Research Article

Exploring the Effect of Telmisartan on Inflammatory, Oxidative, and Hormonal Markers in an Animal Model of Letrozole-induced Polycystic Ovarian Syndrome: Implications for Adolescents with Polycystic Ovarian Syndrome

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting adolescent girls of reproductive age, with a global prevalence of 5 to 20% and as high as 23% in North Africa and the Middle East, including Iraq, among adolescent girls who have features of hyperandrogenism and menstrual irregularities. The major way of diagnosing PCOS is the Rotterdam criteria, characterized by hyperandrogenism, irregular menstrual cycles, and changes in ovarian morphology. In adolescents, the diagnosis requires the fulfillment of criteria for both hyperandrogenism (either clinical or biochemical) and oligomenorrhea/amenorrhea, and ovarian indicators are not relevant. A poor response to standard treatment will necessitate exploring a therapeutic agent targeting a more specific molecular target. Recent data highlight the role of renin-angiotensin system in ovarian function and pathophysiology of PCOS. This study aims at assessing the effects of telmisartan in the letrazole-induced PCOS rat model by measuring levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, interleukin-10 (IL-10), and total antioxidant capacity (TAC). 28 female rats were divided into four groups, with seven rats per group (a control group, a PCOS group (induced by letrozole, 1mg/kg/day for 30 days), metformin group, and telmisartan group. This study showed that administration of letrozole leads to increased levels of LH, testosterone and reduced levels of FSH, IL-10, and TAC, mimicking PCOS features. These abnormalities can be restored by telmisartan at 10 mg/kg/day for 28 days, which reduces LH, testosterone, and enhances FSH, IL-10, and TAC. Such a result revealed that telmisartan has a promising role in COS treatment.

KEYWORDS: Polycystic ovary syndrome, telmisartan, letrozole, interleukin-10, oxidative stress.

1-INTRODUCTION

PCOS is a very common disorder in women of reproductive age, and its global prevalence is estimated at 5-20% [1]. The age standardized prevalence rate of PCOS in the region of North Africa and the Middle East, including Iraq is about 23% of adolescent girls who had features of hyperandrogenism and menstrual irregularities. This indicates the increased health burden associated with this disease, particularly among adolescents [2]. Rotterdam criteria were the most widely used in the diagnosis of PCOS as they confirm the diagnosis of PCOS when two of the three criteria; hyperandrogenism (clinical and/or biochemical), irregular cycles, and morphology of polycystic ovary, are satisfied. However, diagnosing PCOS during adolescence remains challenging because normal pubertal changes, including irregular menstrual cycles and polycystic ovarian morphology, can mimic PCOS. Therefore, current recommendations emphasize persistent menstrual irregularities and clinical and/or biochemical hyperandrogenism when evaluating adolescents for PCOS [3]. According to the Rotterdam criteria, PCOS cases are distinguished into four phenotypes, where phenotype A is linked to rather adverse metabolic and cardiovascular prognosis as compared to phenotype D, which is considered to be the mildest variant [3].

PCOS is identified by hyperandrogenism and persistent oligo-anovulation and various metabolic disorders, whose symptoms vary depending on the age of the patient [4]. The etiology of this condition is connected with genetic and environmental factors. Diet, unhealthy lifestyle, or any infectious mediators increase PCOS risk. The PCOS pathophysiology is complex and is largely associated with insulin resistance (IR). The ovarian functioning is disturbed by means of IR and its high level, therefore, causing an increased amount of androgen, which causes anovulation. PCOS is also characterized by the disruption of the level of gonadotropin-releasing hormone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) level [5]. Moreover, low-grade chronic inflammation and oxidative stress have primary roles in PCOS pathogenesis. Interleukin-10 (IL-10) was involved in the pathophysiology of PCOS. The IL-10 aids in ovarian homeostasis, corpus luteum maturation, and pregnancy maintenance through being anti-inflammatory. Its concentrations play an important role in the restoration of the inflammatory situation in such a range of diseases as PCOS. Low levels of serum and follicular fluid IL-10 have also been mentioned in PCOS patients. This inadequacy results into increased oxidative stress and inflammation, promoting excess of androgen and follicular dysregulation. Reduced IL-10 is also associated with the characteristics of metabolic syndrome and obesity in PCOS. At the same time, the lack of balance between production of reactive oxygen species (ROS) and

