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Exploring the therapeutic potential of metformin in polycystic ovary syndrome: focusing on hyperandrogenism in a sample of Iraqi women

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Polycystic ovary syndrome (PCOS) is the most commonly diagnosed condition in women of reproductive age. This pathology may be linked to an intricate endocrine disorder, given its diverse nature and the unexplained circumstances surrounding its origins. The main clinical features of PCOS include reduced ovulation frequency, irregular menstrual cycles, decreased fertility, polycystic ovaries detected by ultrasound examination, and elevated levels of male hormones like testosterone, which causes excessive facial or body hair growth and acne.
The objective: **to examine the efficacy of metformin in diminishing hyperandrogenism and enhancing clinical outcomes in women diagnosed with PCOS.**
Materials and methods**. A total of 55 women diagnosed with PCOS were included in the study. The participants had a mean age of 31.70 ± 7.79 years, with a range between 18 and 45 years old. The diagnosis of PCOS was made based on the Rotterdam criteria. The patients took metformin, tablets, 500 mg twice a day with two main meals for 3 months. Serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), total and free testosterone were determined before treatment and 3 months after treatment.**
Results**. It was found that after taking metformin for 3 months, the concentrations of total testosterone and free testosterone significantly decreased compared to pre-treatment values ($p < 0.0001$). Similar changes were found in the levels of LH and FSH. Their values significantly decreased after 3 months of treatment compared to pre-treatment values ($p < 0.0001$).**
Conclusions**. Metformin treatment of PCOS induced significant reduction in serum luteinizing hormone, FSH, testosterone concentrations in the PCOS patient after three months treatment duration.**
Keywords: *polycystic ovary syndrome, metformin, hyperandrogenism, follicle-stimulating hormone, luteinizing hormone.*

Вивчення терапевтичного потенціалу метформіну при синдромі полікістозних яєчників: фокусування на гіперандрогенії на прикладі вибірки іракських жінок

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Синдром полікістозних яєчників (СПКЯ) найбільш часто діагностують у жінок репродуктивного віку. Ця патологія може визначатися як складний ендокринний розлад, враховуючи її різноманітну етіологію та не до кінця зрозумілі патогенетичні механізми. Основними клінічними ознаками СПКЯ є: зниження частоти овуляцій; нерегулярний менструальний цикл; зниження фертильності; полікістоз яєчників, виявлений за допомогою ультразвукового дослідження; підвищений рівень чоловічих гормонів, зокрема тестостерону, що спричиняє надмірний ріст волосся на обличчі або тілі та акне.
Мета дослідження: аналіз ефективності метформіну в зменшенні проявів гіперандрогенії та покращенні клінічних результатів у жінок із діагнозом СПКЯ.
Матеріали та методи. У дослідженні взяли участь 55 жінок із діагнозом СПКЯ. Середній вік учасниць становив 31,70 ± 7,79 року (від 18 до 45 років). Діагноз СПКЯ встановлювали на основі Роттердамських критеріїв. Пацієнтки приймали метформін, табл., по 500 мг двічі на добу під час двох основних прийомів їжі протягом 3 міс. До та через 3 міс. після лікування визначали в сироватці крові концентрації фолікулостимулюючого гормону (ФСГ), лютеїнізуючого гормону (ЛГ), загального та вільного тестостерону.
Результати. Встановлено, що після прийому метформіну впродовж 3 міс. концентрації загального та вільного тестостерону достовірно знизилися порівняно з показниками до лікування ($p < 0,0001$). Аналогічні зміни виявлено в рівнях ЛГ та ФСГ: їхні концентрації значуще знизилися після 3 міс. лікування порівняно з початковими значеннями ($p < 0,0001$).
Висновки. Лікування СПКЯ за допомогою метформіну індукує достовірне зниження рівнів ЛГ, ФСГ та тестостерону в сироватці крові у пацієнток із СПКЯ після тримісячного курсу терапії.
Ключові слова: *синдром полікістозних яєчників, метформін, гіперандрогенія, фолікулостимулюючий гормон, лютеїнізуючий гормон.*

Polycystic ovary syndrome (PCOS) is the predominant condition affecting females of reproductive age [1]. The issue may be linked to an intricate endocrine disorder, given its diverse nature and the unexplained circumstances surrounding its origins [2]. The main clinical features of PCOS include reduced ovulation frequency, irregular menstrual cycles, decreased fertility, polycystic ovaries detected by ultrasound, and elevated proportion of male hormones like testosterone, which is a potential contributor of excessive facial or body hair growth and acne [3]. Consequently, PCOS has notable and diverse clinical consequences, encompassing reproductive issues just like

