Advances in Clinical Medicine 临床医学进展, 2023, 13(9), 13901-13907
Published Online September 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.1391943

Hans汉斯

降糖药在超重/肥胖多囊卵巢综合征患者治疗中的研究进展

杨宇萱，刘东方*

重庆医科大学附属第二医院内分泌代谢科，重庆

收稿日期：2023年7月31日；录用日期：2023年8月24日；发布日期：2023年9月1日

摘　要

多囊卵巢综合征是一种常见且复杂的内分泌疾病，在育龄期女性中患病人群占1/10左右。多囊卵巢综合征患者中合并超重或肥胖者占比超过一半，且该部分人群代谢和生殖方面问题往往更严重且对治疗反应性较差，该类人群的代谢治疗方案探索成为研究的热点和难点。目前多囊卵巢综合征代谢调整治疗药物主要有二甲双胍、噻唑烷二酮类和阿卡波糖，近年来胰高血糖素样肽-1类似物和钠葡萄糖共转运蛋白-2抑制剂两类降糖药也逐渐被用于超重/肥胖PCOS患者的代谢调整治疗。本文主要就超重/肥胖PCOS患者代谢治疗药物的研究进展作一综述。

关键词

降糖药，超重，肥胖，多囊卵巢综合征，治疗

Research Progress of Antidiabetic Drugs in the Treatment of Overweight/Obese Patients with Polycystic Ovarian Syndrome

Yuxuan Yang, Dongfang Liu*

Department of Endocrinology and Metabolism, The Second Affiliated Hospital of Chongqing Medical University, Chongqing

Received: Jul. 31st, 2023; accepted: Aug. 24th, 2023; published: Sep. 1st, 2023

Abstract

Polycystic ovarian syndrome (PCOS) is a common and complex reproductive endocrine disorder

*通讯作者。

文章引用：杨宇萱，刘东方．降糖药在超重/肥胖多囊卵巢综合征患者治疗中的研究进展[J]．临床医学进展，2023, 13(9): 13901-13907. DOI: 10.12677/acm.2023.1391943

during the childbearing age in female with a prevalence of about 10%. Overweight and obesity are common comorbidities among females with PCOS, who account for more than 50%. Overweight/Obese patients often have worse symptoms and are less responsive to treatment. Seeking more effective treatment means in metabolic dysfunctions and reproductive abnormalities for these people is a hotspot and difficult point in medical research nowadays. There are three main types of antidiabetic drugs that are used to treat PCOS, including metformin, thiazolidinedione and acarbose. Recently, glucagon-like peptide 1 (GLP-1) analogues and sodium-glucose co-transporter-2 (SGLT-2) inhibitors are progressively used in the treatment of overweight/obese patients with PCOS. This review article aims to summarize the recent development of antidiabetic drugs in overweight/obese patients with PCOS.

Keywords

Antidiabetic Drugs, Overweight, Obese, Polycystic Ovarian Syndrome, Therapy

1. 引言

多囊卵巢综合征(Polycystic Ovarian Syndrome, PCOS)是一种育龄期女性常见的生殖内分泌疾病，其发病率达 5%~18% [1]。该病临床表现具有高度异质性，PCOS 患者除存在月经紊乱和高雄激素以外，还可能合并胰岛素抵抗、肥胖、不孕等代谢及生殖功能障碍，该患病人群的 2 型糖尿病、动脉粥样硬化和子宫内膜癌发生风险亦较正常育龄期女性高[2] [3] [4] [5] [6]，其发病机制尚不明确。PCOS 患者中超重/肥胖者居多，占比高达 60% [7]，基于 PCOS 多基因和表型风险预测研究显示 PCOS 和肥胖之间存在共同的生物学途径[8]，欧洲一项大规模全基因组交叉性状分析结果显示肥胖和 PCOS 具有共同的遗传基础[9]，证明 PCOS 与肥胖息息相关。因肥胖与高雄激素和胰岛素抵抗等多种 PCOS 的关键病理生理机制的交互作用，超重/肥胖 PCOS 患者的代谢紊乱和生育能力障碍较体重正常的 PCOS 患者更为突出[10] [11]，而适度的减重可使得超重/肥胖 PCOS 患者在代谢和生殖两方面获益[12] [13]，故该类人群是代谢治疗的重点对象。

