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REVIEW OPEN ACCESS

The Efficacy of Metformin Treatment on Insulin Resistance and Hyperandrogenism in Lean Women with Polycystic Ovary Syndrome: A Literature Review

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in premenopausal women, characterized by insulin resistance and hyperandrogenism. Previous studies have investigated the use of metformin, a well-known insulin sensitizer, on lean PCOS patients, but it remains unclear as to how effective the treatment is. This literature review was carried out to better assess the effects of metformin on lean PCOS patients.

Methods: Related literature was fully searched using MEDLINE, EMBASE, Web of Science, and COCHRANE for metformin therapy on lean women with PCOS (last updated May 2022). A review was performed to evaluate the effects of continued metformin treatment on relevant hormonal and metabolic indicators in these women.

Results: A total of fourteen studies among 300 related articles were included in the review. Significant changes in total testosterone, sex hormone binding globulin (SHBG), blood insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were reported in majority of the studies. Several studies observed significant changes in Body Mass Index (BMI), luteinizing hormone (LH), and blood glucose. Nearly none of the studies assessed reported significant changes in follicle-stimulating hormone (FSH) and androstenedione.

Discussion: Current literature around the efficacy of metformin treatment on lean PCOS patients remains unclear and uncertain. The majority of studies reviewed indicate that metformin treatment significantly ameliorated total testosterone, SHBG levels, and insulin resistance in lean patients with PCOS. However, the mechanisms and effects of metformin on other treatment outcomes in lean PCOS women is unclear.

Conclusion: Metformin may be a putative treatment for lean PCOS women with significant insulin resistance and/or hyperandrogenism. More research involving larger sample sizes and a greater number of clinical outcomes is required.

Keywords: PCOS; metformin; lean women

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine and metabolic disorder of the female reproductive system, affecting an estimated 5-20% of premenopausal women [1,2]. It is a leading cause of infertility, and is typically characterised by oligomenorrhea, hirsutism, infertility, and hyperinsulinemia [1,3,4]. It is commonly diagnosed in adults using the Rotterdam criteria, which requires two of the three clinical features of oligoovulation, hyperandrogenism, and ovarian morphology to be present [4,5]. In adolescent females, diagnosis is challenging as characteristics of puberty, such as hormonal fluctuations, may mimic symptoms of PCOS [1]. The pathophysiology of PCOS remains unclear, though current hypotheses suggest atypical insulin signalling, oxidative stress, dysregulation of steroidogenesis, and environmental factors [3] may be involved. Many of the clinical features of PCOS are reflective of impaired ovarian function, such as elevated luteinizing hormone (LH) levels, anovulation, metabolic syndrome, insulin resistance (IR), obesity, and dyslipidemia [6].

Hyperinsulinemia and IR are likely central elements to the pathogenesis of PCOS [7] and have been demonstrated to exist intrinsically in PCOS women regardless of obesity [8,9]. However, the cellular mechanisms of IR in PCOS are not clearly defined. Previous studies with adipocytes failed to find significant decreases in insulin receptor numbers or affinity between PCOS women and weight-matched controls [9–11]. Rather, substantial decreases in insulin-mediated glucose uptake observed in adipocytes demonstrated a decrease in insulin sensitivity, possibly due to defects in insulin receptor binding or phosphorylation [10,12]. Later studies implicated post-receptor abnormalities in the development of IR. Significant decreases in GLUT4 glucose transporters likely accounted for decreases in insulin transport and maximal responsiveness [13–15]. Investigations on isolated insulin receptors further demonstrated increased insulin-

independent receptor serine phosphorylation and reduced tyrosine kinase activity, which may have inhibited receptor signalling in a subpopulation of PCOS women [16,17]. Other studies of insulin signalling *in vivo* have shown significant decreases in IRS-1-associated phosphatidylinositol 3-kinase (PI3-K) activation [18], although these findings are inconsistent between studies [19,20].

Hyperinsulinemia in PCOS is known to contribute to the development of hyperandrogenism through direct and indirect mechanisms [21–23]. Insulin can act on the pituitary gland by increasing the responsiveness of the pituitary to gonadotropin-releasing hormone (GnRH) [24–26]. This may contribute to the elevated LH levels and slightly decreased follicle-stimulating hormone (FSH) levels that are typical of the condition. Insulin can also act directly on the ovaries to stimulate the activity of cytochrome P450c17 (CYP450) and aromatase, leading to greater androgens and estrogens synthesis [27,28]. Insulin-sensitizing drugs, including metformin, have been shown to decrease androgen production and improve LH secretion [29,30].

Despite the prevalence of PCOS, there are no existing regulated treatments for it, due to unclear, complex pathophysiology of PCOS and the variety of specific manifestations. Instead, drugs are commonly used to target individualized symptoms, such as clomiphene for infertility and pioglitazone for IR [7]. Metformin, an insulin sensitizing drug, is often used by women with PCOS to improve insulin sensitivity [11]. By working to increase peripheral glucose absorption, metformin can improve the metabolic and reproductive outcomes associated with IR, including increased menstrual frequency, reduced androgen excess, and decreased hyperinsulinemia [31]. However, persistent use of metformin has also been shown to cause gastrointestinal side effects, such as diarrhea and stomach-aches [2].

A common physiological presentation of PCOS is obesity, accounting for an estimated 40-80% of PCOS women [32]. It is unclear as to whether PCOS contributes to obesity or whether the relationship is the other way around. Obesity has been found to worsen insulin-mediated glucose disposal in PCOS patients, while insulin resistance in PCOS can exacerbate a patient's risk of obesity [32]. It was found that hepatic insulin resistance specifically is aggravated in obese PCOS patients, demonstrating a close link between PCOS and the clinical manifestations of weight-gain and obesity [32]. The risk of developing glucose intolerance has also been shown to be directly proportional with body mass index (BMI), although it is likely impacted by a combination of genetic and environmental factors. However, there remains a significant portion of PCOS women who are normal weight (BMI < 25 kg/m²), often termed lean PCOS [33]. Although there is some consensus that clinical manifestations in lean and overweight PCOS women are comparable [32], the efficacy of metformin as a treatment method in lean PCOS women is less known. This is partially due to the decreased physiological prevalence of lean PCOS patients. This review provides an analysis of relevant literature to evaluate the clinical effectiveness and limitations of metformin use in lean women with PCOS.

Materials and Methods

Literature Search

A literature search was conducted on EMBASE, MEDLINE, Web of Science, and Cochrane Library with an end date of May 2022. The search terms used included the following: "polycystic ovary syndrome" or "PCOS," "metformin," and "lean" or "normal weight." Publication date, language, and publication type were not limited.

Outcome Measures

The main outcome was to compare the therapeutic effects of metformin on normal-weight women (BMI < 25 kg/m^2). The measured therapeutic parameters were divided by hormonal and metabolic indicators. Hormonal indicators included FSH, LH, total testosterone, sex hormone binding globulin (SHBG), and androstenedione. Metabolic indicators included Body Mass Index (BMI), fasting blood glucose, fasting insulin, and the Homeostasis Model of Assessment for Insulin Resistance (HOMA-IR).

