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The Metformin-Induced Changes on BMI, TSH, and Thyroid Hormones Profile of Patients with Polycystic Ovarian Syndrome

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Abstract

Objective: The aim of this prospective study was to investigate the effect of metformin on BMI, TSH, thyroid hormones profile, and some clinical symptoms in 32 women with PCOS.

Methods: The patients received metformin at a dose of 500 mg/day which was gradually increased to 1500 mg/day and continued for 3 months. The level of BMI, TSH, T4, and T3 was measured at baseline, 3 months after treatment with metformin and 3 months after drug withdrawal. The association of metformin therapy with prevalence of constipation, hypersomnia, cold intolerance, and dry skin was also determined in these times.

Results: Three months after treatment with metformin, mean BMI and TSH was significantly decreased from baseline to 28.34±2.5 kg/m^2 and 2.27±0.89 μUI/ml, respectively. There was no significant difference in TSH levels before treatment and 3 months after drug withdrawal. Mean T3 and T4 levels was slightly increased during metformin therapy and significantly decreased after drug withdrawal. Treatment with metformin significantly decreased the prevalence of hypersomnia and dry skin in patients.

Conclusion: The effect of metformin on TSH and thyroid hormones profile gives us an idea about the efficacy of metformin as a sole therapy or as an adjuvant in patients with PCOS and subclinical hypothyroidism, respectively.

Keywords: BMI; Metformin; Polycystic ovary syndrome; Thyroid hormone; Thyroid stimulating hormone

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common hormonal and metabolic disorders that affects approximately 5-10% of reproductive-aged women and 20.5-24.5% of 15-19 year-old girls [1-3].

The prevalence of this heterogeneous clinical disorder is likely increasing because obesity and insulin resistance (IR), as the most important etiological factors of PCOS, have dramatically increased in this population [4]. This multigenic syndrome is characterized by clinical or biochemical hyperandrogenism, chronic anovulation, irregular menstruation, pregnancy loss, and infertility resulting in oligo- or amenorrhoea [5].

In addition, several documents demonstrated that many women with PCOS might have metabolic syndrome with reproductive morbidity such as hirsutism, hypertension, ischemic heart disease, diabetes, cardiovascular disease, sleep apnoea, dyslipidemia, and/or a pro-thrombotic state [3,6,7]. The severity of these symptoms in PCOS patients is varied and depends on the degree of hormonal or metabolic dysfunctions, age of women, genetic history, and the other co-morbid issues such as obesity, nutritional factors and lifestyle [1].

The etiology of PCOS is not clearly explained and its referred pathomechanism is very complicated. It is well documented that the insulin resistance seen in 60-70% of PCOS patients is a key etiological factor in development of all manifestations of PCOS.

In addition to increased risk of metabolic syndromes, IR can directly or indirectly lead to hyperinsulinemia, hyperandrogenemia, increased secretion of LH from adenohypophysis, and high LH/FSH ratio.

Furthermore, high levels of insulin can reduce sex hormone binding globulin (SHBG) and increase testosterone from the ovary, leading to irregular periods, miscarriages, hypertension, infertility, hirsutism, and PCOS [4,8-10].

Considering the importance of IR in the pathogenesis of PCOS, it is theoretically possible to improve this syndrome using IR-ameliorating drugs [8]. Metformin, as an insulin-sensitizing agent that inhibits hepatic gluconeogenesis and stimulates peripheral glucose uptake, is introduced for treatment of women with PCOS by improving of hepatic IR. This oral hypoglycemic biguanide can regulate the ovarian functions and induce regular menstrual cycles and ovulation in PCOS patients [3,11,12].

Although, the exact mechanism of metformin-induced therapeutic changes has not been well explained, the experimental studies recently demonstrate that the efficacy of metformin for ovulation induction in

PCOS patients is probably due to a direct inhibitory effect of drug on ovarian steroidogenesis in sensitive ovary, irrespectively to systemic effects [13-15]. In addition to improving the ovarian function and menstrual cycles, metformin enhances the sensitivity of skeletal muscles, reduces appetite, and improves metabolic abnormalities leading to low androgen levels [3,11].