近年来，一些研究发现强调了代谢通路改变是 PCOS 的潜在生物学机制[14]，代谢稳态与生殖之间存在复杂的交互作用，即高胰岛素血症可以通过增加卵巢鞘膜细胞中雄烯二酮的产生和减少肝脏性激素结合球蛋白的合成，导致高雄激素血症；高雄激素血症又可增加黄体生成素的分泌导致下丘脑－垂体－性腺轴紊乱进而引发排卵障碍，也可引起腹型肥胖而加重胰岛素抵抗，胰岛素抵抗通过破坏窦卵泡的发育导致慢性不排卵[15] [16]，一些改善代谢紊乱的方法也可以同时为患者带来生殖方面的获益。目前，超重/肥胖多囊卵巢综合征患者的代谢调整治疗方法主要有生活方式干预、药物治疗和手术治疗，鉴于减重手术对患者创伤较大且部分远期并发症对患者生活质量的影响不容忽视，健康的饮食和运动习惯往往对患者来说又难以长期坚持，目前药物治疗仍然是超重/肥胖 PCOS 患者治疗的主要手段。传统经典药物二甲双胍和噻唑烷二酮类(Thiazolidinedione, TZD)药物在 PCOS 患者的代谢改善治疗中占据重要地位，但其疗效有限，尤其超重/肥胖的患者对胰岛素增敏药物的治疗反应更差一些[12]，近年来钠－葡萄糖共转运体-2 抑制剂(Sodium-Glucose co-Transporter-2, SGLT-2)和胰高血糖素样肽-1 (Glucagon-like Peptide-1, GLP-1)受体激动剂等降糖药物用于改善超重/肥胖 PCOS 患者的代谢紊乱逐渐成为研究热点，本文就近年

来有关超重/肥胖 PCOS 患者的代谢调整药物研究进展进行综述。

2. 二甲双胍

二甲双胍可抑制肠道吸收葡萄糖和肝糖原异生的过程，也可增加外周组织胰岛素敏感性，在 2018 年版《PCOS 临床中国诊疗指南》中被推荐用于 PCOS 患者的代谢调整治疗，主要适用于 PCOS 伴胰岛素抵抗以及 PCOS 合并不孕、枸橼酸氯米酚抵抗的患者。1994 年 Velazquez E M 等[17]首次将二甲双胍用于治疗 PCOS，并在 26 例患者中治疗 8 周后观察到胰岛素敏感性和性激素水平的好转，之后二甲双胍逐渐被用于 PCOS 患者的代谢调节。国内外大量临床研究表明二甲双胍不仅可以调节代谢紊乱，还可在协助调经和恢复正常排卵方面发挥一定作用，一项 meta 分析显示二甲双胍不仅可降低 PCOS 女性的空腹胰岛素和低密度脂蛋白胆固醇水平，还可以改善她们的排卵情况，其促排卵效果显著优于安慰剂，二甲双胍与克罗米芬联合使用的疗效也优于克罗米芬单药治疗，而且二甲双胍与克罗米芬联合治疗方案在改善妊娠率方面也显示出更加优异的疗效[18]。另一项 meta 分析显示了二甲双胍在降低辅助生殖女性卵巢过度刺激综合征发生率、提高临床妊娠率和降低超重/肥胖 PCOS 患者的体重指数方面的疗效[19]。最新研究表明二甲双胍联合控糖饮食可以改善 PCOS 患者的子宫内膜功能，后者与女性生育力和生殖结局密切关联，并指出其内在机制可能与调节 HOXA10 基因启动子的 DNA 甲基化以及子宫内膜容受性和胰岛素信号转导相关基因的表达有关[20]。也有研究指出二甲双胍可能通过调节 PCOS 女性子宫内膜细胞中脂联素/胰岛素信号通路相关分子的表达来改善胰岛素抵抗和生殖功能障碍[21]。二甲双胍是目前 PCOS 代谢治疗中获得认可最多的药物，近年学者们对其的探索还集中在其应用于 PCOS 合并妊娠患者中的疗效与安全性。Tone S Løvvik 等[22]进行的一项随机、安慰剂对照、双盲、多中心研究显示对患有 PCOS 的孕妇予以二甲双胍治疗尽管不能预防妊娠期糖尿病，但可能降低晚期流产与早产的发生风险。

