有文献[37]指出，与 BMI 匹配的对照组相比，PCOS 患者的腹部脂肪堆积似乎更明显。然而，通过 MRI 和 CT 评估，发现两组的脂肪分布相似，这表明腹型肥胖可能与 PCOS 无关。因此，有必要进一步研究 PCOS 患者的腹型肥胖，探讨其发病机制。总之，肥胖会加重 PCOS 的症状及临床结局，因此体重管理(减轻体重、维持体重或预防体重过度增加)被提议作为 PCOS 患者的初始治疗策略[38]。

3.2. PCOS 与高血糖

高血糖是一种因 IR 或胰岛素分泌障碍，表现为持续慢性高血糖的全身代谢性疾病[39]。根据 2018 年的数据，我国约有 1.1 亿糖尿病患者，目前是全球糖尿病发病率最高的国家，且仍逐年增加[40]。大量研究报道，PCOS 患者存在一系列糖代谢紊乱的情况，与其相匹配 BMI 的健康女性相比，PCOS 患者的糖代谢紊乱程度更为严重。黄佳等人[40]研究发现：PCOS 是 T2DM 发生、发展的高危因素之一，PCOS 患者发生糖耐量异常的概率约为 11.7%。Tomlinson J 等人[41]的研究显示：PCOS 患者糖耐量受损及糖尿病的患病率于 2~3 年内分别从 37%和 10%上升到 45% 和 15%，证实了 PCOS 是 T2DM 的危险因素之一。Engin A 等人[42] [43]研究发现，当存在 IR 时，胰岛素受体及胰岛素受体底物-1 的丝氨酸残基磷酸化增加，酪氨酸残基磷酸化减少，导致胰岛素信号通路结合后缺陷，影响了经典胰岛素靶细胞和卵巢细胞的代谢途径。另外，PCOS 患者的慢性炎症状态可导致肠道微生物群的生态失衡，从而增加肠道粘膜通透性和脂多糖(LPS)进入体循环，激活免疫系统，干扰胰岛素受体功能，并增加血清胰岛素的水平。刘媛媛等人[44]认为，PCOS 患者糖代谢异常与 TCF7L2 基因、FTO 基因、LHCG R 基因的异常有关，这会增加 T2DM 的患病率。虽然也有研究表明 PCOS 本身不会导致糖尿病，但 PCOS 的共同特征(如肥胖和高雄激素血症)可能会加速 PCOS 向糖尿病的进展。因此，具有这些特征的 PCOS 女性应该进行早期干预和治疗[45]。目前，一些典型的胰岛素增敏药物，如二甲双胍，已被用于减少 PCOS 患者的 IR 和高胰岛素血症，但由于该疾病的复杂性，对该药物的反应存在差异，因此，需要进一步研究来筛选适用于 PCOS 的特异

性药物[28]。

3.3. PCOS 与血脂异常

血脂谱主要指体内甘油三酯(triglyceride, TG)、总胆固醇(total cholesterol, TC)、高密度脂蛋白(high density lipoprotein, HDL)及低密度脂蛋白(low density lipoprotein, LDL)等指标水平[46]。既往有研究发现，PCOS 患者 TC、TG、LDL 水平升高，HDL 水平下降。PCOS 患者中约 22.7%~70.4%存在血脂紊乱，高脂血症的患病率明显高于健康女性，约为健康人群的 2.5~5 倍[47] [48]。不同特征 PCOS 患者的血脂谱存在差异，证实了血脂代谢与 PCOS 特征之间存在复杂的相关性[49] [50]。Osibogun O 等人[51]认为，肥胖型 PCOS 患者血液中的雄激素、瘦素、脂联素以及神经肽 Y 的分泌存在异常，这些因素在协同作用下进一步加重脂代谢紊乱，从而导致 PCOS 远期并发症的患病率增加。Santoro N 等人[52]发现，正常体重的女性如果暴露于过量的脂质或胰岛素，会导致促性腺激素分泌下降，从而导致代谢紊乱、内分泌紊乱和排卵功能障碍的问题。郭飞等人[49]研究发现，早在青春期，PCOS 就可以通过影响血压和脂质代谢而增加 MetS 的发生率。因此，建议对所有 PCOS 患者进行脂质谱评估，每 2~3 年评估一次脂质状况。此外，预防远期心脑血管疾病是 PCOS 患者临床工作中的一大重点[53]。然而，仅依靠饮食和改变生活习惯往往难以达到预期的疗效。基于此，他汀类药物逐渐成为 PCOS 的常规治疗药物，因其不仅可以改善 PCOS 患者的血脂紊乱，还能够降低其雄激素水平、调节卵巢功能，改善机体炎性状态，以及降低机体的氧化应激水平[54]。然而，目前关于他汀类药物对 PCOS 患者的胰岛素水平、血脂代谢等影响的相关研究较少，其结果也存在一定差异，尚未纳入 PCOS 的标准化治疗。未来需要通过大量临床研究来确定 PCOS 患者降脂治疗的最佳方案，并进一步评估其治疗效果。

3.4. PCOS 与高血压

大量研究已经明确了 PCOS 与远期心血管疾病的关联[24] [25] [51] [53]。除了 PCOS 本身对机体的不良影响外，高血压、血脂异常和血糖异常等个体风险标志物也是导致心血管疾病的重要媒介[55]。Joham AE 等人[56]研究发现，PCOS 女性高血压的患病率显著高于正常女性，PCOS 女性更易从成年早期发展为高血压，并与 BMI 无关[57]。Mills G 等人[58]研究显示，PCOS 患者发生妊娠期高血压的风险增加 50%，先兆子痫的风险增加 30%。此外，先前的研究发现，冠状动脉钙化评分、C-反应蛋白、颈动脉内膜中层厚度和内皮功能障碍等亚临床心血管疾病标志物在 PCOS 女性中更容易增加[51]。另有研究认为，PCOS 患者存在氧化应激增强的情况，这会导致阻断活性氧生成过多，一氧化氮的活性降低，进而形成有毒的过亚硝酸根，这可能会“解偶联”内皮一氧化氮合酶，从而产生一个活性下降的会产生过氧化物的酶，进而产生血管氧化应激，并促进内皮功能紊乱，最后导致动脉粥样硬化的形成[55] [59]。Welt CK 等人[57] [60]认为高雄激素可以改变肾素－血管紧张素－醛固酮系统(RAAS)，RAAS 异常可能引发内皮功能障碍，使 PCOS 患者的动脉血压升高。此外，有研究表明，口服避孕药作为治疗 PCOS 的一线用药，可以激活凝血酶原、白细胞介素和其他炎性细胞因子，进而增加其发生整体心血管疾病的风险[61] [62]。另有文献报道，雄激素和 RAAS 在 PCOS 的动脉粥样硬化过程中发挥重要作用，这也提示螺内酯治疗可能逆转 PCOS 引发内皮功能障碍[55]。

4. 小结

综上所述，PCOS 与 MetS 各组分的发生、发展密切相关，包括肥胖、血脂异常、糖代谢紊乱等。因此，对于 PCOS 合并 MetS 的患者，我们不仅需要关注其生殖系统异常，还需密切关注其与代谢紊乱相关的问题，以制定更为个体化和合理化的管理方案，从而促进其生育能力、提高生活质量并预防远期潜在并发症的发生。

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