Several studies confirmed the positive effect of metformin on many metabolic functions such as; increased insulin sensitivity, better blood glucose levels, lipid profile improvement, increased fatty acid oxidation, and decrease in weight, body mass index (BMI), blood pressure, and inflammation [3,11,16-18].

PCOS is a complex syndrome with different manifestations, because sometimes the other complications such as hypothyroidism occur with this syndrome in patients. Several documents demonstrated that approximately 43% of women with PCOS suffered from subclinical hypothyroidism [15,19] and treatment of this complication (hypothyroidism-PCOS) can be more difficult in women.

Recently, it has been reported that metformin is able to interfere with thyroid hormone profile and thyrotropin levels in obese diabetic women, especially type 2 diabetic patients, with primary hypothyroidism [20-22]. Therefore, it seems that the administration of metformin can be an effective therapeutic strategy to improvement of PCOS in patients suffered from or suspected to subclinical hypothyroidism.

Given that the prevalence of IR in pathogenesis of PCOS, the insulin-reducing effect of metformin, and its potential negative effect on TSH levels, we characterized the interplay between metformin therapy and circulating thyroid function parameters (T3 and T4) in PCOS patients at the beginning of treatment and three months after metformin administration.

In order to investigate the persistence of therapeutic effects of metformin in patients, we also investigated serum concentrations of T3 and T4 in 3 months after metformin withdrawal. As well as, the effect of treatment with metformin on TSH levels and BMI in women with PCOS was also considered in the above mentioned periods (before treatment, 3 months after metformin therapy, and 3 months after drug withdrawal).

In present study, we also evaluated the effect of metformin in prevalence of some hypothyroidism symptoms including constipation, hypersomnia, cold intolerance, and dry skin that were frequently seen in PCOS patients. These symptoms were considered as an indicator for successful treatment of metformin and examined after metformin therapy and drug withdrawal.

Material and Methods

This prospective study was performed on women with PCOS who were referred to public obstetric clinics in Hajar hospital, Shahrekord, Iran from September 2013 to March 2014. The study was approved by the Scientific Ethics Committee of Shahrekord University of Medical Sciences.

On the basis of inclusion and exclusion criteria and considering a 95% confidence interval with 80% power, 32 PCOS patients with the age of 31.2 ± 4.8 years were participated in this study.

All patients were invited to participate in this study and informed of our goals and objectives. An informed consent which had been approved by the Scientific Ethics Committee was provided before enrollment and all participants signed it before entering the study. PCOS was diagnosed in accordance with Rotterdam consensus diagnostic criteria [23].

According to the Rotterdam criteria, a woman must have two of the three following manifestations;

- Irregular ovulation (oligo- or anovulation) and oligo- or amenorrhoea (Less than 6-9 menses per year),
- Elevated levels of androgenic hormones (clinical or biochemical hyperandrogenism),
- Enlarged ovaries contain at least 12 follicles in each ovary (polycystic ovary in abdominal ultrasonography).

Considering the similarity of compound confounding variables, the patients were selected on the basis of similar variables including age, marriage duration, parities and abortion numbers, FSH and AMH levels, pregnancy history, occupation, and education levels.

Inclusion criteria were infertility for at least one year, having patent tubes on hysterosalpingogram, and normal semen analysis of the patients' partners. None of the women had received any hormonal or infertility therapies.

Exclusion criteria included patients with a history of liver and kidney failure, diabetes mellitus, cardiovascular disease, premature ovarian failure (POF), Cushing's syndrome, adrenal hyperplasia, pituitary tumors, and any androgen-secreting tumors. Polycystic ovaries with normal ovarian function and without hyperandrogenism were not considered as a PCOS without further workup. The patients were visited and examined by gynecologists. If pregnancy occurred, the patient was excluded from the study.

In present study, we rejected 68 patients of 100 women with PCOS who were referred to obstetric clinics and selected 32 satisfied patients based on inclusion and exclusion criteria (Figure 1).

The patients received one tablet (500 mg orally) metformin (Soojeh Company, Iran) per day at baseline, which was gradually increased to three tablets (1500 mg orally) per day over the succeeding two weeks. The treatment with high dose (1500 mg) was continued for 3 months in patients. The participants were also advised to continue their routine daily activities and nutrition but avoid smoking and drinking alcohol. As well as, patients did not receive any other medications for treatment of PCOS during the study.