3. 噻唑烷二酮类药物(TZD)

TZD 主要通过激活过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor gamma, PPARγ)增加外周组织对胰岛素的敏感性，此类型药物目前有吡格列酮和罗格列酮，它们在改善胰岛素抵抗方面已显示出肯定的疗效。有研究显示，与二甲双胍相比，罗格列酮可以更大程度地降低超重肥胖 PCOS 患者的甘油三酯和总胆固醇，二者均可改善体重、BMI、腰围、腰臀比、月经周期、血清胰岛素和睾酮，但罗格列酮减重效果不如二甲双胍[23]。鉴于罗格列酮理论上并不具有减重的效果，该研究所观察到的两组患者体重均有下降可能是药物治疗联合生活方式改善的结果。最近有动物研究显示吡格列酮可能通过上调肝细胞核因子-4α 表达来增加性激素结合球蛋白水平，而达到改善胰岛素抵抗以及一定程度上降低血脂的效果[24]。

4. 阿卡波糖

阿卡波糖是一种 α-葡萄糖苷酶抑制剂，其作用机制为抑制体内多糖分解为单糖的进程从而减缓碳水化合物的吸收，达到减轻高胰岛素血症的效果，尽管其临床地位与二甲双胍相差甚远，但也被中华医学会妇产科学分会 2018 年版的《多囊卵巢综合征临床诊疗指南》所推荐，用于改善 PCOS 患者的代谢紊乱。2005 年一项纳入 30 例肥胖 PCOS 合并高胰岛素血症患者的双盲安慰剂对照试验结果显示阿卡波糖(每日 150 mg)与安慰剂相比可改善患者 BMI ((35.87 ± 2.60) kg/m^2 vs (33.10 ± 2.94) kg/m^2)、月经周期、性激素结合球蛋白((21.01 ± 7.9) nmol/l vs (23.85 ± 7.77) nmol/l)和游离睾酮指数(14.81 ± 9.06 vs 11.48 ± 6.18) [25]。同年还有一项临床研究证明阿卡波糖与二甲双胍一样有望改善合并克罗米芬抵抗的 PCOS 患者的排卵状况，研究者在 20 例柠檬酸克罗米芬抵抗的 PCOS 患者中将阿卡波糖与二甲双胍的疗效进行比较，治疗 3 个月后两组 LH/FSH (2.3 ± 0.2 vs 1.1 ± 0.4; 2.3 ± 0.3 vs 1.2 ± 0.6)和总睾酮(89 ± 22 vs 62 ± 24; 86 ± 19 vs 67

± 9)均降低且排卵率均升高，且阿卡波糖组体重下降较二甲双胍更为显著(68 ± 6.0 vs 66 ± 6.8; 69 ± 6.4 vs 67 ± 6.5) [26]。随后甚至有临床研究显示低剂量的阿卡波糖(每日 150 mg)治疗可降低肥胖 PCOS 患者的心血管风险血清标志物[27]。因为阿卡波糖可能导致一定的胃肠道反应，加之其减重和改善胰岛素敏感性效果有限，其临床应用较少。近年阿卡波糖治疗 PCOS 患者相关的临床研究就不如后续两种降糖药物多，但也有王雪娇等人对 25 例 PCOS 患者进行的临床研究证明阿卡波糖联合高纤维饮食可一定程度改善患者的临床表型[28]。

5. 胰高血糖素样肽-1 类似物(GLP-1)

GLP-1 可激活 GLP-1 受体刺激胰岛素分泌、增加肌肉脂肪组织摄取葡萄糖、抑制肝糖原的生成和释放，亦可通过抑制胃排空和降低食欲达到减重的效果。目前常用的有利拉鲁肽、司美格鲁肽、度拉糖肽和艾塞那肽等。GLP-1 受体激动剂可观的减重效果可能为超重/肥胖 PCOS 患者的治疗提供一个新机遇[10] [29]。