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(hirsutism, infertility, hyperandrogenism), metabolic disturbances including insulin resistance, impaired glucose tolerance, type two diabetes mellitus, unfavorable cardiovascular risk profiles; and psychological aspects comprising depression and increased anxiety that can negatively impact quality of life [2]. The defining feature of PCOS is the presence of hyperandrogenic signs and clinical symptoms. The majority of women with PCOS exhibit clinical manifestations of hyperandrogenism, such as hirsutism, acne, greasy skin, and occasionally, male pattern balding or alopecia. Infrequently, individuals may experience virilizing symptoms, such as heightened muscular mass, depth of the voice, or clitoromegaly. However, the presence of these symptoms should lead to an investigation for an underlying ovarian or adrenal tumor, or a previously undiscovered congenital adrenal hyperplasia in its classic form [4]. PCOS is estimated to impact 116 million women globally, which accounts for around 3.4% of the female population, according to the World Health Organization [5].

Since the majority of research conducted in the Middle East use all three major diagnostic criteria for PCOS, it is possible to derive prevalence rates for females in the Middle East based on different criteria. A study conducted in Kurdistan, Iraq, found that polycystic ovary is a disorder that is influenced by age, with its prevalence decreasing as individuals become older [6]. The age group with the highest prevalence was 18–27 years, whereas the age group with the lowest prevalence was 38–47 years. No individuals diagnosed with polycystic ovarian syndrome were identified who were older than 48 years [6]. The origin of PCOS is still unknown, although it presents with numerous phenotypes including obesity and insulin resistance. Women diagnosed with PCOS typically exhibit a distinct metabolic profile, characterized by insulin resistance, central obesity, which manifest early in life [7]. Prolonged unveiling to these factors right through a woman's reproductive years can worsen the negative effects and increase their susceptibility to metabolic syndrome, cardiovascular diseases, and type 2 diabetic mellitus [8]. Polycystic ovarian syndrome is a multifactorial disorder characterized by increased levels of androgens, irregularities in menstrual cycles, and the presence of tiny cysts on one or both ovaries [9]. The disorder can be morphological (ovaries) or predominantly biochemical (hyperandrogenemia) [10]. Hyperandrogenism, a characteristic feature of PCOS, can lead to the suppression of follicular growth, the formation of small cysts in the ovaries, the absence of ovulation, and alterations in the menstrual cycle [11]. Consequently, serum free testosterone is considered the most sensitive indicator for diagnosing PCOS [12].

Pharmacotherapy is employed in the treatment of PCOS, encompassing the utilization of the hormonal contraceptives, insulin sensitizer (metformin), progestins, anti-androgens, and fertility medication (clomiphene citrate) [13]. Metformin is an oral medication commonly used as an antihyperglycemic agent and approved by the US Food and Administration (FDA) for the treatment of type 2 diabetic mellitus. Evidence has demonstrated the positive effects of metformin on insulin sensitivity in non-diabetic women with PCOS [14]. Metformin improves insulin sensitivity by reducing the production of new glucose, the formation of new lipids, and by promoting the absorption of glucose in the liver, skeletal muscle, adipose tissue, and ovaries. As women with PCOS have a heightened susceptibility to insulin resistance, metformin effectively enhances the process of insulin-mediated glucose elimination in women diagnosed with PCOS [15]. Preliminary investigations into the impact of metformin on women with PCOS have indicated a rise in insulin sensitivity, combined with a decline in insulin and androgen levels. The majority of studies have shown a reduction in the levels of freely circulating testosterone and androstenedione, as well as changes in adrenal androgen regulation and a decrease in the production of androgens inside the ovaries. Metformin inhibits the generation of ovarian androgens via affecting the steroidogenic acute regulatory protein and 17α-hydroxylase [16]. The study's significance lies in its capacity to offer useful insights on the efficacy and safety of metformin in the management of hyperandrogenism, a prevalent hormonal imbalance linked to PCOS.

The objective: to examine the efficacy of metformin in diminishing hyperandrogenism and enhancing clinical outcomes in women diagnosed with PCOS.

MATERIALS AND METHODS

This observational study was carried out in Tikrit Teaching Hospital, obstetrics and gynecology department, and in private clinic (Tikrit, Iraq) from November 2023 till May 2024. Prior to data collection, signed consent was obtained from each participant. The study protocol was approved by the Scientific Research Ethical Committee (SREC) in the college of pharmacy, Tikrit University (approval number SREC 7). A total of 55 women diagnosed with PCOS were included in the study, the diagnosis was based on Rotterdam criteria. The participants had a mean age of 31.70 ± 7.79 years, with range was between 18 and 45 years old. Participants underwent an in-depth interview, completing a detailed questionnaire form developed by the investigator, which included their age, weight, length, and other relevant information. Participants who fulfilled the inclusion criteria at the beginning of the study were given instructions to consume 500 mg metformin tablets twice daily, with their two main meals, for a duration of 3 months.