At the end of treatment process, we evaluated BMI and serum concentration of TSH, T4 and T3 in patients at three stages; in the beginning of treatment (baseline), 3 months after treatment with metformin, and then 3 months after discontinuation of drug (metformin withdrawal).

In addition, we evaluated the most common signs of hypothyroidism including constipation, hypersomnia, cold intolerance, and dry skin before and after metformin therapy and compared the prevalence of those symptoms with 3 months after drug withdrawal in patients.

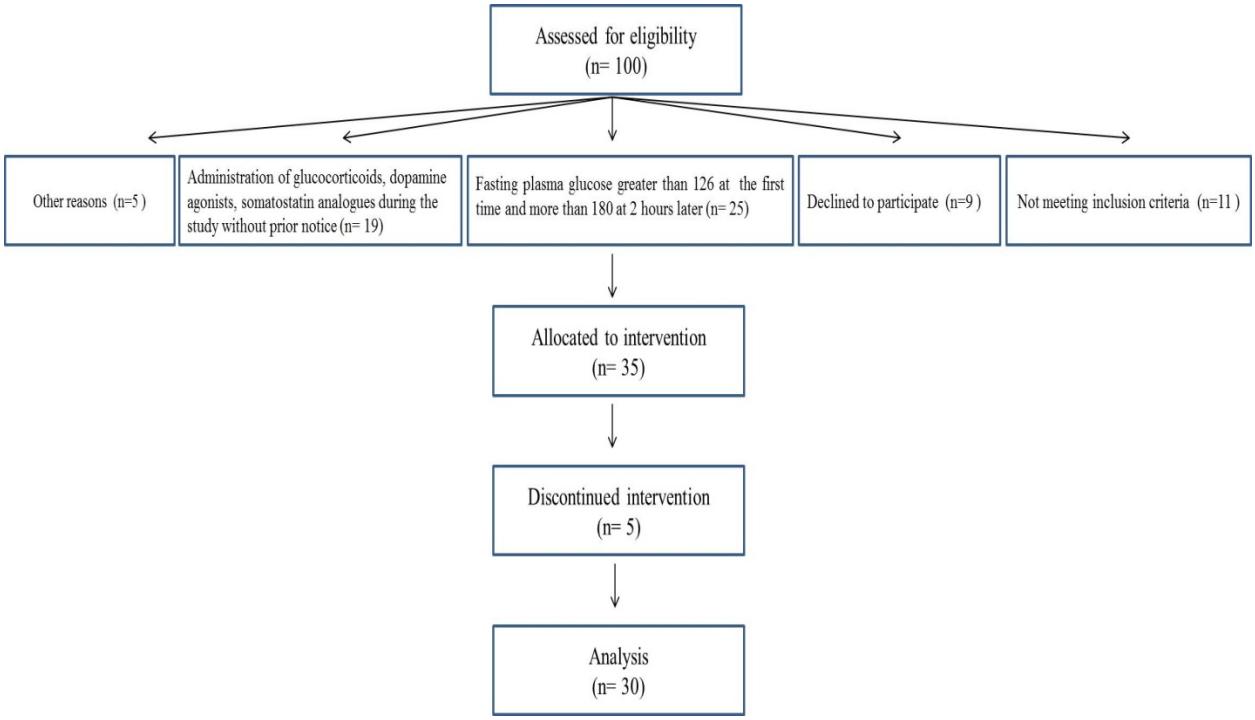

Figure 1: Flow chart of the study patients.

Statistical Analysis

The results were expressed as mean ± SD. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software, version 16. Data was analyzed with repeated measured and Cochrans Q test were used. A value of $P<0.05$ was defined as statistical significance.

Result

Effect of metformin on clinical symptoms in PCOS patients

Demographic data and baseline characteristics of participants in this study were demonstrated in Table 1. The average age and weight of women who participated in the study were 31.2 ± 4.8 years and 163.2 ± 3.9 kg, respectively.