动物研究证明了 GLP-1 在 PCOS 中的减重、改善糖代谢和雄激素的功效。Shen H F 等[30]证明度拉糖肽可改善双氢睾酮诱导 PCOS 大鼠的体重、睾酮、性激素结合球蛋白和卵巢组织胰岛素水平，其改善激素的过程可能与 3βHSD、CYP19α1 和 StAR 基因表达有关。研究发现与对照组相比，度拉糖肽治疗组的大鼠体重有所下降、血清雄激素水平明显降低且血清性激素结合蛋白含量明显升高，差异有统计学意义。在蛋白表达和基因调控方面，度拉糖肽治疗组大鼠卵巢组织中 3βHSD、CYP19α1 和 StAR 的表达较对照组明显下降。也有研究表明 GLP-1 可缓解脱氢表雄酮诱导的 PCOS 小鼠的高胰岛素血症和高雄激素血症，这一过程与其减轻机体慢性炎症和刺激白色脂肪组织褐变相关[31]。

一些临床研究也初步证实了 PCOS 患者可以从 GLP-1 中获益。Shuo Yang 等[32]纳入共 2626 例 PCOS 患者的网状 Meta 分析报道 GLP-1 与二甲双胍联合治疗降低游离雄激素指数的效果优于二甲双胍单药治疗。一项针对超重肥胖 PCOS 患者的随机对照试验结果显示，与单独使用热量限制饮食相比，度拉糖肽联合热量限制饮食在降低糖化血红蛋白和餐后血糖水平方面具有显著的优势[33]。此外，GLP-1 在改善妊娠率方面也已初显疗效，一项在 26 例 PCOS 合并肥胖和不孕的患者中进行的随机对照试验发现在备孕前短期使用小剂量利拉鲁肽联合二甲双胍治疗可改善妊娠率，其效果比单用二甲双胍好[34]。尤其针对超重/肥胖的 PCOS 患者，有不少临床研究对 GLP-1 的疗效进行了探索。Xing C 等人进行了一项前瞻性随机临床试验，他们将 52 名超重/肥胖 PCOS 患者随机分为二甲双胍联合利拉鲁肽治疗组和二甲双胍单药治疗组，治疗 12 周后两组均观察到月经周期和糖代谢的改善且二者效果相当，但联合治疗组的总睾酮、促黄体生成素、游离睾酮指数和孕酮水平改善效果更佳[35]。Rui-Lin Ma 等[36]以使用艾塞那肽联合二甲双胍治疗超重/肥胖 PCOS 患者，除减重((3.8 ± 2.4) kg vs (2.1 ± 3.0) kg, P = 0.041)和缩小腰围((4.63 ± 4.42) cm vs (1.72 ± 4.07) cm，P = 0.023)的效果较二甲双胍单药治疗更显著外，还能改善患者的空腹血糖、口服糖耐量试验 2 小时血糖和口服糖耐量试验 2 小时胰岛素水平。Elkind-Hirsch 等[37]通过一项随机、双盲、安慰剂对照试验证明利拉鲁肽(每日 3 mg 皮下注射)可改善肥胖 PCOS 女性的体重、游离睾酮指数和心脏代谢参数。总体而言，GLP-1 对 PCOS 患者，尤其是合并超重或肥胖者，体重、糖代谢和生殖能力改善有较为肯定的疗效，临床应用前景可观。

6. 钠葡萄糖共转运蛋白-2 (SGLT-2)抑制剂

SGLT-2 抑制剂包括恩格列净、达格列净和卡格列净等，这类药物通过在肾脏近曲小管与葡萄糖竞争性结合 SGLT-2 来减少肾小管对葡萄糖的重吸收，从而增加尿糖排泄，达到减重和降糖的效果。Jacob E 等[38]证明了在高雄激素血症的 PCOS 大鼠模型中，SGLT-2 抑制剂对减重和降压有益。目前学者们对

