Effect of Metformin and Antioxidant Agents on Hirsutism in Women with Polycystic Ovary Syndrome

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ABSTRACT

Forty six Iraqi women with PCOS were involved in this study . They were treated with metformin alone and with antioxidant agents (vitamin E or C).It was found that all patients who treated with metformin or with combination of metformin with antioxidant agents showed significant decrease in hirsutism score. The treatment of metformin with antioxidant agents is of great benefit in treatment of hirsutism in PCOS due to that there was no worsening effect after treatment. This may indicate that antioxidant agents may participate in alleviation of hirsutism so it can be said that oxidative stress may play an important role in developing of hirsutism in PCOS.

الخلاصة :-

ستة وأربعون امرأة عراقية مصابات بمتلازمة المبيض متعدد الأكياس شاركن في هذه الدراسة بعد إن قسمن إلى ثلاث مجموعات .إحدى هذه المجموعات أعطيت عقار المبتفورين منفردا إما المجموعتان الباقيتان فقد عولجن بمركب مؤلف من عقار الميتفورمين مع مضادات التأكسد (فيتامين C او E) على الترتيب . وجد في هذه الدراسة إن كل المريضات اللواتي عولجن بعقار الميتفورين منفردا أو مركبا مع مضادات التأكسد له اثر كبير لعلاج الشعرانية في متلازمة المبيض متعدد الاكياس ودلك لانه لم يكن هناك تدهور في مقدار الشعرانية بعد العلاج .هدا التأثير يبين ان مضادات التأكسد قد تشارك في تخفيف مقدار الشعرانية لدلك يمكن القول ان الجهد التاكسدي قد يلعب دورا رئيسيا في تطور الشعرانية عند النساء المصابات بمتلازمة المبيض متعدد الاكياس .

INTRODUCTION

Hirsutism is the presence of excess hair growth in women and affects 5% - 8% of the total female population of fertile age [(1)].The hirsutism in polycystic ovary syndrome (PCOS) is mainly caused by ovarian androgen overproduction and in idiopathic hirsutism there is peripheral hypersensitivity to normal androgen circulating levels [(2)].5α – reductase type 2 has been studied for the differentiation of external genitalia and prostate in males and is essential for hair growth in both sexes (3). A prerequisite for the cellular action of androgen on the pilosebaceous unit is the conversion of testosterone to dihydrotestosterone through the enzymatic action of 5α- reductase [(4)]. However the women with PCOS may amplify the manifestation of hirsutism by the available of insulin growth factor -1 due to induction of 5α-reductase activity which is mediated by insulin growth factor -1[(5)].

Antiandrogens are substances that prevent androgens from expressing their activity at target sites. The inhibiting effects of antiandrogen are different from those compounds that decrease release or inhibit biosynthesis of hypothalamic and anterior pituitary hormones(6).Oral contraceptive treatment of hirsutism is most effective in women with ovarian hyperandrogenism especially with PCOS.The attempt to alleviate hirsutism caused by androgen excess with oral contraceptive represents temporary measure. The preferred treatment is to target the pathogenic site of hyperandrogenism or the site of action. Metformin treatment of women with PCOS results in a decline of insulin as well as total and bioavailable testosterone leading to significant improvement of clinical manifestations of hyperandrogenism [(7)].Therefore the use of metformin in PCOS may afford an alternative way in management of hirsutism**.**

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MATERIALS and METHODS

Forty –six Iraqi PCOS women with mean age (28 ±4.5 years) and eleven control women with comparable age were enrolled in this study. The patients were attending the out patients clinic at Al-Elwea Hospital for Obstetric & Gynecology (Baghdad) and they had a mean hirsutism score (20.8±3.6) according to the modified Ferriman – Gallwey scoring system [8].

The PCOS women had menstrual irregularities (oligomenorrhea), chronic anovulation, obesity; elevated serum androgen levels, a serum LH/FSH ≥ 2 and typical arrested follicles were shown by ultrasound study. All patients had normal fasting glucose levels and normal markers of thyroid, and kidney function. None of them had taking any drug for at least 6 months before enrollment. The patients were classified according to the type of treatment:

Group I: 16 patients were treated with metformin (500 mg t.i.d).

Group Ⅱ: 14 patients treated with combination of metformin (500 mg t.i.d) and vitamin C (250 mg t.i.d).

Group Ⅲ: 16 patients were treated with combination of metformin (500 mg t.i.d) and (vitamin E 200 mg t.i.d).

The patients in all these groups were maintained on the treatment for a period of three months.

Clinical Study:-

A modified Ferriman – Gallwey System was used to clinically grade body hair growth (8). In particular, the degree of hirsutism was rated on a scale from 0 to 4 on 8 body regions. The hirsutism score was obtained by totaling the score for each body region and was determined before the study and again after each month for a period of 3 months of treatment. The score evaluation was performed by a single physician who was unaware of the treatment .

Biochemical Analysis:-

Blood samples for serum testosterone were collected before the treatment and after intervals of 1 month of treatment for 3 successive months. The serum levels of testosterone were measured by TESTO-CTZ which is radioimmunoassay Kit (CIS bio international – ORIS Group – France).

Statiscal Analysis:-

Values are expressed as means ± SD. Student's paired test was used for comparison of the parameters before and after treatment. A p value < 0.05 was considered statistically significant.

RESULTS

The age of the patients in group 1 was (29.2 ±2.9 years) , in group 2 the mean age was (27±3.9 years) and in the group 3 the mean age was (30.1±3.6 years) .

The basal values of total serum testosterone of each group are shown in table 1.

Table – 1
Effect of metformin and antioxidant agents on serum testosterone (nmol/l).