There was a significant difference in pregnancy history and mean serum concentrations of FSH and AMH between PCOS patients and women who rejected from study ($P<0.05$; Table 1). The effect of treatment with metformin on clinical symptoms in PCOS patients were shown in Figure 2. Our data demonstrated a significant correlation between metformin therapy with prevalence of hypersomnia and dry skin in PCOS patients (Figure 2).

Three months after treatment with metformin, hypersomnia and dry skin were significantly decreased to 3.1% and 37.5%, respectively ($P<0.05$). Although, the abundance of constipation and cold intolerance was also decreased after metformin therapy, however these differences were not significant with patients before treatment. After drug withdrawal, the severity of all symptoms was slightly increased in patients ($P>0.05$; Figure 2).

Variable		PCOS patients	Women without PCOS	P value
Age (year)		31.2 ± 1.8	30.66 ± 2.9	0.62
Weight (kg)		69.64 ± 16.9	67.9 ± 16.2	0.3
BMI (kg/m^2)		29.53 ± 2.75	32.2 ± 1.3	0.64
Abortion number (Mean ± SD)		0.3 ± 0.5	0.5 ± 0.1	0.6
Pregnancy history % (n)		65.6% (21/32)	79.4.% (54/68)	0.04
Occupation % (n)	Housewife	62.5% (20/32)	67.6% (46/68)	0.6
	Employee	37.5% (12/3)	32.35% (22/68)	0.62
	High school	0% (0/32)	2.9% (2/68)	0.78
Education levels % (n)	Diploma	6.3% (2/32)	11.8% (8/68)	
	College	93.7% (30/32)	85.3% (58/68)	
FSH level (IU/L)		4.39 ± 1.47	6.3 ± 1.3	0.74
AMH level (ng/ml)		8.5 ± 1.1	3.53 ± 0.5	0.61
P values less than 0.05 were considered significant.				

Table 1: Demographic data and baseline characteristics in PCOS patients and women without PCOS who rejected from study.

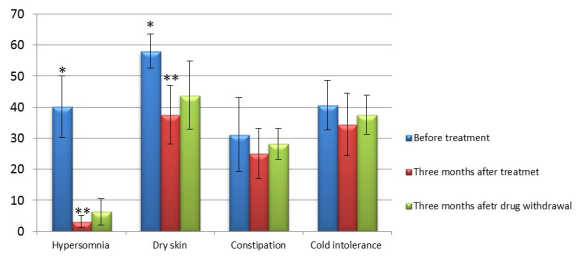

Figure 2: Clinical characteristics in PCOS patients before and after treatment with metformin. *, **; P<0.05.

BMI and TSH lowering effect of metformin

Mean BMI in PCOS patients before metformin therapy was significantly higher than the patients who treatment with metformin (P=0.001; Table 2). After treatment with metformin, the mean BMI decreased from 29.53 ± 2.75 kg/m^2 at the baseline to 28.34 ± 2.5 kg/m^2 (P=0.001). Three months after metformin withdrawal, BMI of patients increased slightly and reached to 28.94 ± 2.5 kg/m^2, but this difference was not significant with the time of metformin therapy (P>0.05). There was a significant difference in mean BMI before treatment (baseline) and 3 months after drug withdrawal (P=0.001; Table 2).

Metformin Interventions	BMI (kg/m^2)	TSH (µUI/ml)	T3 (nmol/l)	T4 (nmol/l)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Before treatment	29.53 ± 2.75 ^{A}	2.57 ± 1.3 ^{A}	2.18 ± 0.5 ^{A}	117.8 ± 37.1 ^{A}
3 months after treatment	28.34 ± 2.5 ^{B}	2.27 ± 0.9 ^{B}	2.23 ± 0.4 ^{A}	118.5 ± 36.5 ^{A}
3 months after drug removal	28.94 ± 2.5 ^{B}	2.61 ± 1.1 ^{A}	1.98 ± 0.4 ^{B}	116.2 ± 36.4 ^{B}
A-B; Numbers with different upper case superscript letters in the same column differ significantly (P<0.05).				

Table 2: The effect of treatment with metformin on BMI, TSH, and thyroid hormones profile in women with PCOS.