antioxidant defense mechanisms causes oxidative stress and exacerbates the state of insulin signaling, as well as damages ovarian tissues. Metabolic problems, impaired follicle development, and aggravated hyperandrogenism in PCOS are vicious cycles that are promoted by oxidative stress and inflammation [6] [7]. PCOS is not yet completely treatable. Clinical therapy focuses only on managing its symptoms. Early PCOS diagnosis can enable proper management of the disease using lifestyle modifications that might delay or prevent the onset of secondary diseases such as type 2 diabetes mellitus [8]. The treatment of PCOS is aimed at patient-centered approaches to improve the symptoms of hyperandrogenism, induce ovulation, regulate menstrual cycle, and prevent cardiometabolic complications.

Unfortunately, the ineffective response to traditional therapy might require the exploration of the therapeutic agents that focus on more specific molecular targets [9]. Recent report indicated that there is a relationship between major pathogenesis of PCOS and the renin-angiotensin system (RAS). Ovarian renin-angiotensin system is an important regulator of ovarian function and pathogenesis of most ovarian diseases [9]. The RAS regulates the electrolyte balance of the body, the volume of circulation, and the hemodynamic homeostasis. The human ovary has been found to contain all the RAS components and it plays an essential role in follicular atresia and folliculogenesis [10]. At different stages of oocyte development the ovarian follicular cells synthesize prorenin, the inactive renin. The levels of prorenin increase along with the development of the ovarian follicle and continue to stay high until the end of the luteal phase, coinciding with the onset of menstruation, after which they drop accordingly with the levels of progesterone. Prorenin is normally found in high concentration compared to renin in the reproductive system. PCOS is usually linked to follicular atresia. Angiotensin II (AT2) receptor isoform is the most expressed in atretic granulosa cells and has been demonstrated to induce apoptosis. FSH assumes a moderating role in inhibiting the expression of AT2R in follicles. In the luteal phase, the decrease in FSH will relieve inhibition of the AT2R expression. Consequently, the increased AT2 levels lead to granulosa cell apoptosis and thereby encourage immature atresia of follicles [11]. The plasma renin levels and activity, and plasma prorenin, were high in young women with PCOS. Similarly, PCOS women were found to have high levels of Ang II compared to the control patients. Moreover, it is possible to indicate that through the use of AT1R antagonists (ARBs) and the activation of AT2R, the normalization of androgen levels in PCOS women occurs [12]. Components of RAS are capable of inducing endothelial dysfunction in PCOS patient which is an early and reversible marker of cardiovascular disease. Androgens, as well as RAS components, are involved in atherogenesis in PCOS [13]. Telmisartan is an insulin-sensitizing drug through the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ). Telmisartan might also change the expression of PPAR-γ target genes involved in carbohydrate and lipid metabolism, thereby lowering the levels of glucose, insulin, and triglycerides. Moreover, telmisartan prevented androgen secretion and enhanced the menstrual cycles of women with PCOS [13]. RAAS is intimately associated with IR and inhibiting of RAAS reduces the probability of IR associated disease. Telmisartan may also certainly enhance IR and lower the level of insulin, alongside inhibiting RAAS [14]. These reasons may give rise to the need to investigate the molecular mechanism of how telmisartan may impact PCOS.

2-METHODOLOGY

Twenty-eight albino Wistar female rats of 120 to 180 gram, aged between 6-9 weeks were used in the study. They obtain from the Ministry of Science and Technology, Baghdad, Iraq. The animals were kept in the animal facility of the Faculty of Pharmacy of the University of Babylon.

The rats were maintained in plastic cages at 22-24°C, with a 12 hour light/dark cycle and with a humidity of 45 +/- 2%. The control group received a normal diet and the induction groups were fed with a high fat diet. One week of adaptive feeding was observed after which the twenty-eight rats were chosen at random in four experimental groups (n = 7 each):

Group I (control) was provided with a normal laboratory diet and water.
Group II (PCOS): PCOS was inducted in rats with letrozole at 1mg/kg/day in DMSO [15] by administration in 30 consecutive days, followed by no additional treatment [16].
Group III (PCOS + Metformin): In this group, all rats were received 300mg/kg/day of metformin dissolved in distilled water through oral gavage [17].