SGLT-2 抑制剂用于治疗 PCOS 患者的临床研究多为小样本量和短疗程试验。Cai M 等[39]进行的一项单中心、前瞻性随机对照试验对 68 例 PCOS 患者分别予以卡格列净每日 100 mg (n = 33)和二甲双胍每日 1.5 g~2.0 g (n = 35)治疗 12 周，结果显示卡格列净降低胰岛素抵抗指数的效果不亚于二甲双胍[95% CI (2.13, 0.51)]，两种药物均可改善月经周期、降低体重及降低血清甘油三酯水平，卡格列净降低血尿酸和硫酸脱氢表雄酮的效果甚至优于二甲双胍。同年 Zhang J 等[40]进行的一项随机对照研究将 51 例超重/肥胖 PCOS 患者随机分为卡格列净联合二甲双胍组(n = 26)和二甲双胍单药组(n = 25)，进行了为期 3 个月的随访，他们观察到联合治疗组的总睾酮水平、葡萄糖曲线下面积和胰岛素曲线下面积/葡萄糖曲线下面积比值均较二甲双胍单药组更低。目前 SGLT-2 抑制剂对 PCOS 患者的治疗探索尚少，其改善超重肥胖 PCOS 患者的体重、代谢及性激素的疗效值得进一步探索，需要更多多中心、大样本量的随机对照试验进行证实。

7. 总结

综上所述，目前药物治疗是超重/肥胖 PCOS 患者代谢调整的重要手段，除传统经典药物二甲双胍和 TZD 类外，其他降糖药物如 GLP-1 受体激动剂和 SGLT-2 受体抑制剂，近年来作为 PCOS 治疗的新兴的药物治疗选择已越来越受到业内学者的关注，它们尤其适用于本身存在体重超标的患者，它们改善人体测量指标和胰岛素敏感性方面的疗效在动物研究和临床研究中均得到初步肯定，在改善性激素水平以及增加妊娠率等方面的作用还需进一步探索。近年关于上述新药的治疗多为与二甲双胍联合用药所得到的临床数据与二甲双胍单药治疗进行的对比，且样本量偏小，未来期望更多的大规模前瞻性临床研究对上述新药单药治疗的效果进行评估以全面了解其疗效及安全性。相信随着研究的深入，未来超重/肥胖的 PCOS 患者能有更多疗效优良且安全性高的代谢调节药物可选择。

参考文献

[1] Joham, A.E., Norman, R.J., Stener-Victorin, E., *et al*. (2022) Polycystic Ovary Syndrome. *The Lancet Diabetes & Endocrinology*, **10**, 668-680. https://doi.org/10.1016/S2213-8587(22)00163-2

[2] Kakoly, N.S., Earnest, A., Teede, H.J., *et al*. (2019) The Impact of Obesity on the Incidence of Type 2 Diabetes among Women with Polycystic Ovary Syndrome. *Diabetes Care*, **42**, 560-567. https://doi.org/10.2337/dc18-1738

[3] Wekker, V., van Dammen, L., Koning, A., *et al*. (2020) Long-Term Cardiometabolic Disease Risk in Women with PCOS: A Systematic Review and Meta-Analysis. *Human Reproduction Update*, **26**, 942-960. https://doi.org/10.1093/humupd/dmaa029

[4] Barry, J.A., Azizia, M.M. and Hardiman, P.J. (2014) Risk of Endometrial, Ovarian and Breast Cancer in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. *Human Reproduction Update*, **20**, 748-758. https://doi.org/10.1093/humupd/dmu012

[5] Persson, S., Elenis, E., Turkmen, S., *et al*. (2021) Higher Risk of Type 2 Diabetes in Women with Hyperandrogenic Polycystic Ovary Syndrome. *Fertility and Sterility*, **116**, 862-871. https://doi.org/10.1016/j.fertnstert.2021.04.018

[6] Liu, Q., Tang, B., Zhu, Z., *et al*. (2022) A Genome-Wide Cross-Trait Analysis Identifies Shared Loci and Causal Relationships of Type 2 Diabetes and Glycaemic Traits with Polycystic Ovary Syndrome. *Diabetologia*, **65**, 1483-1494. https://doi.org/10.1007/s00125-022-05746-x