TSH-lowering effect of metformin was also demonstrated in Table 2. Mean basal TSH level was 2.57 ± 1.3 µIU/ml at the beginning of study (before treatment). Three months after treatment with metformin, a significant reduction up to 2.27 ± 0.9 µIU/ml was observed in TSH levels (P=0.001; Table 2). Metformin removal in these patients led to a significant increase on TSH levels, which returned to 2.61 ± 1.1 µIU/ml within 3 months. There was no significant difference in the mean concentration of TSH at baseline and three months after drug withdrawal (P=0.001).

Metformin-induced changes on thyroid hormones profile

Serum levels of thyroid hormones at baseline and their variations after treatment with metformin and its withdrawal were shown in Table 2. There was no significant difference in serum concentrations of T3 and T4 before and after treatment with metformin (P>0.05). Three months after metformin therapy, T3 level was slightly increased from 2.18 ± 0.5 nmol/l at the baseline to 2.23 ± 0.4 nmol/l. However, this hormone was significantly decreased to 1.98 ± 0.4 nmol/l after drug removal (P=0.01; Table 2). The pattern of hormonal changes in T4 levels was similar to T3 in patients who treated with metformin. Three months after treatment with metformin, serum T4 levels was slightly increased from 117.8 ± 37.1 nmol/l at baseline to 118.5 ± 36.5 nmol/l (P>0.05). Withdrawal of metformin significantly decreased level of T4 to 116.22 ± 36.4 nmol/l (P=0.01; Table 2).

Discussion

PCOS accompanied by hyperandrogenemia and hyperinsulinemia is one of the most common endocrinological disorders amongst women of childbearing age. Currently, this multigenic syndrome also describe as a disorder with combination of reproductive and metabolic characteristics because several symptoms including; high plasma concentrations of ovarian and adrenal androgens, gonadotropin abnormalities, a relative increase in estrogen levels (especially estrone), reduced levels of SHBG, and high levels of prolactin and insulin are characterized in the endocrine profile of women with PCOS [10,24]. PCOS is usually described with menstrual irregularities, anovulatory infertility, polycystic ovaries, and biochemical (elevated androgens) and clinical (hirsutism, acne and/or alopecia) hyperandrogenism. It is important to note that the clinical feature of this syndrome may change throughout a life span, starting from adolescence to postmenopausal age [25]. In epidemiological studies in USA, PCOS was observed in 35% of amenorrhea cases, 85% of oligomenorrhea women, 95% of hirsutism patients, and 75% of congenital adrenal hyperplasia cases [26].

Although, the etiology of PCOS is unknown, but it is considered that PCOS has some genetic causes [25]. As well as, there are several studies demonstrated that the insulin resistance and obesity are closely linked to the development of PCOS and its clinical features [27]. Considering the high prevalence of obesity and IR among female population, it seems that the PCOS will increase in the near future [28]. Unfortunately, 38-50% of patients who suffered from PCOS are obese or overweight with BMI >25 kg/m^2 and deposited fat mainly around their waist [29]. There are several reports about the high prevalence of IR and compensatory hyperinsulinemia in women with PCOS (60-70%). Approximately, 70-80% of obese (BMI >30) and 20-25% of lean (BMI <25) PCOS patients are insulin resistant [30]. In the other words, 2 of 3 women with PCOS have IR that can directly or indirectly lead to hyperinsulinemia, hyperandrogenemia, higher secretion of LH from adenohypophysis, and ultimately more severe symptoms of PCOS in patients [4,9].

The contribution of IR in development of PCOS led to introduction of insulin-sensitizing drugs in attempt to restore ovulation and enhance pregnancy. Metformin, as the first insulin sensitizing drug, was used successfully in treatment of patients with PCOS who were insulin resistant. The first published report about the administration of metformin as a treatment for PCOS was in 1994, when Velazquez and colleagues reported the significant improvement in menstrual regularity, BMI, and circulating androgen levels after metformin therapy [31]. Since then, metformin occupies a unique place in treatment of PCOS because it offers both metabolic and gynecologic benefits by lowering insulin levels. In addition to reduce appetite, body weight and blood pressure and also improvement in lipid profile and metabolic abnormalities, metformin decreases hyperinsulinemia and hyperandrogenemia that lead to improvement in menstrual

abnormalities and resumption of ovulation, as baseline predictors of clinical response to metformin [10-12,17,26,32].