Group IV (PCOS + Telmisartan): Rats in group IV received a dose of 10mg/kg/day of telmisartan [18] dissolved in distilled water by oral gavage.

Telmisartan was obtained from MACKLIN Express in China as a powder (98% purity) and formulated into a solution with distilled water (D.W.). It was administered orally at a dose of 10 mg/kg. Based on rat weight, 20 mg of the drug was broken up in 7 mL of D.W., and each rat in group IV received 1 mL of the resulting solution orally once daily for 28 days. PCOS was induced in rats by giving a daily dose of letrozole (1 mg/kg) through gavage for 30 days [16]. The successful development of the PCOS model was verified through vaginal smear cytology. Vaginal smears were taken over the entire period between 17 and 30 days of letrazole treatment to observe irregularity of the estrous cycle and confirm the development of PCOS [19]. Vaginal smears were repeated at the end of the study to assess the effect of the treatment in restoring normal cyclicity. The stages of the cycle were discovered according to the cell

types: leukocytes dominate in the diestrus phase, nucleated epithelial cells in the proestrus phase, cornified epithelial cells in the estrus phase, and all three types of cells in the metestrus phase [19]. Anovulation was indicated by the continued presence of the same predominant cell type—such as leukocytes or keratinized epithelial cells—for at least 10 days, following established criteria [15].

At the end of the treatment, rats were anesthetized using the diethyl ether. blood was obtained by Cardiac puncture in order to isolate serum. Biochemical analysis of the serum was done by ELISA kits for IL-10, LH, FSH, and testosterone and total antioxidant capacity was evaluated by CUPRAC assay.

3-RESULTS AND DISCUSSION

Data entry, processing and analysis were done using the 25th version of the Statistical Package of the Social Sciences (SPSS). The study findings were compared using a one-way ANOVA and post hoc least significant difference test. The results were given out in the form of mean, standard deviation and standard error of the mean. Differences were considered as statistically significant at $p \leq 0.05$ and extremely significant at $p \leq 0.001$.

Telmisartan effect on the serum levels of testosterone, luteinizing hormone, and follicle-stimulating hormone.

The data in Figure 1, indicated that the levels of serum testosterone were different across the groups of the experiment. The testosterone levels of the letrozole group were found to increase by an extremely significant difference compared to the control group ($p < 0.001$). No significant differences between the metformin and the control groups and between the telmisartan and control groups. The results of the comparisons of the letrozole group with the metformin ($p = 0.004$) and the letrozole group with telmisartan ($p < 0.001$) were statistically significant. There was no significant difference between telmisartan and metformin. (Table 1).

Based on the data in Figure 2, there was a significant increase in the levels of LH in the letrozole group over the control group ($p = 0.012$). There were no significant differences between the control and the metformin and between the control and the telmisartan groups. There were also no statistically significant comparisons between the groups of letrozole and metformin and groups of letrozole and telmisartan. Also, no significant differences were found between metformin and telmisartan groups. (Table 2)

Figure 3 shows that there was a difference between serum FSH level in the experimental groups. The reduction in the FSH levels in the group taking letrozole was significant compared to that of the control group ($p = 0.001$). There were no significant differences between the control and the metformin and the control and the telmisartan groups. The comparisons between letrozole versus metformin and letrozole versus telmisartan were not all significant. Also, no considerable differences were found between metformin and telmisartan. (Table 3)

In the current study, the use of letrozole for 30 days causes the PCOS-like characteristics, such as the enhancement of LH levels, hyperandrogenism, and reduction of FSH. These results are similar to [20], which demonstrated that letrozole disrupts the hormonal balance, which encourages the development of PCOS. The study outcome showed that 28 days of telmisartan administration of 10 mg/kg/day had been linked to decreases in LH and testosterone levels and an increase in FSH levels as compared to the group receiving letrozole alone, probably by suppressing excessive renin-angiotensin system overstimulation. This followed many evidence that indicate that renin-angiotensin system is of great importance in the regulation of the hormones involved in the pathogenesis of PCOS [9] [21].