Selection Criteria

Published studies that investigated the effect of metformin on lean women with PCOS were considered. Studies were included in the review if [1] the diagnosis of PCOS was confirmed using the Rotterdam diagnostic criteria, [2] the treatment group consisted of normal-weight women with PCOS, [3] measured outcomes in the study included at least one of the above therapeutic indicators, with measurements taken before and after metformin treatment, [4] study participants had not used confounding medication, including oral contraceptive agents, insulin-sensitizing agents, hypertensive medication, or anti-androgen agents, for at least 3 months prior to enrolment, and [5] approval from ethics committees and informed participant consent were provided. The control group was defined as BMI-matched, healthy women who did not have PCOS.

Studies were excluded if [1] the therapeutic group consisted of both normal weight and overweight/obese patients, [2] comparisons between therapeutic indicators before and after metformin treatment were not included, [3] other ovulation induction drugs were used, such as clomiphene citrate and gonadotrophins, and [4] if the study did not include measurements between 3 to 6 months of metformin treatment, or a minimum of 15 trials.

Data Extraction and Statistical Analysis

Articles were independently collected and reviewed to determine eligibility of studies. Then, the following

information was extracted from each study: name of first author and year of publication, study characteristics, number of patients measured before and after treatment, study duration, study dose, and significant findings.

Measured therapeutic parameters were then extracted from the articles. Methods used for statistical analysis in each article were evaluated for consistency and accuracy. A p-value of < 0.05 between the before and after groups, as determined by a paired t-test or an Analysis of Variance test, was deemed statistically significant.

Results

Search Results and Eligible Studies

A total of 503 articles were returned, and 300 remained after duplicates were removed. Abstracts were then read to determine relevancy, and 34 articles remained. Finally, 14 literature studies met the study selection criteria after the abstract and full text were read [3,4,34–45]. **Figure 1** shows the search strategy for the selection of included studies. Extracted characteristics and data from the included studies are presented in **Tables 1-3**.

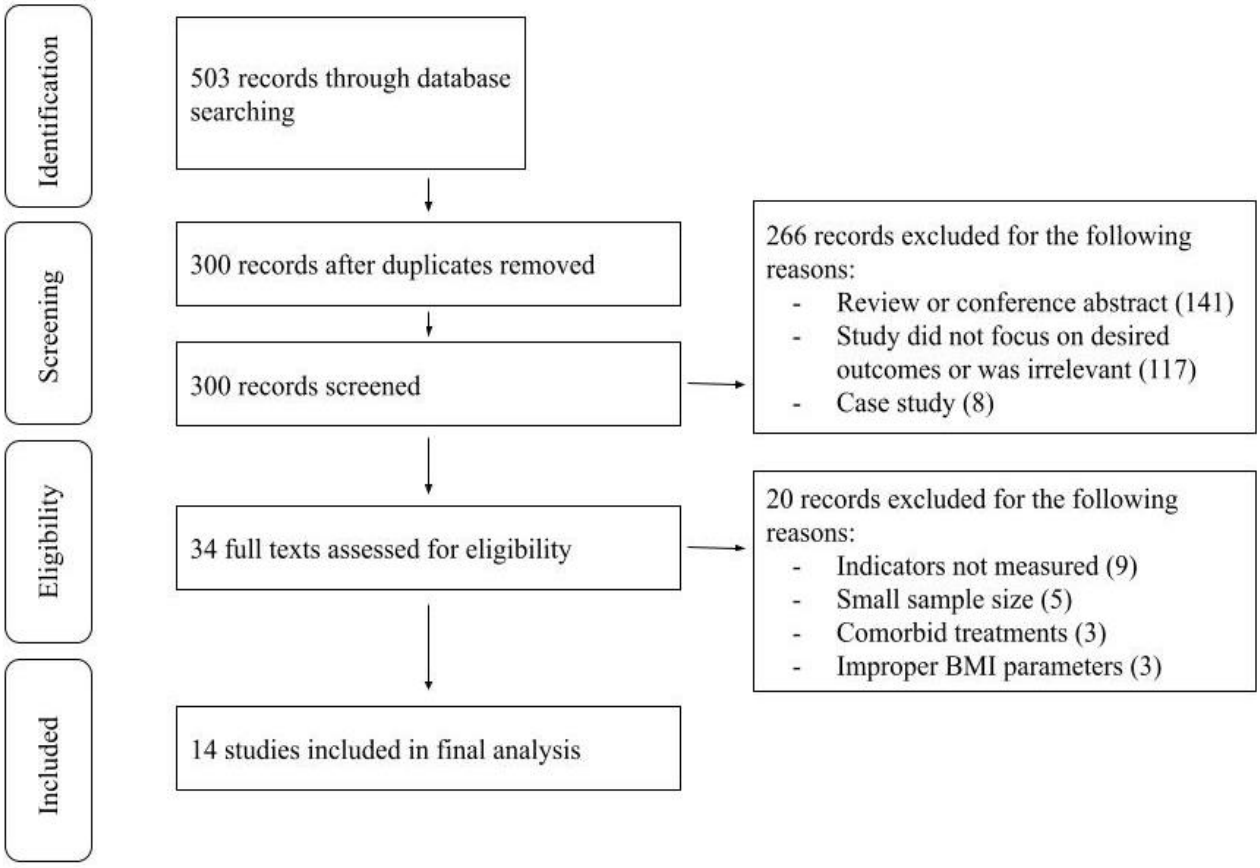

Figure 1. Flowchart for number of studies after application of selection criteria.

Table 1. General information of included studies in the meta-analysis

Author and publication year	Study characteristics	Cases (b/a)	Duration (months)	Dose	Significant findings
Sahin, 2007	Prospective	20/20	6	2550 mg daily	Significant decreases in LH and glucose levels
Tan, 2007	Prospective	44/44	6	Weight-adapted doses (body weight <60 kg: 500 mg of metformin twice a day (BID); 60–100 kg: 850 mg BID; >100 kg: 1000 mg BID)	Significant decreases in testosterone, insulin, and HOMA-IR
Kumari, 2005	Prospective	17/17	3	500 mg three times a day (TID)	Significant decreases in FSH, LH, testosterone, and insulin levels
Kialka, 2016	Randomized	15/15	6	1500 mg daily	Significant changes in LH, testosterone, SHBG, and insulin levels
Orio, 2005	Prospective	30/30	6	850 mg BID	Significant changes in SHBG, FAI and insulin levels
Yilmaz, 2005a	Randomized	25/25	3	850 mg BID	Significant decreases in BMI and HOMA-IR
Christakou, 2014	Prospective, open-labelled	35/35	6	425 mg BID for one week, then increased to 850 mg BID	Significant changes in BMI, and testosterone levels
Foda, 2019	Cross-sectional	35/35	3	500 mg once a day for one week, then 500 mg BID for second week, then 500 mg TID for remainder of study	Significant decreases in testosterone, glucose and insulin levels
Koiou, 2011	Prospective	25/25	6	850 mg BID	Significant decreases in BMI, testosterone, and glucose levels
Soldat-Stanjovic, 2021	Randomized	15/15	6	1500 mg daily	No significant changes observed
Yilmaz, 2005b	Randomized	20/19	3	850 mg BID	Significant decreases in BMI, glucose, and HOMA-IR
Hasan, 2018	Prospective	21/21	6	1500 mg daily	Significant decreases in insulin and HOMA-IR
Singh, 2012	Prospective	19/19	6	850 mg BID	Significant decrease in HOMA-IR
Ozgurtas, 2008	Randomized	22/20	3	850 mg BID	Significant decrease in BMI

Abbreviations: before metformin treatment (b), after metformin treatment (a), twice a day (BID), three times a day (TID)