In present study, we evaluated the effect of metformin on BMI and demonstrated the beneficial therapeutic effect of metformin in reducing body weight and BMI in PCOS patients. In accordance with our results, many researchers investigated the biochemical and clinical aspects of metformin in PCOS patients and confirmed our results about the effect of this drug on weight loss and BMI reduction [11,15,28,31,33-35]. In a RCT designed specifically to investigate the effect of different doses of metformin (1500 or 2550 mg/day) on body weight, circulating hormones, markers of inflammation, and lipid profiles, [33] reported a significant decrease in BMI in obese and morbidly obese women with PCOS, independent of lifestyle modification. They described BMI as a feature of metformin therapy and demonstrated the direct relationship between higher doses of metformin and further reduction in BMI [33]. Nieuwenhuis-Ruifrok et al. [34] also confirmed the effect of metformin on BMI reduction and reported that this effect was related to dosage and duration of treatment. They demonstrated the most decrease in weight and BMI in patient who received high dose of metformin (>1500 mg/day) and/or longer duration of treatments (>8 weeks) in women of reproductive age [34]. Recently, Velija-Ašimi [35] evaluated the BMI and endocrine changes in women with PCOS during metformin therapy and described that the metformin significantly decreased weight, BMI, waist circumference, and insulin resistance after 6 and 12 months. They confirmed that the metformin therapy improved IR, imbalance of endocrine hormones, and menstrual cyclicity in women with PCOS, as well as reduced the irregular menstrual cycle from 69% to 20%. They also introduced the waist circumference, BMI, age, and FSH levels as indicators of anovulation in PCOS patients by using multiple regression models [35]. Despite approval of BMI-lowering effect of metformin, there are some evidences suggested a combination of low-calorie diet and metformin therapy for reduction of body weight, BMI, visceral fat, and serum concentrations of testosterone and insulin in PCOS patients [25,36,37]. Although, the biological mechanisms of metformin on reduction of BMI is still largely unknown, but some experimental studies have demonstrated that metformin reduces body weight and BMI by decreasing insulin resistance and modulating the level of various peptides involved in controlling appetite like ghrelin, neuropeptide YY and adipokines, via hypothalamic adenosine 5′-monophosphate-activated kinase (AMPKinase) [12,38]. The other documents describe that metformin decreases BMI by its beneficial effects on lipids profile, which include decreased fatty acid synthesis by inhibition of fatty acid oxidation and by phosphorylation or inactivation of Acetyl-CoA-Carboxylase (ACC) by AMPKinase [3,38].

Here, we also demonstrated the TSH-lowering effect of metformin in PCOS patients. Three months after metformin withdrawal, serum concentration of TSH was significantly higher than TSH level after metformin therapy, but not different from basal TSH. In consistent with our results, Isidro et al. [21] reported that the TSH levels were decreased after 3 months of metformin therapy in obese and diabetic women with primary hypothyroidism. They also confirmed our findings about the effect of metformin withdrawal on increasing of TSH levels 3 months after drug removal [21]. Taghavi et al. [15] also evaluated the effect of metformin administration on TSH level and thyroid function in overweight women with PCOS and confirmed the TSH-suppressive effect of metformin in patients who was taking metformin. In obese PCOS patients with primary hypothyroidism, metformin resulted in a significant fall of TSH levels, which sometimes returned to the normal range after drug withdrawal in 30% of cases [15]. Cappelli et al. [22] also indicated that metformin was able to interfere with thyroid hormone profile through a decrease in TSH to subnormal levels in hypothyroid patients. They demonstrated that the discontinuation of metformin in these patients led to an increase in TSH levels, which returned to the baseline (pre-metformin) within 3 months [22]. Recently, Fournier et al. [39] evaluated the association of TSH levels with metformin monotherapy and supported the hypothesis that metformin monotherapy was associated with a 55% increased risk of low TSH levels in patients with hypothyroidism. They demonstrated the highest risk of TSH reduction in 90–180 days after metformin treatment [39]. Additionally, the many other studies also confirmed our finding about the TSH-suppressive effect of metformin in patients [5,20-22,24,39-44]. In present study, we also observed the metformin-induced TSH changes after 3 months of treatment initiation. This finding is also consistent with the other studies that demonstrated the TSH-lowering effects of metformin after 3 months [20-22,39] or 100-120 days [42] after treatment initiation. So far, the biological mechanisms explaining the TSH-lowering property of metformin are uncertain [45]. However, there are several possible explanations that suggested for TSH-reducing effect of metformin, including; an increase in the number and sensitivity of TSH and thyroid receptors, sensitization of cells in anterior pituitary to the effects of thyroxine, augmentation of the central hypothalamic dopaminergic response in TSH secretion, and/or a direct effect of metformin on TSH secretion through the hypothalamic AMPKinase using recruitment of various co-regulators [5,20,41,45]. The last hypothesis, the central effect of metformin through the AMPK system, is the most common and widely accepted hypothesis [46].