Telmisartan effect on serum levels of interleukin-10.
As shown in Figure 4, serum IL-10 levels differed among the experimental groups. IL-10 levels were extremely significantly lower in the letrozole group than in the control group ($p < 0.001$). No significant differences were observed between the control and metformin groups or between the control and telmisartan groups. Comparisons between the letrozole group and metformin ($p = 0.017$), and letrozole and telmisartan ($p = 0.027$) were statistically significant. Additionally, no significant differences were detected between metformin and telmisartan. (Table 4)

In the current study, the use of letrozole for 30 days was associated with increases systemic and ovarian inflammatory condition. These results are similar to [20], which demonstrated that letrozole disrupts the inflammatory homeostasis and produces PCOS-like features. It was revealed that the group subjected to telmisartan at 10mg/kg/day for 28 days had more IL-10 levels. These results are in agreement with [22], [23], [24], [25], that demonstrated the telmisartan suppresses angiotensin II-mediated inflammatory signaling and influencing the nuclear transcription pathway. By antagonizing angiotensin II type-1 (AT1) receptors, telmisartan inhibits the nuclear factor-kB (NF-KB) pathway, which is an essential mediator of pro-inflammatory cytokine gene transcription, and thereby suppresses the production of TNF-α. Moreover, the partial agonistic activity of telmisartan at the PPAR-y also suppresses the inflammatory gene transcription and reduces macrophage-derived cytokines synthesis. Furthermore, it has been demonstrated in experimental research that telmisartan inhibits inflammatory mediators such as cyclooxygenase-2 (COX-2), matrix metalloproteinase (MMP-2 and MMP-9), and RANK/RANKL signaling. Therefore,

by reducing levels of pro-inflammatory cytokines and mediators, telmisartan augments anti-inflammatory cytokines like IL-10, together altering the cytokine profile to an anti-inflammatory one. The fact that PPAR-γ expression is modulated in various inflammatory diseases gives solid justification for the use of powerful PPAR-γ ligands, including telmisartan, to suppress or alter the inflammatory pathogenesis. This observation indicates the therapeutic potential of PPAR-γ in inflammatory diseases, as its expression in most inflammatory diseases is altered. All these effects of telmisartan contribute to decrease tissue inflammation, independent of its role in blood pressure reduction.

Telmisartan effect on serum levels of total antioxidant capacity.
As shown in Figure 5, serum TAC levels differed among the experimental groups. The letrozole group showed a significant decrease in TAC levels compared with the control group ($p < 0.001$). No significant difference was observed between the control and metformin groups, whereas the difference between the control and telmisartan groups was significant ($p = 0.016$). Comparisons between the letrozole group and metformin and between the letrozole group and telmisartan were not statistically significant. Additionally, no significant differences were detected between metformin and telmisartan. (Table 5)

In the current study, the use of letrozole for 30 days was associated with reduced antioxidant ability and activity of key antioxidant enzymes, causing oxidative stress associated with PCOS pathophysiology. These results are similar to [20], which demonstrated that letrozole disrupts the oxidative homeostasis, which produces PCOS-like features. The outcome of this study indicated that telmisartan increased the levels of TAC, in agreement with [26], which indicated that telmisartan enhanced the activity of antioxidant enzymes, perhaps through acting as a partial PPAR-γ agonist. PPAR-γ receptors activation evokes the extracellular signal-regulated kinase mitogen-activated protein kinase cascade, promotes the differentiation of macrophages with upregulating the expression of CD36, and enhances cell survival in the presence of oxidative stress [27]. The action of telmisartan on antioxidant enzymes is significant since oxidative stress was also stated to have an effect on the pathogenesis of PCOS, possibly by inducing IR and worsening hyperandrogenism, apoptosis, and chronic inflammation [28].

4-CONCLUSION

The dual renin-angiotensin system/PPAR-γ activity of telmisartan has significant effects on the regulation of insulin sensitization, hormonal levels, inflammation, and oxidative stress. This renders it a promising agent in the management of PCOS.

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CONFLICT OF INTEREST STATEMENT: None to declare.

Table 1. Serum testosterone levels (ng/ml) of the experimental groups.