Control levels	*Base line levels of patients*	*After 1 month of treatment*	*After 2 months of treatment*	*After 3 months of treatment*
1.1± 0.37 (n=11)	**4.1± 1.3** (n=16)**	**2.4± 1.3****	**2.4± 1.02****	**1.5± 0.7****
1.1± 0.37 (n=11)	**4.5± 1.7** (n=14)**	**3.1± 1.1****	**2.5± 0.92****	**2.3 ± 1.2****
1.1± 0.37 (n=11)	**5.2± 2.2** (n=16)**	**3.31± 1.2****	**3 ± 1.5****	**2 ± 0.7****

****P<0.05**
n=number of the subjects

Clinical and Hormonal Effects:

Clinical results are summarized in table 2 and figures 1,2 and 3 .

Table - 2-

Effect of metformin and antioxidant agents on hirsutism score in PCOS patients.

Groups	*Before treatment*	*After 1 month*	*After 2 months*	*After 3 months*
I	20.5± 5.3	19.3 ± 5.4*	19.7± 5.5*	16.6± 7.7*
II	20.8± 20	19± 1.75**	17.5± 3.8*	16± 4.8*
III	21.2± 2.2	19.1 ± 1.5**	16.1± 5.4**	14.2± 6.3**

***P<0.05**

****P<0.005**

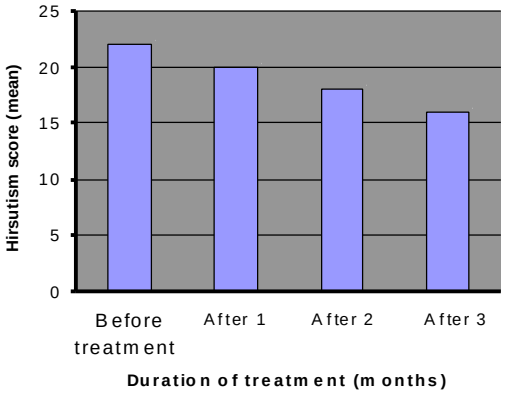

Fig .1: Hirsutism score after treatment with metformin

Fig.2 :Hirsutism score after treatment with Combination of metformin and vitamin C

Fig.3:Hirsutism score after treatment with combination of metformin and vitamin E

In all groups metformin and antioxidant agents decreased the histurism score significantly after 1,2 and 3 months of treatment .The levels of serum testosterone in all groups were higher than normal levels and the serum testosterone decreased significantly in all groups after 1,2 and 3 months of treatment (table -1).

Evaluation of Clinical Outcome

The evaluation of the clinical outcome at the end of the treatment is summarized in table -3.

Table - 3

Rating of clinical outcome at the end of treatment

Rating	*No. (group1)*	*No. (group 2)*	*No. (group 3)*
Excellent	1(6.25%)	2(14.2%)	6(37.5%)
Good effect	4(25%)	4(28.5%)	4(25%)
No effect	9(56.2%)	8(57.1%)	6(37.5%)
Bad effect	2(12.5%)	0	0

The patients treated with metformin showed 12.5% bad (worsening) effects while the patients treated with combination of metformin and antioxidant agents show no worsening effects .The patients treated with metformin and vitamin E reported 37.5% of an excellent effect.

DISCUSSION

The common underlying causes of hirsutism are PCOS and idiopathic hirsutism [9]. The goal of treatment is to interrupt the steps leading to the increased androgen expression of the pilosebaceous unit. Several strategies are available. Mechanical hair removal can improve histurism, but it is a temporary measure. In most cases hirsutism results from a combination of mildly increased androgen production and increased skin sensitivity to androgen [10].The polycystic

ovary syndrome is characterized clinically by a history of chronic anovulation in combination with some evidence of androgen excess, such as histurism and acne [11]. Many drugs with antiandrogenic properties, such as cyproterone [12] , spironolactone [13] and flutamide [14] have been used to treat histurism in PCOS, but the efficacy of these drugs has been shown to be only partial.The hyperinsulinemia in PCOS was recognized as the cardinal manifestation of insulin resistance. It was hypothesized that in PCOS, insulin may directly stimulate ovarian cytochrome P450c17α, resulting in an increase production of androstenedione which is then may converted to testosterone by the enzyme 17β- reductase[15]. However the use of metformin in this study may resolve the main challenge of PCOS which is insulin resistance and this may reduce the action of insulin on the ovary and consequently reduce the overproduction of testosterone (table 1).This result is in agreement with that of kolodziejczyk et al. who found that metformin treatment with PCOS results in improvement of clinical manifestation of hyperandrogenism [7]..Recently it was found that PCOS is associated with oxidative stress [16].In present study the use of metformin alone and combination of metformin with antioxidant agents (vitamins C or E) ,decreases the histurism score significantly after 1,2 and 3 months of treatment (table -2,figure 1,2,and 3). The decrement of total serum testosterone associated with decline of histurism score in all groups and this may support the hypothesis that hirsutism in PCOS is mainly due to androgen overproduction.

In this study, it was found that the percentage of patients who get excellent effect (table -3) was more in group of metformin with vitamins C (14.2%) and E (37.5%) than that in group of metformin alone (6.25%). Moreover the worsening effect in patients who treated with metformin alone is (12.6%) while the patients who treated with metformin and antioxidant agents show no such bad effect. This may indicate that antioxidant agents participate in alleviation of hirsutism so it can be said that oxidative stress may play an important role in developing of hirsutism in PCOS.Therefore, the pathogenesis of histurism in PCOS may differ from other conditions where it may caused by the androgen overproduction in addition to oxidative stress. In conclusion, it can be said that use of antioxidant agents are of great benefit in PCOS; in addition to their excellent effect on histurism score at least they may prevent worsening effect.

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