Table 2. Hormonal indicators measured in included studies

Author and publication year	Groups	FSH (mIU/mL)	LH (mIU/mL)	T (nmol/L)	SHBG (nmol/L)	A (ng/mL)
Sahin, 2007	b	5.20 ± 1.10	11.50 ± 7.60		33.90 ± 21.90	3.10 ± 1.00
	a	5.10 ± 1.80	2.20 ± 3.60*		40.70 ± 29.20	2.50 ± 1.20
Tan, 2007	b			2.60 ± 0.90		
	a			1.80 ± 0.70*		
Kumari, 2005	b	6.30 ± 1.62	16.20 ± 6.90	2.50 ± 0.10		4.80 ± 1.50
	a	5.20 ± 1.60*	11.20 ± 1.20*	1.40 ± 0.80*		4.30 ± 0.90
Kialka, 2016	b	6.87 ± 1.08	11.46 ± 2.74	2.51 ± 0.34	37.59 ± 6.33	
	a	6.79 ± 1.04	5.55 ± 1.51*	1.80 ± 0.29*	46.70 ± 4.75*	
Orio, 2005	b	10.50 ± 1.20	24.60 ± 3.70	2.60 ± 0.40	28.10 ± 5.10	1.48 ± 0.20
	a	9.80 ± 1.60	23.20 ± 3.10	2.30 ± 0.90	35.50 ± 5.20*	1.40 ± 0.17
Yilmaz, 2005a	b	5.96 ± 2.47	9.89 ± 5.62			2.96 ± 1.46
	a	5.12 ± 2.38	8.12 ± 4.62			2.65 ± 1.41
Christakou, 2014	b			2.85 ± 0.09	45.80 ± 3.40	
	a			2.32 ± 0.07*	44.90 ± 3.00*	
Foda, 2019	b	4.11 ± 0.35	8.65 ± 0.98	2.16 ± 0.31		
	a	4.37 ± 0.40*	5.06 ± 0.85*	2.05 ± 0.15*		
Koiou, 2011	b	5.90 ± 1.80	10.90 ± 6.80	2.83 ± 0.60		2.90 ± 0.90
	a	6.10 ± 3.20	12.60 ± 13.50	2.50 ± 0.57*		2.80 ± 0.80
Soldat-Stanjovic, 2021	b	6.80 ± 1.80	7.99 ± 3.37	1.87 ± 0.49	59.60 ± 31.66	
	a	6.77 ± 1.23	7.58 ± 3.49	1.70 ± 0.49	63.41 ± 24.96	
Yilmaz, 2005b	b	6.45 ± 1.86	10.73 ± 7.68			2.89 ± 1.63
	a	6.20 ± 2.39	9.79 ± 8.05			2.71 ± 1.17
Hasan, 2018	b					
	a					
Singh, 2012	b					
	a					
Ozgurtas, 2008	b	5.43 ± 1.77	9.19 ± 1.79	3.44 ± 0.26	30.59 ± 7.21	2.90 ± 0.30
	a	5.52 ± 1.95	7.51 ± 3.44	3.24 ± 1.08	31.48 ± 6.79	2.80 ± 0.40

All values were rounded to 2 decimal places for consistency
* Change after metformin treatment had a significance of $p < 0.05$
Abbreviations: before metformin treatment (b), after metformin treatment (a), total testosterone (T), androstenedione (A)

Table 3. Metabolic indicators measured in included studies

Author and publication year	Groups	BMI (kg/m²)	G (mg/dL)	I (μIU/mL)	HOMA-IR
Sahin, 2007	b	22.40 ± 2.10	90.40 ± 7.80	9.80 ± 6.10	1.90 ± 1.20
	a	22.30 ± 2.60	85.50 ± 5.20*	14.10 ± 8.80	2.80 ± 1.80
Tan, 2007	b	22.00 ± 1.60	84.60 ± 8.60	7.70 ± 4.20	1.70 ± 1.00
	a	21.60 ± 1.60	82.60 ± 8.20	5.40 ± 3.90*	1.10 ± 0.70*
Kumari, 2005	b	24.30 ± 4.30		12.00 ± 3.20	
	a	22.10 ± 3.20		9.10 ± 1.20*	
Kialka, 2016	b	21.19 ± 1.27	86.40 ± 10.80	14.40 ± 5.50	
	a	20.95 ± 1.23	84.10 ± 6.10	10.20 ± 3.50*	
Orio, 2005	b	22.40 ± 2.10	109.90 ± 37.80	18.80 ± 5.50	
	a	22.20 ± 2.30	93.60 ± 28.80	8.20 ± 3.50*	
Yilmaz, 2005a	b	22.16 ± 3.57			3.18 ± 1.19
	a	20.08 ± 3.14*			2.32 ± 0.87*
Christakou, 2014	b	23.03 ± 0.67			
	a	22.44 ± 0.67			
Foda, 2019	b	24.66 ± 0.33	108.02 ± 7.87	12.36 ± 2.43	3.33 ± 0.87
	a	24.47 ± 0.25	84.23 ± 6.53*	8.54 ± 0.95*	1.79 ± 0.32*
Koiou, 2011	b	23.20 ± 4.40	99.80 ± 16.30	18.40 ± 30.40	4.40 ± 6.40
	a	22.90 ± 3.00*	87.00 ± 7.30*	10.80 ± 9.30	2.30 ± 1.90
Soldat-Stanjovic, 2021	b	20.96 ± 2.04	84.10 ± 7.70	9.80 ± 3.73	2.03 ± 0.76
	a	20.61 ± 1.79	80.10 ± 10.60	8.69 ± 2.61	1.76 ± 0.60
Yilmaz, 2005b	b	21.51 ± 1.74	80.51 ± 7.36	11.88 ± 5.46	2.29 ± 0.81
	a	20.12 ± 1.57*	80.09 ± 7.23	7.96 ± 2.92*	1.48 ± 0.56*
Hasan, 2018	b	23.17 ± 0.94	84.05 ± 7.40	9.84 ± 2.55	2.90 ± 0.70
	a	23.05 ± 0.90	53.52 ± 6.74	7.04 ± 2.26*	1.47 ± 0.49
Singh, 2012	b				3.62 ± 1.38
	a				2.90 ± 0.04*
Ozgurtas, 2008	b	21.81 ± 1.27			
	a	21.12 ± 1.06*			

All values were rounded to 2 decimal places for consistency
* Change after metformin treatment had a significance of $p < 0.05$
Abbreviations: before metformin treatment (b), after metformin treatment (a), fasting blood glucose (G), fasting blood insulin (I)

Follicle-Stimulating Hormone (FSH)

FSH levels were measured in 10 articles, with significant changes observed in two of them [3,39]. Three of the 10 articles observed increases in FSH levels, with Foda et al. finding a significant increase from 4.11 ± 0.35 mIU/mL to 4.37 ± 0.40 mIU/mL following metformin treatment [39]. Conversely, Kumari et al. noted a significant decrease in FSH after metformin treatment, from 6.30 ± 1.62 mIU/mL to 5.20 ± 1.60 mIU/mL.

Luteinizing Hormone (LH)

LH levels were measured in 10 articles, with significant reductions observed in four of them [3,34,35,39]. Nine of the articles reported decreases in LH, although these findings are also not consistent with Koiou et al., who observed an increase in LH levels from 10.90 ± 6.80 mIU/mL to 12.60 ± 13.50 mIU/mL, though not significant [40].