[7] Escobar-Morreale, H.F. (2018) Polycystic Ovary Syndrome: Definition, Aetiology, Diagnosis and Treatment. *Nature Reviews Endocrinology*, **14**, 270-284. https://doi.org/10.1038/nrendo.2018.24

[8] Joo, Y.Y., Actkins, K., Pacheco, J.A., *et al*. (2020) A Polygenic and Phenotypic Risk Prediction for Polycystic Ovary Syndrome Evaluated by Phenome-Wide Association Studies. *The Journal of Clinical Endocrinology & Metabolism*, **105**, 1918-1936. https://doi.org/10.1210/clinem/dgz326

[9] Liu, Q., Zhu, Z., Kraft, P., *et al*. (2022) Genomic Correlation, Shared Loci, and Causal Relationship between Obesity and Polycystic Ovary Syndrome: A Large-Scale Genome-Wide Cross-Trait Analysis. *BMC Medicine*, **20**, Article No. 66. https://doi.org/10.1186/s12916-022-02238-y

[10] Cena, H., Chiovato, L. and Nappi, R.E. (2020) Obesity, Polycystic Ovary Syndrome, and Infertility: A New Avenue for GLP-1 Receptor Agonists. *The Journal of Clinical Endocrinology & Metabolism*, **105**, e2695-e2709. https://doi.org/10.1210/clinem/dgaa285

[11] Zhang, H., Wang, W., Zhao, J., *et al*. (2022) Relationship between Body Composition, Insulin Resistance, and Hormonal Profiles in Women with Polycystic Ovary Syndrome. *Frontiers in Endocrinology* (*Lausanne*), **13**, Article ID: 1085656. https://doi.org/10.3389/fendo.2022.1085656

[12] Glueck, C.J. and Goldenberg, N. (2019) Characteristics of Obesity in Polycystic Ovary Syndrome: Etiology, Treatment, and Genetics. *Metabolism*, **92**, 108-120. https://doi.org/10.1016/j.metabol.2018.11.002

[13] Wu, L., Fang, Q., Wang, M., *et al*. (2022) Effect of Weight Loss on Pregnancy Outcomes, Neuronal-Reproductive-Metabolic Hormones and Gene Expression Profiles in Granulosa Cells in Obese Infertile PCOS Patients Undergoing IVF-ET. *Frontiers in Endocrinology* (*Lausanne*), **13**, Article ID: 954428. https://doi.org/10.3389/fendo.2022.954428

[14] Visser, J.A. (2021) The Importance of Metabolic Dysfunction in Polycystic Ovary Syndrome. *Nature Reviews Endocrinology*, **17**, 77-78. https://doi.org/10.1038/s41574-020-00456-z

[15] Zeng, X., Xie, Y.J., Liu, Y.T., *et al*. (2020) Polycystic Ovarian Syndrome: Correlation between Hyperandrogenism, Insulin Resistance and Obesity. *Clinica Chimica Acta*, **502**, 214-221. https://doi.org/10.1016/j.cca.2019.11.003

[16] de Medeiros, S.F., Rodgers, R.J. and Norman, R.J. (2021) Adipocyte and Steroidogenic Cell Cross-Talk in Polycystic Ovary Syndrome. *Human Reproduction Update*, **27**, 771-796. https://doi.org/10.1093/humupd/dmab004

[17] Velazquez, E.M., Mendoza, S., Hamer, T., *et al*. (1994) Metformin Therapy in Polycystic Ovary Syndrome Reduces Hyperinsulinemia, Insulin Resistance, Hyperandrogenemia, and Systolic Blood Pressure, While Facilitating Normal Menses and Pregnancy. *Metabolism*, **43**, 647-654. https://doi.org/10.1016/0026-0495(94)90209-7

[18] Lord, J.M., Flight, I.H. and Norman, R.J. (2003) Metformin in Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. *BMJ*, **327**, 951-953. https://doi.org/10.1136/bmj.327.7421.951