Inclusion criteria: women with irregular menstrual cycles and evidence of polycystic ovaries on ultrasound.

Exclusion criteria: pregnancy or lactation, diabetes mellitus type 1 or 2, patients with hyperprolactenimea, patients with hypothyroidism, patients with congenital adrenal hyperplasia, concurrent hormonal therapies.

Data collection. The study enrolled women who had polycystic ovaries as observed on ultrasonography. Each patient provided a comprehensive menstrual history, which included information about the age at which they first started menstruating (menarche), the characteristics of their menstrual cycle, and the length of time they had been unable to conceive (infertility duration). Data on previous occurrences and familial background of diabetes mellitus and hypertension were also gathered. The body mass index (BMI) was computed using the measured height and weight according to the formula:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2\ (\text{m}^2)}$$

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A clinical examination specifically targeting hirsutism was conducted. Appropriate examinations, such as ultrasound, were performed.

Sample collection and preparation. A venous puncture was performed on each individual involved in this trial to obtain a 5 ml blood sample before metformin medication and 3 months after the initial visit. The blood samples were collected and placed into test tubes. Once the blood had clotted, the serum was obtained by centrifuging the drawn blood sample at 4000 × g for 10 minutes in a gel tube. The separated serum was maintained in an Eppendorf tube and frozen at –20°C. The stored serum samples were intended for the measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and free testosterone levels.

Statistical analysis. Statistical analysis utilized SPSS software (version 22, IBM Corporation, NY). The comparison was conducted using t-test probability; p-value < 0.05 was deemed statistically significant, while a p-value < 0.01 was regarded extremely significant.

RESULTS AND DISCUSSION

Data regarding the demographics and characteristics of patients with PCOS

The demographic data and clinical characteristics factors of the research participants are presented in Table 1.

Table 1

Demographic data and the disease characteristics variables of participants (N = 55)

Parameters		Results
Age (years) (mean ± SD)		31.70 ± 7.79
BMI (kg/m^2) (mean ± SD)		30.05 ± 4.55
Disease duration category	< 5 years, n (%)	22 (40.00)
	≥ 5 years, n (%)	33 (60.00)
Family history of PCOS, n (%)		30 (55.00)
Presence of	Alopecia, n (%)	14 (25.00)
	Acne, n (%)	37 (67.00)
	Hirsutism, n (%)	55 (100.00)

Notes: BMI – body mass index; PCOS – polycystic ovary syndrome; SD – standard deviation.

Metformin's impact on testosterone levels in PCOS patients

According to Table 2, research found women with PCOS exhibited the highest average level of total testosterone (2.49 ± 0.74 ng/mL) prior to receiving metformin medication. Following treatment, this level reduced to 1.44 ± 0.47 ng/mL, with a significant (p < 0.0001) and noteworthy difference at the level –42.00%, which was determined between the two measurements. Women had the greatest average level of free testosterone prior to the treatment (14.33 ± 2.73 ng/mL), which subsequently reduced after the administration of metformin (10.53 ± 1.07 ng/mL) with a very significant correlation (p < 0.0001), a marked decline of –26.00% was detected between the baseline and follow-up measurements. Normal value of total testosterone is 0.4–0.9 ng/mL and for free testosterone is 0.8–9.2 ng/mL.

Metformin's impact on LH and FSH in PCOS patients

The current study's findings revealed that women with PCOS exhibited the greatest average levels of LH and FSH prior to receiving metformin treatment, measuring at 8.45 ± 2.58 and 9.19 ± 2.01 μIU/mL, respectively (Table 3). In comparison, after undergoing metformin treatment, these same women demonstrated a very significant (p-value < 0.0001) decrease regarding LH, FSH levels (–42.00%, –21.00%, respectively). Normal range in follicular phase for LH is 1.5–8 μIU/mL and for FSH is 2.9–12 μIU/mL.

Correlation between total and free testosterone serum levels after metformin treatment with BMI measured for women diagnosed with PCOS

Table 4 demonstrate the association between total testosterone, free testosterone serum level after metformin treatment, with BMI measured for each participant who took part in the research. The current investigations showed a non-significant negative correlation between total testosterone, free testosterone serum level and BMI scores after treatment (r = –0.054, p-value = 0.692; r = –0.187, p-value = 0.170; respectively).