Total Testosterone (T)

Total testosterone was found to be reduced after metformin treatment in all 9 articles it was measured in, though significant reductions were observed in only 6 of them [3,4,35,38–40].

Sex Hormone Binding Globulin (SHBG)

SHBG levels were measured before and after metformin treatment in six articles, with significant changes observed in three of them [35,36,38]. Of the three articles, both Kialka et al. and Orio et al. measured significant increases in SHBG levels [35,36], while Christakou et al. observed a significant decrease after metformin treatment, from 45.80 ± 3.40 nmol/L to 44.90 ± 3.00 nmol/L [38].

Androstenedione (A)

Androstenedione levels were reported in seven articles, with reductions in all of them, though none were found to be statistically significant.

Body Mass Index (BMI)

BMI was measured in 13 articles. The change in BMI after metformin treatment was found to be statistically significant in five of these articles [37,38,40,42,45].

Fasting Blood Glucose (G)

Fasting blood glucose levels were measured in nine of the articles observed, with significant reductions demonstrated in three of them [34,39,40]. The articles reporting significant reductions generally had higher starting glucose concentrations, with the exception of Orio et al., which reported the greatest deviations in measurements [36].

Fasting Blood Insulin (I)

Fasting blood insulin levels were measured in 10 articles, with significant reductions observed in seven of them [3,34–36,39,42,43]. Only Sahin et al. reported an increase in insulin after metformin treatment, from 9.80 ± 6.10 µIU/mL to 14.10 ± 8.80 µIU/mL [34].

HOMA-IR

HOMA-IR measured before and after metformin treatment in 10 articles, with significant reductions observed in six of them [37,39,42,42–44]. Of note, all articles that observed significant decreases in HOMA-IR also observed significant decreases in fasting blood insulin levels.

Discussion

Metformin, a widely used insulin sensitizing agent, was investigated for its effects on insulin resistance and hyperandrogenism in lean women with PCOS. Significant changes in total testosterone, SHBG, blood insulin, and HOMA-IR were reported in majority of the studies included. Some also observed significant changes in BMI, LH, and blood glucose levels. Meanwhile, only 2 out of the 10 studies measuring FSH levels reported significant changes, while androstenedione levels were not significantly reduced after metformin treatment in any of the included studies.

This study found significant changes in blood insulin and HOMA-IR in most observed articles. The beneficial effect of metformin observed in PCOS symptomology could be due to metformin's effect on insulin receptors, reducing both insulin and proinsulin production [46,47]. Muscle sensitivity to insulin also improves, increasing insulin-stimulated systematic glucose disposal and leading to more efficient glucose uptake [48–50]. The specific mechanism for metformin's action remains unclear. Body of evidence has elucidated the role of AMP-activated protein kinases (AMPK) through complex I of mitochondrial oxidative phosphorylation, which activate in response to metformin-induced reductions of AMP/ATP ratios [51–53]. However, Foretz et al. demonstrated that metformin acts on an AMPK-independent pathway, reducing ATP concentrations in liver kinase B1 (LKB1)-dependent pathways and resulting in CREB regulated transcription coactivator 2 (CRTC2) production [54]. CRTC2 then causes the inhibition of gluconeogenic genes in the liver. Alternatively, Foretz et al. also demonstrated that metformin can inhibit gluconeogenesis in LKB1- and AMPK- independent pathways, suggesting an action of metformin through the regulation of gluconeogenesis flux [54]. Metformin ultimately increases peripheral insulin sensitivity and reduces insulin resistance, with some literature suggesting that the reduction is greater in lean PCOS women [55].

Blood glucose levels were not consistently reduced by significant amounts when compared to insulin levels. The results observed may be due to the pathophysiology of lean PCOS patients compared to obese patients, as studies have suggested that lean women with PCOS have similar blood

glucose concentrations when compared to BMI-matched controls [50,55]. A further examination of the measured indicators in lean PCOS patients against BMI-matched controls in each study may help clarify these findings.

In this study, SHBG levels changed significantly after metformin treatment in half of the articles examined. Low levels of SHBG are known to be associated with type 2 diabetes mellitus [56,57], and it has been suggested that hyperinsulinemia directly inhibits hepatic SHBG synthesis [56], though the mechanism is not well-known. *In vitro* experiments in human hepatoma cell lines demonstrated that insulin and prolactin inhibited SHBG production [58]. Later *in vivo* experiments by Nestler et al. further demonstrated that insulin-reduction therapy directly increased serum SHBG levels when ovarian steroidogenesis was inhibited, suggesting that the rise in SHBG levels were due solely to the suppression of insulin release [59]. However, it is unclear whether reductions in SHBG levels are directly due to decreases in endogenous insulin production, or rather general improvements in insulin resistance [60,61]. Selva et al. found that regulation of SHBG production in the liver was not affected by insulin, but rather a monosaccharide-induced downregulation of HNF-4α [60]. Metformin has been shown to downregulate HNF-4α expression via an AMPK signalling pathway, which may explain the decrease in SHBG levels observed after metformin therapy [62,63]. This study also demonstrated that changes in SHBG levels were inconsistent between articles observed. This may be due to markedly higher SHBG levels in lean PCOS women compared to their obese counterparts [64–66], leading to less significant changes after metformin therapy.

A significant decrease in total testosterone levels was reported in most observed studies. This supports the observation that decreases in testosterone levels are more pronounced in lean PCOS women compared to obese women [67]. Insulin has been shown to stimulate the activity of CYP450 through direct and indirect mechanisms [28,68,69]. Metformin treatment reduces LH pulse amplitude [70], potentially reducing the activation of CYP450 by LH. In theca cells, insulin also increases the sensitivity of theca cells to LH, enabling the co-activation of CYP450 expression [71,72]. Moreover, insulin may stimulate testosterone biosynthesis directly by activating its own receptor and inducing signal transduction via inositolglycan mediators [73]. Metformin may also have a direct inhibitory effect on androgen synthesis [74,75]. Hirsch et al. demonstrated that metformin can directly inhibit the mitochondrial complex I, decreasing the expression of 17-Hydroxylase/17,20 lyase and 3-hydroxysteroid dehydrogenase type 2, steroid enzymes involved in androgen biosynthesis [76]. These mechanisms may also account for the consistent, though not significant, decreases in androstenedione observed [75].

Elevated LH levels due to higher LH pulse amplitudes are also well documented in PCOS. This is possibly due to the increased sensitivity of the pituitary gland to GnRH [77–79], although it is unclear whether this hypothalamic-pituitary hyperactivity is intrinsic in PCOS [77,80]. Insulin signalling has been shown to be an indirect factor on LH synthesis in PCOS, as insulin can have direct effects on GnRH neurons and stimulate GnRH gene expression [25,26]. However, it is unclear whether the mechanism of metformin's action on LH levels is related to improvements in insulin resistance or hyperinsulinemia [29]. It has been suggested that metformin may target the hypothalamic-pituitary unit directly, reducing the strength of GnRH signalling and, subsequently, LH synthesis [30,70]. Alternatively, metformin may exert its actions on the ovary directly by attenuating CYP450 activity [75,81], leading to decreased testosterone biosynthesis that then corrects inappropriate LH secretion [27]. The efficacy of metformin in reducing LH levels is also variable, with some studies demonstrating significant changes [30,81,82], while others show little change [83–85]. This may be more variable in lean PCOS patients, as BMI has been shown to influence LH pulse amplitude in PCOS women [86–88]. This studies' results are reflective of this, as they demonstrate the inconsistency of significant changes in LH levels among lean PCOS women.