[19] Li, X., Celotto, S., Pizzol, D., *et al*. (2021) Metformin and Health Outcomes: An Umbrella Review of Systematic Reviews with Meta-Analyses. *European Journal of Clinical Investigation*, **51**, e13536. https://doi.org/10.1111/eci.13536

[20] Garcia-Gomez, E., Gomez-Viais, Y.I., Cruz-Aranda, M.M., *et al*. (2023) The Effect of Metformin and Carbohydrate-Controlled Diet on DNA Methylation and Gene Expression in the Endometrium of Women with Polycystic Ovary Syndrome. *International Journal of Molecular Sciences*, **24**, Article No. 6857. https://doi.org/10.3390/ijms24076857

[21] Orostica, M.L., Astorga, I., Plaza-Parrochia, F., *et al*. (2022) Metformin Treatment Regulates the Expression of Molecules Involved in Adiponectin and Insulin Signaling Pathways in Endometria from Women with Obesity-Associated Insulin Resistance and PCOS. *International Journal of Molecular Sciences*, **23**, Article No. 3922. https://doi.org/10.3390/ijms23073922

[22] Lovvik, T.S., Carlsen, S.M., Salvesen, O., *et al*. (2019) Use of Metformin to Treat Pregnant Women with Polycystic Ovary Syndrome (PregMet2): A Randomised, Double-Blind, Placebo-Controlled Trial. *The Lancet Diabetes & Endocrinology*, **7**, 256-266. https://doi.org/10.1016/S2213-8587(19)30002-6

[23] Li, Y., Tan, J., Wang, Q., *et al*. (2020) Comparing the Individual Effects of Metformin and Rosiglitazone and Their Combination in Obese Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. *Fertility and Sterility*, **113**, 197-204. https://doi.org/10.1016/j.fertnstert.2019.09.011

[24] Zhao, H., Wang, D., Xing, C., *et al*. (2023) Pioglitazone Can Improve Liver Sex Hormone-Binding Globulin Levels and Lipid Metabolism in Polycystic Ovary Syndrome by Regulating Hepatocyte Nuclear Factor-4α. *The Journal of Steroid Biochemistry and Molecular Biology*, **229**, Article ID: 106265. https://doi.org/10.1016/j.jsbmb.2023.106265

[25] Penna, I.A., Canella, P.R., Reis, R.M., *et al*. (2005) Acarbose in Obese Patients with Polycystic Ovarian Syndrome: A Double-Blind, Randomized, Placebo-Controlled Study. *Human Reproduction*, **20**, 2396-2401. https://doi.org/10.1093/humrep/dei104

[26] Sonmez, A.S., Yasar, L., Savan, K., *et al*. (2005) Comparison of the Effects of Acarbose and Metformin Use on Ovulation Rates in Clomiphene Citrate-Resistant Polycystic Ovary Syndrome. *Human Reproduction*, **20**, 175-179. https://doi.org/10.1093/humrep/deh580

[27] Araujo, P.I., Canella, P.R., Vieira, C.S., *et al*. (2007) Cardiovascular Risk Factors Are Reduced with a Low Dose of Acarbose in Obese Patients with Polycystic Ovary Syndrome. *Fertility and Sterility*, **88**, 519-522. https://doi.org/10.1016/j.fertnstert.2006.11.073

[28] Wang, X., Xu, T., Liu, R., *et al*. (2021) High-Fiber Diet or Combined with Acarbose Alleviates Heterogeneous Phenotypes of Polycystic Ovary Syndrome by Regulating Gut Microbiota. *Frontiers in Endocrinology* (*Lausanne*), **12**, Article ID: 806331. https://doi.org/10.3389/fendo.2021.806331

[29] Bednarz, K., Kowalczyk, K., Cwynar, M., *et al*. (2022) The Role of Glp-1 Receptor Agonists in Insulin Resistance with Concomitant Obesity Treatment in Polycystic Ovary Syndrome. *International Journal of Molecular Sciences*, **23**, Article No. 4334. https://doi.org/10.3390/ijms23084334