Groups	Mean	Std. Deviation	Std. Error
control	.95443	.300430	.113552
letrozole	2.78243*	.990898	.374524
Metformin	1.36757**	.799027	.302004
Telmisartan	1.06500***	.369242	.139561

Data are presented as mean, standard deviation, and standard error of the mean.
* Significant compared to the control group.
Significant compared to the letrozole group.**
***Significant compared to the letrozole group.

Table 2. Serum luteinizing hormone levels (IU/L) of the experimental groups.

Groups	Mean	Std. Deviation	Std. Error
control	1.08143	.443600	.167665
letrazole	2.00286*	.130220	.049218
Metformin	1.28471	.679065	.256662
Telmisartan	1.35829	.568590	.214907

Data are presented as mean, standard deviation, and standard error of the mean.

* Significant compared to the control group.

Table 3. Serum follicle-stimulating hormone levels (ng/ml) of the experimental groups.

Groups	Mean	Std. Deviation	Std. Error
control	5.34400	1.509180	.570416
letrazole	2.66443*	1.167979	.441455
Metformin	4.07057	.754058	.285007
Telmisartan	3.73300	.938001	.354531

Data are presented as mean, standard deviation, and standard error of the mean.

*Significant compared to the control group.

Table 4. Serum interleukin-10 levels (pg/ml) of the experimental groups.

Groups	Mean	Std. Deviation	Std. Error
control	80.40229	6.786096	2.564903
letrazole	55.21429*	7.908489	2.989128
Metformin	72.29129**	12.998091	4.912817
Telmisartan	71.31786***	9.645932	3.645819

Data are presented as mean, standard deviation, and standard error of the mean.
* Significant compared to the control group.
Significant compared to the letrozole group.**
*** Significant compared to the letrozole group.

Table 5. Serum total antioxidant capacity levels (mmol/L) of the experimental groups.

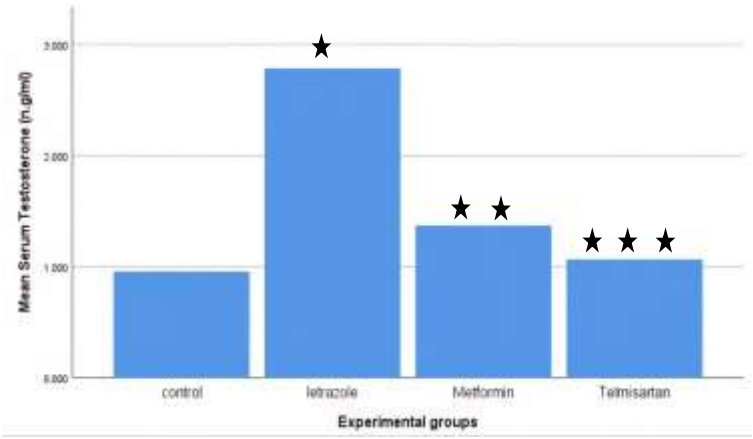
Groups	Mean	Std. Deviation	Std. Error
control	885.91957	187.479104	70.860441
letrazole	480.47371*	173.777979	65.681902
Metformin	685.21029	131.908074	49.856566
Telmisartan	614.14457+	98.436475	37.205490

Data are presented as mean, standard deviation, and standard error of the mean.

Significant compared to the control group.*

+Significant compared to the control group.

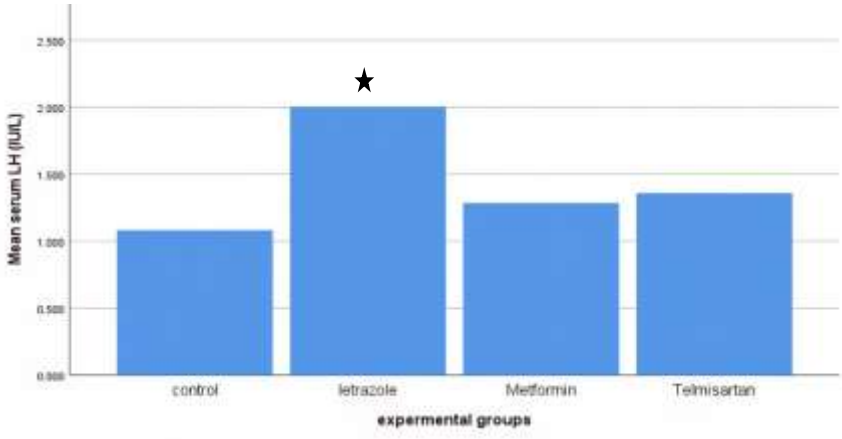
Figure 1. Serum Testosterone Level (ng/ml) of the experimental groups