Conversely, FSH levels were unaffected in nearly all the articles observed in this study. In PCOS women, baseline FSH levels are known to be slightly decreased or unchanged compared to normal women [89,90]. This may be attributable to the differential regulation of FSH synthesis by GnRH, which has been shown to be less effective at stimulating FSH with increased concentrations in comparison to LH [91,92]. Further, estradiol and progesterone are typically found at higher levels in PCOS women due to increased aromatase activity [77,93]. This may contribute to a regulation of FSH levels by preferential negative feedback [94–96], although it is unclear whether our data supports this. An expanded study to include the analysis of more sex hormones may clarify this in the future.

The strengths of this review include its rigorous, specific criteria for the studies included, and its focus on assessing metformin in relation to lean women with PCOS only. There are, however, several limitations. For one, the studies included in this review use BMI measures to separate lean from obese PCOS women. BMI divides weight in kilograms by height in meters squared, and does not account for body fat versus muscle content [97]. This can lead to a more pronounced presentation of obesity in taller, more muscular people and a diminished presentation in shorter people [97]. Thus, its use as a means to determine obesity in scientific studies is controversial, and may have affected this review's conclusions on the significance of metformin's side effects. However, other metrics of body weight such as PBF (percent body fat) and BAI (body adiposity index) have not been found to be consistently more accurate at predicting the risk of diabetes or cardiovascular diseases than BMI [98]. As such, BMI is

still the most widely used metric of body fat and arguably the most reliable, hence its use in this literature review. Additionally, many of the studies included in this review used small sample sizes, ranging from 15-44 participants in each study. This makes it more difficult to interpret the significance of the data reliably or account for potential risks and inaccuracies due to chance. This review also would have benefitted from a comparison between metformin's effects on obese and lean PCOS women, in order to further elucidate the differences between metformin's treatment of insulin resistance in each demographic. Finally, since the p values reported in each study were used to determine the significance of results rather than conducting our own significance testing to verify parameters, no conclusions could be drawn. Further research should be conducted to determine the significance of metformin's impact in lean women with PCOS.

Conclusion

This review demonstrates the efficacy of metformin in improving total testosterone, SHBG, and insulin resistance in a majority of studies in lean PCOS patients. Metformin also improved BMI, LH, and blood glucose levels, although in a smaller percentage of studies. The results indicate that metformin may be an effective treatment choice in cases with significant insulin resistance and hyperandrogenism, though the specific benefits in lean PCOS patients need to be further elucidated. Further, studies into the efficacy of metformin treatment in lean PCOS patients without insulin resistance, or with other desired therapeutic outcomes, is required. More studies with larger trial populations, randomized placebo-controlled, double-blind protocols should be carried out to examine the effects of metformin on a larger range of desired treatment outcomes in PCOS women.

List of Abbreviations

A: androstenedione
AMPK: AMP-activated protein kinases
BID: twice a day
BMI: body mass index
CRTC2: CREB regulated transcription coactivator 2
CYP450: Cytochrome P450c17
FSH: follicle-stimulating hormone
G: fasting blood glucose
GnRH: gonadotropin-releasing hormone
HOMA-IR: homeostatic model assessment for insulin resistance
I: gasting blood insulin
IR: insulin resistance
LKB1: liver kinase B1
PCOS: polycystic ovary syndrome
PI3-K: phosphatidylinositol 3-kinase
SHBG: sex hormone binding globulin
T: total testosterone
TID: three times a day

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

No patient consent or ethical approval was required because analyses were based on previous published studies.

Authors' Contributions

RG: made substantial contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
NS: made substantial contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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References

[1] Goyal M, Dawood AS. Debates regarding lean patients with polycystic ovary ayndrome: A narrative review. J Hum Reprod Sci. 2017;10(3):154–61. https://doi.org/10.4103/jhrs.jhrs_77_17
[2] Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. Reprod Health. 2021 Aug 18;18(1):171. https://doi.org/10.1186/s12978-021-01207-7
[3] Kumari A, Haq A, Jayasundaram R, Abdel-Wareth L, al Haija S, Alvares M. Metformin monotherapy in lean women with polycystic ovary syndrome. Reprod Biomed Online. 2005 Jan;10(1):100–4. https://doi.org/10.1016/s1472-6483(10)60809-7
[4] Tan S, Hahn S, Benson S, Dietz T, Lahner H, Moeller LC, et al. Metformin improves polycystic ovary syndrome symptoms irrespective of pre-treatment insulin resistance. Eur J Endocrinol. 2007 Nov 1;157(5):669–76. https://doi.org/10.1530/eje-07-0294
[5] The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004 Jan 1;19(1):41–7. https://doi.org/10.1016/j.fertnstert.2003.10.004
[6] Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): The hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev. 2016 Oct 1;37(5):467–520. https://doi.org/10.1210/er.2015-1104