[30] Wu, L.M., Wang, Y.X., Zhan, Y., *et al*. (2021) Dulaglutide, a Long-Acting GLP-1 Receptor Agonist, Can Improve Hyperandrogenemia and Ovarian Function in DHEA-Induced PCOS Rats. *Peptides*, **145**, Article ID: 170624.

https://doi.org/10.1016/j.peptides.2021.170624

[31] Zhang, Y., Lin, Y., Li, G., *et al*. (2023) Glucagon-Like Peptide-1 Receptor Agonists Decrease Hyperinsulinemia and Hyperandrogenemia in Dehydroepiandrosterone-Induced Polycystic Ovary Syndrome Mice and Are Associated with Mitigating Inflammation and Inducing Browning of White Adipose Tissuedagger. *Biology of Reproduction*, **108**, 945-959. https://doi.org/10.1093/biolre/ioad032

[32] Yang, S., Zhao, L., He, W., *et al*. (2022) The Effect of Oral Antidiabetic Drugs on Improving the Endocrine and Metabolic States in Women with Polycystic Ovary Syndrome: A Systematic Review and Network Meta-Analysis. *Drugs*, **82**, 1469-1480. https://doi.org/10.1007/s40265-022-01779-z

[33] Zhang, Y., Qu, Z., Lu, T., *et al*. (2023) Effects of a Dulaglutide plus Calorie-Restricted Diet versus a Calorie-Restricted Diet on Visceral Fat and Metabolic Profiles in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. *Nutrients*, **15**, Article No. 556. https://doi.org/10.3390/nu15030556

[34] Salamun, V., Jensterle, M., Janez, A., *et al*. (2018) Liraglutide Increases IVF Pregnancy Rates in Obese PCOS Women with Poor Response to First-Line Reproductive Treatments: A Pilot Randomized Study. *European Journal of Endocrinology*, **179**, 1-11. https://doi.org/10.1530/EJE-18-0175

[35] Xing, C., Zhao, H., Zhang, J., *et al*. (2022) Effect of Metformin versus Metformin plus Liraglutide on Gonadal and Metabolic Profiles in Overweight Patients with Polycystic Ovary Syndrome. *Frontiers in Endocrinology* (*Lausanne*), **13**, Article ID: 945609. https://doi.org/10.3389/fendo.2022.945609

[36] Ma, R.L., Deng, Y., Wang, Y.F., *et al*. (2021) Short-Term Combined Treatment with Exenatide and Metformin for Overweight/Obese Women with Polycystic Ovary Syndrome. *Chinese Medical Journal* (*England*), **134**, 2882-2889. https://doi.org/10.1097/CM9.0000000000001712

[37] Elkind-Hirsch, K.E., Chappell, N., Shaler, D., *et al*. (2022) Liraglutide 3 mg on Weight, Body Composition, and Hormonal and Metabolic Parameters in Women with Obesity and Polycystic Ovary Syndrome: A Randomized Placebo-Controlled-Phase 3 Study. *Fertility and Sterility*, **118**, 371-381. https://doi.org/10.1016/j.fertnstert.2022.04.027

[38] Pruett, J.E., Torres, F.E., Everman, S.J., *et al*. (2021) Impact of SGLT-2 Inhibition on Cardiometabolic Abnormalities in a Rat Model of Polycystic Ovary Syndrome. *International Journal of Molecular Sciences*, **22**, Article No. 2576. https://doi.org/10.3390/ijms22052576

[39] Cai, M., Shao, X., Xing, F., *et al*. (2022) Efficacy of Canagliflozin versus Metformin in Women with Polycystic Ovary Syndrome: A Randomized, Open-Label, Noninferiority Trial. *Diabetes, Obesity and Metabolism*, **24**, 312-320. https://doi.org/10.1111/dom.14583

[40] Zhang, J., Xing, C., Cheng, X., *et al*. (2022) Canagliflozin Combined with Metformin versus Metformin Monotherapy for Endocrine and Metabolic Profiles in Overweight and Obese Women with Polycystic Ovary Syndrome: A Single-Center, Open-Labeled Prospective Randomized Controlled Trial. *Frontiers in Endocrinology* (*Lausanne*), **13**, Article ID: 1003238. https://doi.org/10.3389/fendo.2022.1003238