* Significant compared to the control group.
Significant compared to the letrozole group.**

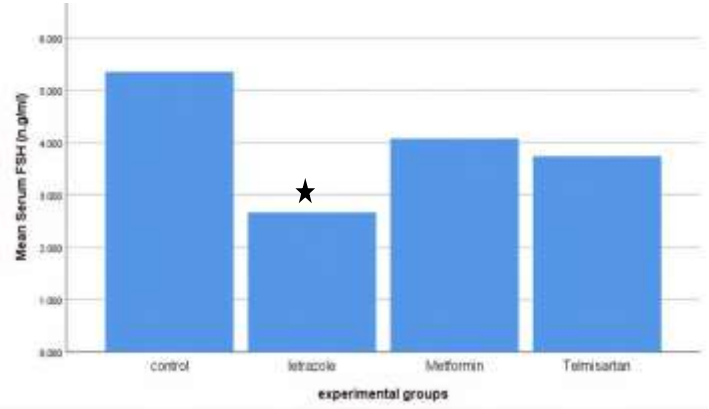
***Significant compared to the letrozole group.

Figure 2. Serum luteinizing hormone level (IU/L) of the experimental groups



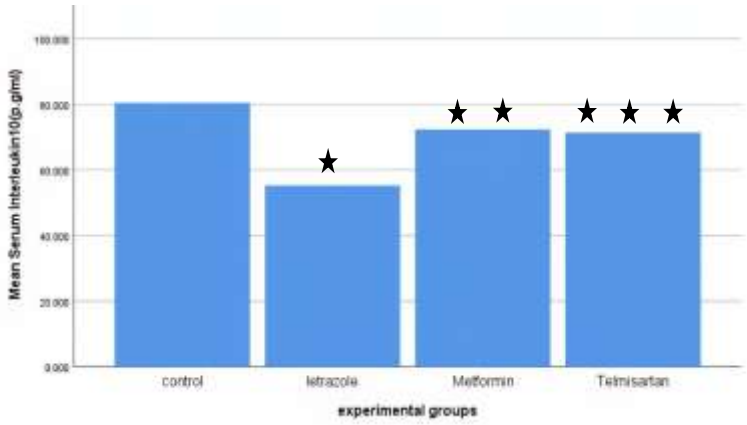
* Significant compared to the control group.

Figure 3. Serum Follicule stimulating hormone level (ng/ml) of the experimental groups



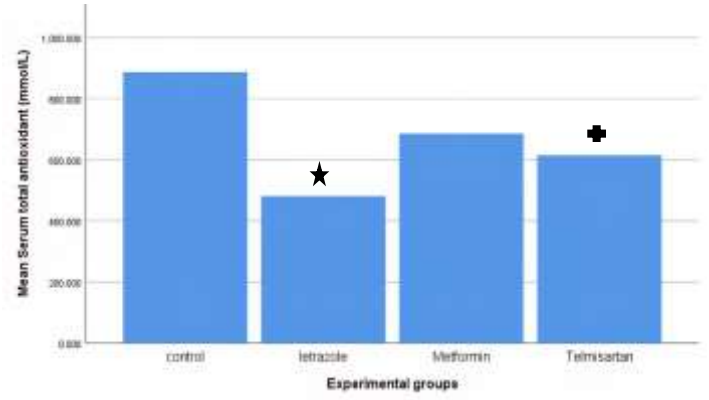
*Significant compared to the control group

Figure 4. Serum interleukin-10 level (pg/ml) of the experimental groups



* Significant compared to the control group.
Significant compared to the letrozole group.**
*** Significant compared to the letrozole group.

Figure 5. Serum total antioxidant level (mmol/L) of the experimental groups



*Significant compared to the control group.
+Significant compared to the control group.

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