[7] Diamanti-Kandarakis E. Polycystic ovarian syndrome: pathophysiology, molecular aspects and clinical implications. Expert Rev Mol Med. 2008 Jan 30;10:e3. https://doi.org/10.1017/s1462399408000598
[8] Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989 Sep;38(9):1165–74. https://doi.org/10.2337/diab.38.9.1165
[9] Dunaif A, Segal KR, Shelley DR, Green G, Dobrjansky A, Licholai T. Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. Diabetes. 1992 Oct;41(10):1257–66. https://doi.org/10.2337/diab.41.10.1257
[10] Ciaraldi TP, el-Roeiy A, Madar Z, Reichart D, Olefsky JM, Yen SS. Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. J Clin Endocrinol Metab. 1992 Aug;75(2):577–83. https://doi.org/10.1210/jcem.75.2.1322430
[11] Nosadini R, Avogaro A, Trevisan R, Valerio A, Tessari P, Duner E, et al. Effect of metformin on insulin-stimulated glucose turnover and insulin binding to receptors in type II diabetes. Diabetes Care. 1987 Feb;10(1):62–7. https://doi.org/10.2337/diacare.10.1.62
[12] Kahn CR. The molecular mechanism of insulin action. Annu Rev Med. 1985;36:429–51. https://doi.org/10.1172/jci113711
[13] Fornes R, Ormazabal P, Rosas C, Gabler F, Vantman D, Romero C, et al. Changes in the expression of insulin signaling pathway molecules in endometria from polycystic ovary syndrome women with or without hyperinsulinemia. Mol Med. 2010 Mar;16(3):129–36. https://doi.org/10.2119/molmed.2009.00118
[14] Zhai J, Liu C xi, Tian Z rong, Jiang Q hui, Sun Y pu. Effects of Metformin on the Expression of GLUT4 in Endometrium of Obese Women with Polycystic Ovary Syndrome1. Biol Reprod. 2012 Aug 1;87(2):29, 1–5. https://doi.org/10.1095/biolreprod.112.099788
[15] Chen YH, Heneidi S, Lee JM, Layman LC, Stepp DW, Gamboa GM, et al. miRNA-93 Inhibits GLUT4 and Is Overexpressed in Adipose Tissue of Polycystic Ovary Syndrome Patients and Women With Insulin Resistance. Diabetes. 2013 Jun 14;62(7):2278–86. https://doi.org/10.2337/db12-0963
[16] Dunaif A, Xia J, Book CB, Schenker E, Tang Z. Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. J Clin Invest. 1995 Aug;96(2):801–10. https://doi.org/10.1172/jci118126
[17] Li M, Youngren JF, Dunaif A, Goldfine ID, Maddux BA, Zhang BB, et al. Decreased insulin receptor (IR) autophosphorylation in fibroblasts from patients with PCOS: effects of serine kinase inhibitors and IR activators. J Clin Endocrinol Metab. 2002 Sep;87(9):4088–93. https://doi.org/10.1210/jc.2002-020363
[18] Dunaif A, Wu X, Lee A, Diamanti-Kandarakis E. Defects in insulin receptor signaling in vivo in the polycystic ovary syndrome (PCOS). Am J Physiol Endocrinol Metab. 2001 Aug;281(2):E392-399. https://doi.org/10.1152/ajpendo.2001.281.2.e392
[19] Højlund K, Glintborg D, Andersen NR, Birk JB, Treebak JT, Frøsig C, et al. Impaired insulin-stimulated phosphorylation of Akt and AS160 in skeletal muscle of women with polycystic ovary syndrome is reversed by pioglitazone treatment. Diabetes. 2008 Feb;57(2):357–66. https://doi.org/10.2337/db07-0706
[20] Ciaraldi TP, Aroda V, Mudaliar S, Chang RJ, Henry RR. Polycystic ovary syndrome is associated with tissue-specific differences in insulin resistance. J Clin Endocrinol Metab. 2009 Jan;94(1):157–63. https://doi.org/10.1210/jc.2008-1492
[21] Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ. Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. J Clin Endocrinol Metab. 1986 May;62(5):904–10. https://doi.org/10.1210/jcem-62-5-904
[22] Barbieri RL, Hornstein MD. Hyperinsulinemia and ovarian hyperandrogenism. Cause and effect. Endocrinol Metab Clin North Am. 1988 Dec;17(4):685–703. https://doi.org/10.1016/S0889-8529(18)30405-5
[23] Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol. 2010 Oct;122(1–3):42–52. https://doi.org/10.1016/j.jsbmb.2009.12.010
[24] Brüning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, et al. Role of brain insulin receptor in control of body weight and reproduction. Science. 2000 Sep 22;289(5487):2122–5. https://doi.org/10.1126/science.289.5487.2122
[25] Kim HH, DiVall SA, Deneau RM, Wolfe A. Insulin regulation of GnRH gene expression through MAP kinase signaling pathways. Mol Cell Endocrinol. 2005 Oct 20;242(1–2):42–9. https://doi.org/10.1016/j.mce.2005.07.002
[26] DiVall SA, Herrera D, Sklar B, Wu S, Wondisford F, Radovick S, et al. Insulin receptor signaling in the GnRH neuron plays a role in the abnormal GnRH pulsatility of obese female mice. PLoS ONE. 2015 Mar 17;10(3):e0119995. https://doi.org/10.1371/journal.pone.0119995
[27] Tosi F, Negri C, Perrone F, Dorizzi R, Castello R, Bonora E, et al. Hyperinsulinemia amplifies GnRH agonist stimulated ovarian ateroid aecretion in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2012 May 1;97(5):1712–9. https://doi.org/10.1210/jc.2011-29392

[28] Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med. 1996 Aug 29;335(9):617–23. https://doi.org/10.1056/nejm199608293350902

[29] Ulloa-Aguirre A, Portocarrero L, Zariñán T, Olivares A, Carranza-Lira S, Veldhuis JD, et al. Effects of metformin on inappropriate LH release in women with polycystic ovarian syndrome and insulin resistance. Reprod Biomed Online. 2006 Jan 1;12(6):669–83. https://doi.org/10.1016/s1472-6483(10)61079-6

[30] Genazzani AD, Strucchi C, Luisi M, Casarosa E, Lanzoni C, Baraldi E, et al. Metformin administration modulates neurosteroids secretion in non-obese amenorrhoic patients with polycystic ovary syndrome. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2006 Jan;22(1):36–43. https://doi.org/10.1080/09513590500476164

[31] Seli E, Duleba AJ. Should patients with polycystic ovarian syndrome be treated with metformin? Hum Reprod. 2002 Sep 1;17(9):2230–6. https://doi.org/10.1093/humrep/17.9.2230

[32] Sam S. Obesity and Polycystic Ovary Syndrome. Obes Manag. 2007 Apr;3(2):69–73. https://doi.org/10.1089%2Fobe.2007.0019

[33] Barrea L, Frias-Toral E, Verde L, Ceriani F, Cucalón G, Garcia-Velasquez E, et al. PCOS and nutritional approaches: Differences between lean and obese phenotype. Metab Open. 2021 Sep 13;12:100123. https://doi.org/10.1016%2Fj.metop.2021.100123

[34] Sahin Y, Unluhizarci K, Yilmazsoy A, Yikilmaz A, Aygen E, Kelestimur F. The effects of metformin on metabolic and cardiovascular risk factors in nonobese women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2007;67(6):904–8. https://doi.org/10.1111/j.1365-2265.2007.02985.x

[35] Kiałka M, Milewicz T, Sztefko K, Rogatko I, Majewska R. Metformin increases pressure pain threshold in lean women with polycystic ovary syndrome. Drug Des Devel Ther. 2016 Aug 3;10:2483–90. https://doi.org/10.2147/dddt.s109086

[36] Orio F Jr, Palomba S, Cascella T, De Simone B, Manguso F, Savastano S, et al. Improvement in endothelial structure and function after metformin treatment in young normal-weight women with polycystic ovary syndrome: Results of a 6-month study. J Clin Endocrinol Metab. 2005 Nov 1;90(11):6072–6. https://doi.org/10.1210/jc.2005-0965

[37] Yilmaz M, Bukan N, Ayvaz G, Karakoç A, Törüner F, Çakir N, et al. The effects of rosiglitazone and metformin on oxidative stress and homocysteine levels in lean patients with polycystic ovary syndrome. Hum Reprod. 2005 Dec 1;20(12):3333–40. https://doi.org/10.1093/humrep/dei258

[38] Christakou C, Kollias A, Piperi C, Katsikis I, Panidis D, Diamanti-Kandarakis E. The benefit-to-risk ratio of common treatments in PCOS: effect of oral contraceptives versus metformin on atherogenic markers. Horm Athens Greece. 2014 Dec;13(4):488–97. https://doi.org/10.14310/horm.2002.1553

[39] Foda AA, Foda EA, El-Negeri MA, El-Said ZH. Serum chemerin levels in Polycystic Ovary Syndrome after metformin therapy. Diabetes Metab Syndr Clin Res Rev. 2019 Mar 1;13(2):1309–15. https://doi.org/10.1016/j.dsx.2019.01.050

[40] Koiou E, Tziomalos K, Dinas K, Katsikis I, Kalaitzakis E, Delkos D, et al. The effect of weight loss and treatment with metformin on serum vaspin levels in women with polycystic ovary syndrome. Endocr J. 2011;58(4):237–46. https://doi.org/10.1507/endocrj.k10e-330

[41] Soldat-Stanković V, Popović-Pejičić S, Stanković S, Prtina A, Malešević G, Bjekić-Macut J, et al. The effect of metformin and myoinositol on metabolic outcomes in women with polycystic ovary syndrome: role of body mass and adiponectin in a randomized controlled trial. J Endocrinol Invest. 2022 Mar 1;45(3):583–95. https://doi.org/10.1007/s40618-021-01691-5