Table 2

Metformin's effect testosterone concentration in PCOS patients

Parameters	PCOS patients (N = 55)		p-value	% of change
	Before treatment	After 3-month treatment		
Total testosterone level (ng/mL)	2.49 ± 0.74	1.44 ± 0.47	< 0.0001*	–42.00
Free testosterone level (ng/mL)	14.33 ± 2.73	10.53 ± 1.07	< 0.0001*	–26.00

Notes: values are presented as mean ± SD; * – very highly significantly different compared to baseline within the same group (p < 0.001).

Table 3

Metformin's effect on LH and FSH concentrations in PCOS patients

Parameters	PCOS patients (N = 55)		p-value	% of change
	Before treatment	After 3-month treatment		
LH (μIU/mL)	8.45 ± 2.58	4.91 ± 0.27	< 0.0001*	–42.00
FSH (μIU/mL)	9.19 ± 2.01	7.26 ± 0.70	< 0.0001*	–21.00

Notes: values are presented as mean ± SD; * – very highly significantly different compared to baseline within the same group (p < 0.001).

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Table 4

Metformin's impact on hormonal balance: BMI-Testosterone correlations in PCOS patients

Variable	Total testosterone level after treatment		Free testosterone level after treatment	
	r	p-value	r	p-value
BMI	–0.054	0.692	–0.187	0.170

Note: r – correlation coefficient.

PCOS is a multifactorial disorder distinguished by excess testosterone levels, irregular menstruation cycles, and the presence of tiny cysts on one or both ovaries. The condition can manifest as either morphological, characterized by the presence of polycystic ovaries, or predominantly biochemical, characterized by hyperandrogenemia. Hyperandrogenism, a characteristic feature of PCOS, can lead to the suppression of follicular development, the formation of small cysts in the ovaries, the absence of ovulation, and irregular menstrual cycles [10]. In the current research, the mean age was 31.70 ± 7.79 years. Hirsutism was observed in the entirety of the patient cohort (100.00%), this results is consistent to various previous studies [17, 18]. Hirsutism severity is potentially mediated by variations in 5α-reductase enzyme activity [12]. Additionally, the comorbidity of obesity and PCOS perpetuates menstrual dysregulation [19, 20]. In regard to the frequency of acne occurrence in all patients with PCOS, this study revealed that acne was more prevalent in patients with a frequency of 67.00%, compared to patients without acne, who had a frequency of 33.00%. This finding is consistent with the research conducted by S. Mukkamala et al., which also demonstrated that acne is the most common skin manifestation in the PCOS population [21]. PCOS patients have a cascade of skin abnormalities, such as hirsutism, acne, seborrhea, and androgenetic alopecia, due to the overproduction of androgens [22]. The current study demonstrated that metformin treatment led to a significant decrease in total testosterone levels in women with PCOS. Specifically, the levels decreased from 2.49 ± 0.74 to 1.44 ± 0.47 ng/mL. This finding aligns with a previous study by D. Kurzthaler et al., which also observed a decrease in testosterone and androgen levels after three months of metformin treatment in women with PCOS [23]. In the present research, we report initial findings suggesting that the drug's ability to reduce androgen and testosterone production may occur even more quickly, potentially within a few days. Due to the prevalence of hyperandrogenemia among patients participated in the current study, we cannot guarantee that our findings can be applied to normoandrogenemic women with PCOS who may not experience similar improvements. Despite the limited number of patients in this investigation, our sample size calculation was designed to detect within-group differences, with each subject serving as their own control. M. F. Sanoee et al. conducted a study to assess the impact of metformin therapy for three months (1500 mg/day) on clinical and hormonal measures in a cohort of women with PCOS [24]. The results showed that metformin dramatically decreased testosterone levels [24] in consistent with present study result.

Inquiring about the impact of metformin on LH and FSH levels in women diagnosed with PCOS. A. Ulloa-Aguirre et al. conducted a study showing that in a specific group of women with PCOS, the treatment of metformin for a duration of 3 months resulted in a reduction in LH secretion [25], this finding partially aligns with the results of the current study, which also observed a significant reduction in LH levels after three months of treatment. However, the current study found a significant reduction in FSH levels following metformin treatment. A study conducted in Iraq by L. Baqer et al. found that metformin decreased the average serum levels of LH and FSH following treatment, although the reduction did not reach a statistically significant level. This finding is inconsistent with the results of the current research, which showed a significant decrease in FSH levels [26]. The study found no significant correlation between total testosterone, free testosterone serum levels, and BMI scores after metformin treatment. Conversely, a study by R. Pasquali et al. reported a significant negative correlation between testosterone levels and BMI in patients [27].

CONCLUSIONS

The findings of our study have limited generalizability, and it is important to consider these limitations. The study is restricted by its small sample size. The study's duration may be too short to capture long-term outcomes. Metformin treatment of PCOS induced a significant reduction in serum LH, FSH and Testosterone levels in the PCOS patients after a 3-month treatment duration.

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