In addition to TSH-suppressive effect of metformin, we also demonstrated the effect of metformin in modification of thyroid hormones, including T3 and T4. Our results about the thyroid hormones profile demonstrated the slightly increasing of T3 and T4 in PCOS patients 3 months after treatment with metformin, however, these differences was not significant. As well as, the level of these hormones was significantly decreased after drug withdrawal. In accordance with our results, Isidro et al. [21] demonstrated that mean free T4 levels increased during metformin administration from 1.23 ± 0.06 ng/dl at the baseline to 1.32 ± 0.04 ng/dl after treatment. They showed the decrease of T4 levels after discontinuation of metformin and confirmed our results [21]. Taghavi et al. [15] also observed no significant change in free T3 and free T4 throughout their study in overweight women with PCOS. Furthermore, Ibraheem, reported a slightly and non-significant increase of T3 and T4 to 1.756 ± 0.84 nmol/l and 102.3 ± 16.50 nmol/l, respectively, after 3 months of metformin therapy. They also described metformin as an adjunct for treatment of patients with thyroid cancer and subclinical hypothyroidism [24]. In the other study, Rotondi et al. evaluated the effect of metformin on the thyroid hormone profile in patients with PCOS and demonstrated no significant change T4 levels in 4 months after treatment initiation [42].

In conclusion, we introduced the TSH- and BMI- lowering effect of metformin and the other covariates such as variation in T3, T4 levels as predictors of metformin-induced changes in PCOS patients. It is well documented that PCOS and hypothyroidism are closely associated with each other. Subclinical hypothyroidism and overt hypothyroidism occur in 43% and 22.5% of PCOS patients, respectively [19]. Although PCOS and hypothyroidism share a bidirectional relationship, but the reasons of this association and the exact nature of this link is still uncertain. Some evidence demonstrated that the same etiopathogenetic factors were involved in formation of these

dysfunctions. Both syndromes share certain common characteristics, risk factors, and pathophysiological abnormalities. Adiposity, increased IR, high leptin levels, and deranged autoimmunity seemed to play a complex role in connecting of these diseases [47,48]. Although, our results have not disclosed the precise mechanism by which metformin exerts its thyroid effect, but provide further insights for future investigations.

The strengths of this study include strict inclusion and exclusion criteria for selection of patients, close monitoring of treatment fidelity, and the community-based nature of the sample which minimizes selection bias. However, this study has been limited by issues in design, including lack of randomization, small sample size, relatively short intervention duration, and limited time of follow-up. Even though the number of PCOS patients was limited, it was still sufficient for medium standardized effect size. However, larger sample size of patients with long-term prospective studies would remove the confounding effects of variables such as familiar history, environmental factors, and lifestyle methods in this regard and clarify the role of metformin in PCOS management.

Conclusions

PCOS is a multisystem condition and treatment of this multigenic syndrome will require a multidisciplinary approach. Metformin, as an insulin-reducing agent, considered to be a promising treatment for women with PCOS. Metformin, apart from its beneficial effects on clinical and biochemical parameters, causes a significant fall in BMI and serum TSH levels without causing any reciprocal changes in thyroid function parameters. Hence it can be introduced as a first-line pharmacotherapy for management of PCOS and administered in women with PCOS and subclinical hypothyroidism.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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