[42] Yilmaz M, Biri A, Karakoç A, Törüner F, Bingöl B, Çakir N, et al. The effects of rosiglitazone and metformin on insulin resistance and serum androgen levels in obese and lean patients with polycystic ovary syndrome. J Endocrinol Invest. 2005 Feb 1;28(2):1003–8. https://doi.org/10.1093/humrep/dei258

[43] Hasan MM, Abd El Hameed AA. Serum adipokine (apelin) in lean and obese polycystic ovary syndrome patients before and after metformin treatment. Middle East Fertil Soc J. 2018 Dec 1;23(4):315–8. https://doi.org/10.1016/j.mefs.2018.04.003

[44] Singh S, Akhtar N, Ahmad J. Plasma adiponectin levels in women with polycystic ovary syndrome: Impact of Metformin treatment in a case–control study. Diabetes Metab Syndr Clin Res Rev. 2012 Oct 1;6(4):207–11. https://doi.org/10.1016/j.dsx.2012.05.013

[45] Ozgurtas T, Oktenli C, Dede M, Tapan S, Kenar L, Sanisoglu SY, et al. Metformin and oral contraceptive treatments reduced circulating asymmetric dimethylarginine (ADMA) levels in patients with polycystic ovary syndrome (PCOS). Atherosclerosis. 2008 Oct 1;200(2):336–44. https://doi.org/10.1016/j.atherosclerosis.2007.12.054

[46] Lashen H. Role of metformin in the management of polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2010 Jun;1(3):117–28. https://doi.org/10.1177/2042018810380215

[47] Yan Y, Kover KL, Moore WV. New insight into metformin mechanism of action and clinical application [Internet]. Metformin. IntechOpen; 2020 [cited 2022 Aug 1]. Available from: https://www.intechopen.com/chapters/undefined/state.item.id

[48] Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med. 1995 Aug 31;333(9):550–4. https://doi.org/10.1056/nejm199508313330903

[49] Klip A, Leiter LA. Cellular mechanism of action of metformin. Diabetes Care. 1990 Jun;13(6):696–704. https://doi.org/10.2337/diacare.13.6.696

[50] DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. J Clin Endocrinol Metab. 1991 Dec;73(6):1294–301. https://doi.org/10.1210/jcem-73-6-1294

[51] Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001 Oct 15;108(8):1167–74. https://doi.org/10.1172/JCI13505

[52] El-Mir MY, Nogueira V, Fontaine E, Avéret N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem. 2000 Jan 7;275(1):223–8. https://doi.org/10.1074/jbc.275.1.223

[53] Foretz M, Ancellin N, Andreelli F, Saintillan Y, Grondin P, Kahn A, et al. Short-term overexpression of a constitutively active form of AMP-activated protein kinase in the liver leads to mild hypoglycemia and fatty liver. Diabetes. 2005 May;54(5):1331–9. https://doi.org/10.2337/diabetes.54.5.1331

[54] Foretz M, Hébrard S, Leclerc J, Zarrinpashneh E, Soty M, Mithieux G, et al. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. J Clin Invest. 2010 Jul 1;120(7):2355–69. https://doi.org/10.1172/JCI40671

[55] Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997 Dec;18(6):774–800. https://doi.org/10.1210/edrv.18.6.0318

[56] Wallace IR, McKinley MC, Bell PM, Hunter SJ. Sex hormone binding globulin and insulin resistance. Clin Endocrinol (Oxf). 2013 Mar;78(3):321–9. https://doi.org/10.1111/cen.12086

[57] Haffner SM, Katz MS, Stern MP, Dunn JF. The relationship of sex hormones to hyperinsulinemia and hyperglycemia. Metabolism. 1988 Jul 1;37(7):683–8. https://doi.org/10.1016/0026-0495(88)90091-1

[58] Plymate SR, Matej LA, Jones RE, Friedl KE. Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin*. J Clin Endocrinol Metab. 1988 Sep 1;67(3):460–4. https://doi.org/10.1210/jcem-67-3-460

[59] Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 1991 Jan;72(1):83–9. https://doi.org/10.1210/jcem-72-1-83

[60] Selva DM, Hogeveen KN, Innis SM, Hammond GL. Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone–binding globulin gene. J Clin Invest. 2007 Dec 3;117(12):3979–87. https://doi.org/10.1172/JCI32249

[61] Tong G, Hua X, Zhong Y, Zhang K, Gu G, Feng W, et al. Intensive insulin therapy increases sex hormone-binding globulin in newly diagnosed type 2 diabetic patients. Eur J Endocrinol. 2014 Feb 1;170(2):237–45. https://doi.org/10.1530/EJE-13-0557

[62] Chang HR, Nam S, Kook MC, Kim KT, Liu X, Yao H, et al. HNF4α is a therapeutic target that links AMPK to WNT signalling in early-stage gastric cancer. Gut. 2016 Jan 1;65(1):19–32. http://dx.doi.org/10.1136/gutjnl-2014-307918

[63] Jablonski KA, McAteer JB, de Bakker PIW, Franks PW, Pollin TI, Hanson RL, et al. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. Diabetes. 2010 Oct;59(10):2672–81. https://doi.org/10.2337/db10-0543

[64] Dunaif A, Mandeli J, Fluhr H, Dobrjansky A. The impact of obesity and chronic hyperinsulinemia on gonadotropin release and gonadal steroid secretion in the polycystic ovary syndrome. J Clin Endocrinol Metab. 1988 Jan;66(1):131–9. https://doi.org/10.1210/jcem-66-1-131

[65] Plymate SR, Fariss BL, Bassett ML, Matej L. Obesity and its role in polycystic ovary syndrome. J Clin Endocrinol Metab. 1981 Jun;52(6):1246–8. https://doi.org/10.1210/jcem-52-6-1246

[66] Kiddy DS, Sharp PS, White DM, Scanlon MF, Mason HD, Bray CS, et al. Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. Clin Endocrinol (Oxf). 1990 Feb;32(2):213–20. https://doi.org/10.1111/j.1365-2265.1990.tb00857.x

[67] Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2017 Nov 29;11(11):CD003053. https://doi.org/10.1002/14651858.CD003053.pub6

[68] Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17 alpha activity and serum androgens. J Clin Endocrinol Metab. 1997 Dec;82(12):4075–9. https://doi.org/10.1210/jcem.82.12.4431

[69] Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. Diabetologia. 2017 Sep;60(9):1656–61. https://doi.org/10.1007/s00125-017-4306-3

[70] Adashi EY, Hsueh AJ, Yen SS. Insulin enhancement of luteinizing hormone and follicle-stimulating hormone release by cultured pituitary cells. Endocrinology. 1981 Apr;108(4):1441–9. https://doi.org/10.1210/endo-108-4-1441

[71] Cadagan D, Khan R, Amer S. Thecal cell sensitivity to luteinizing hormone and insulin in polycystic ovarian syndrome. Reprod Biol. 2016 Mar 1;16(1):53–60. https://doi.org/10.1016/j.repbio.2015.12.006

[72] Willis D, Mason H, Gilling-Smith C, Franks S. Modulation by insulin of follicle-stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic ovaries. J Clin Endocrinol Metab. 1996 Jan;81(1):302–9. https://doi.org/10.1210/jcem.81.1.8550768

[73] Nestler JE, Jakubowicz DJ, Falcon de Vargas A, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system1. J Clin Endocrinol Metab. 1998 Jun 1;83(6):2001–5. https://doi.org/10.1210/jcem.83.6.4886

[74] Mansfield R, Galea R, Brincat M, Hole D, Mason H. Metformin has direct effects on human ovarian steroidogenesis. Fertil Steril. 2003 Apr 1;79(4):956–62. https://doi.org/10.1016/S0015-0282(02)04925-7

[75] Attia GR, Rainey WE, Carr BR. Metformin directly inhibits androgen production in human thecal cells. Fertil Steril. 2001 Sep;76(3):517–24. https://doi.org/10.1016/S0015-0282(01)01975-6

[76] Hirsch A, Hahn D, Kempná P, Hofer G, Nuoffer JM, Mullis PE, et al. Metformin inhibits human androgen production by regulating steroidogenic enzymes HSD3B2 and CYP17A1 and complex I activity of the respiratory chain. Endocrinology. 2012 Sep 1;153(9):4354–66. https://doi.org/10.1210/en.2012-1145

[77] Rebar R, Judd HL, Yen SS, Rakoff J, Vandenberg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. J Clin Invest. 1976 May;57(5):1320–9. https://doi.org/10.1172/JCI108400

[78] Smith PF, Frawley LS, Neill JD. Detection of LH release from individual pituitary cells by the reverse hemolytic plaque assay: estrogen increases the fraction of gonadotropes responding to GnRH. Endocrinology. 1984 Dec;115(6):2484–6. https://doi.org/10.1210/endo-115-6-2484

[79] Hayes FJ, Taylor AE, Martin KA, Hall JE. Use of a Gonadotropin-releasing hormone antagonist as a physiologic probe in polycystic ovary syndrome: Assessment of neuroendocrine and androgen dynamics1. J Clin Endocrinol Metab. 1998 Jul 1;83(7):2343–9. https://doi.org/10.1210/jcem.83.7.4925

[80] Cheung AP, Lu JK, Chang RJ. Pulsatile gonadotrophin secretion in women with polycystic ovary syndrome after gonadotrophin-releasing hormone agonist treatment. Hum Reprod Oxf Engl. 1997 Jun;12(6):1156–64. https://doi.org/10.1093/humrep/12.6.1156

[81] Genazzani A. Metformin administration modulates and restores luteinizing hormone spontaneous episodic secretion and ovarian function in nonobese patients with polycystic ovary syndrome. Fertil Steril. 2004 Jan;81(1):114–9. https://doi.org/10.1016/j.fertnstert.2003.05.020

[82] Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism. 1994 May;43(5):647–54. https://doi.org/10.1016/0026-0495(94)90209-7

[83] la Marca A, Egbe TO, Morgante G, Paglia T, Cianci A, De Leo V, et al. Metformin treatment reduces ovarian cytochrome P-450c17alpha response to human chorionic gonadotrophin in women with insulin resistance-related polycystic ovary syndrome. Hum Reprod Oxf Engl. 2000 Jan;15(1):21–3. https://doi.org/10.1093/humrep/15.1.21

[84] Morin-Papunen LC, Koivunen RM, Ruokonen A, Martikainen HK. Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. Fertil Steril. 1998 Apr;69(4):691–6. https://doi.org/10.1016/S0015-0282(98)00011-9

[85] De Leo V, La Marca A, Orvieto R, Morgante G. Effect of metformin on insulin-like growth factor (IGF) I and IGF-binding protein I in polycystic ovary syndrome. J Clin Endocrinol Metab. 2000 Apr;85(4):1598–600. https://doi.org/10.1210/jcem.85.4.6560

[86] Patel K, Coffler MS, Dahan MH, Malcom PJ, Deutsch R, Chang RJ. Relationship of GnRH-stimulated LH release to episodic LH secretion and baseline endocrine-metabolic measures in women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2004;60(1):67–74. https://doi.org/10.1111/j.1365-2265.2004.01945.x

[87] Arroyo A, Laughlin GA, Morales AJ, Yen SSC. Inappropriate gonadotropin secretion in polycystic ovary syndrome: Influence of adiposity1. J Clin Endocrinol Metab. 1997 Nov 1;82(11):3728–33. https://doi.org/10.1210/jcem.82.11.4377

[88] Taylor AE, McCourt B, Martin KA, Anderson EJ, Adams JM, Schoenfeld D, et al. Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1997 Jul;82(7):2248–56. https://doi.org/10.1210/jcem.82.7.4105

[89] Saadia Z. Follicle stimulating hormone (LH: FSH) ratio in polycystic ovary syndrome (PCOS) - Obese vs. non-obese women. Med Arch. 2020 Aug;74(4): 289–93. https://doi.org/10.5455/medarh.2020.74.289-293

[90] Balen AH, Laven JSE, Tan S, Dewailly D. Ultrasound assessment of the polycystic ovary: International consensus definitions. Hum Reprod Update. 2003 Nov 1;9(6):505–14. https://doi.org/10.1093/humupd/dmg044

[91] McCartney CR, Eagleson CA, Marshall JC. Regulation of gonadotropin secretion: Implications for polycystic ovary syndrome. Semin Reprod Med. 2002 Nov;20(4):317–26. https://doi.org/10.1055/s-2002-36706

[92] Stamatiades GA, Kaiser UB. Gonadotropin regulation by pulsatile GnRH: signaling and gene expression. Mol Cell Endocrinol. 2018 Mar 5;463:131–41. https://doi.org/10.1016/j.mce.2017.10.015

[93] McNeilly AS, Crawford JL, Taragnat C, Nicol L, McNeilly JR. The differential secretion of FSH and LH: regulation through genes, feedback and packaging. Reprod Camb Engl Suppl. 2003;61:463–76. https://doi.org/10.1530/biosciprocs.5.034

[94] Shaw ND, Histed SN, Srouji SS, Yang J, Lee H, Hall JE. Estrogen negative feedback on gonadotropin secretion: Evidence for a direct pituitary effect in women. J Clin Endocrinol Metab. 2010 Apr;95(4):1955–61. https://doi.org/10.1210%2Fjc.2009-2108

[95] Messinis IE. Ovarian feedback, mechanism of action and possible clinical implications. Hum Reprod Update. 2006 Sep 1;12(5):557–71. https://doi.org/10.1093/humupd/dml020

[96] Bhatnagar AS, Batzl C, Häusler A, Nogués V. The role of estrogen in the feedback regulation of follicle-stimulating hormone secretion in the female rat. J Steroid Biochem Mol Biol. 1993 Dec 1;47(1):161–6. https://doi.org/10.1016/0960-0760(93)90070-d

[97] Moosaie F, Fatemi Abhari SM, Deravi N, Karimi Behnagh A, Esteghamati S, Dehghani Firouzabadi F, et al. Waist-to-height ratio is a more accurate tool for predicting hypertension than waist-to-hip circumference and BMI in patients with type 2 diabetes: A prospective study. Front Public Health. 2021 Oct 7;9: 726288. https://doi.org/10.3389/fpubh.2021.726288

[98] Freedman DS, Thornton J, Pi-Sunyer FX, Heymsfield SB, Wang J, Pierson RN, et al. The body adiposity index (hip circumference ÷ height1.5) is not a more accurate measure of adiposity than is BMI, waist circumference, or hip circumference. Obes Silver Spring Md. 2012 Dec;20(12):2438–44. https://doi.org/10.1038/oby.2012.81

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