مجلة العلوم البحثة والتطبيقية
Journal of Pure & Applied Sciences
www.Suj.sebhau.edu.ly ISSN 2521-9200
Received 20/03/2016 Revised 29/09/2017 Published online 15/10/2017

# The effect of metaformin treatment on insulin resistance in women with polycystic ovary syndrome

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**Abstract:** Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women in reproductive age. It is defined as a syndrome of ovarian dysfunction associated with hyperandrogenism and polycystic ovary morphology, give rise to continuous follicular growth. Insulin resistance (IR) is characterized by impaired glucose response to particular concentration of insulin. The aim of this study was to find if there is an association between PCOS and IR in Sebha region, Libya, and to determine the effect of using metaformin treatment in these women. Samples were collected from a clinic of infertility, Sebha, Libya. Questionnaire was filled for all volunteers including information about treatment by metaformin. A total of 44 women were recruited. 19 healthy women and 25 diagnosed PCOS conditions with matched age and body mass index (BMI). At least two of the following three features were present for PCOS: polycystic ovaries on ultrasound, oligomenorrhea or amenorrhea and clinical or biochemical hyperandrogenism. Age, weight and height were taken. Serum Insulin concentrations were estimated by using ELISA kit and plasma glucose levels was measured spectrophotometrically by glucose oxidase-peroxidase method. Body Mass Index (BMI) and Homeostatic Model Assessment- Insulin Resistance (HOMA-IR) were calculated by their formulas. **The results** showed PCOS patients had significantly higher values of fasting serum insulin levels and HOMA-IR. No significant difference between fasting plasma glucose which was in the normal range in both groups. Significantly lower insulin concentration and HOMA-IR in group using the metaformin treatment. **In conclusion** this study illustrated a strong association of PCOS with insulin resistance. The treatment by metaformin has positive effect on hyperinsulinaemia.
**Keywords:** Polycystic ovarian syndrome, Insulin resistance, HOMA-IR.

# تـــأثير العلاج بالمتفورمين على حالة مقاومة الانسولين في النساء المصابات بمرض تكيس المبايض

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**الملخص** متلازمة تكيس المبايض Polycystic ovary syndrome (PCOS) عبارة عن إضطراب في عملية الأيض مع إختلالات هرمونية متعددة، تظهر بإرتفاع مفرط للهرمونات الاندروجينية، متسببه في النمو المستمر للجريبات. النساء المصابات يعانين من خطر الإصابة بالنوع الثاني من الداء السكري ومقاومة مفرطة للانسولين بغض النظر عن الاصابة بالسمنة. تهدف هذه الدراسة الى معرفة ما إذا كان هناك علاقة بين الإصابة بتكيس المبايض ومقاومة الانسولين في النساء المصابات بتكيس المبايض المترددات على مركز العقم بمدينة سبها جنوب ليبيا، ومدى تأثير العلاج بالمتفورمين عليهن. المواد والطرق: جُمعت العينات من 44 سيدة من المترددات على مركز العقم بمدينة سبها، جنوب ليبيا. سُجلت البيانات الخاصة بالمتطوعات من خلال إستبيان وزع عليهن. قُسمت هذه العينات على مجموعتين إحتوت المجموعة الأولى على عدد 25 سيدة مصابات بحالة تكيس المبايض و 19 سيدة سليمات مماثلة في الفئة العمرية ومؤشر كتلة الجسم. تم تشخيصه الإصابة بتكيس المبايض بالاعتماد على وجود على الاقل أثنين من الاعراض الاتية: وجود مبيض متعدد الأكياس باستخدام الموجات فوق الصوتية، انقطاع كلي أو جزئي للدورة الشهرية بالإضافة الى وجود علامات سريرية أوظاهرية لارتفاع الهرمونات الجنسية. تم قياس الطول، الوزن لحساب موشر كتلة الجسم. كما تم قياس تركيز هرمون الانسولين باستخدام محاليل المقايسة المناعية على جهاز AIA 360 وتركيز السكر في الدم باستخدام طريقة glucose oxidase-peroxidase. بالإضافة إلى حساب Homeostatic Model Assessment- Insulin Resistance (HOMA-IR) بالمعادلة المخصصة لذلك. أظهرت النتائج أن تركيز الانسولين في الدم و HOMA-IR أعلى معنوياً في النساء المصابات بتكيس المبايض من النساء السليمات، في حين لم يوجد فرق معنوي بين المجموعتين في تركيز السكر في الدم والذي كان في المعدل الطبيعي في المجموعتين. بعد تقسيم النساء المصابات بتكيس المبايض إلى مجموعتين على حسب العلاج، تبين أن تركيز الانسولين و HOMA-IR إنخفض معنوياً في النساء المصابات بتكيس المبايض المستخدمات المتفورمين

كعلاج. خلصت هذه الدراسة الى وجود علاقة بين الإصابة بتكيس المبايض وحالة مقاومة الأنسولين في النساء المترددات على مركز العقم بمدينة سبها، جنوب ليبيا. كما تبين أن للعلاج بالمتفورمين تأثير إيجابي على تركيز هرمون الأنسولين في الدم.

**الكلمات المفتاحية:** متلازمة تكيس المبايض، مقاومة الانسولين، تقييم التماثل لمقاومة الأنسولين HOMA-IR.

**Introduction**

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive-age women however; its aetiology remains unclear [1]. It affects between 5-10% of women in the reproductive age worldwide [2]. Its clinical features include hyperandrogenism, obesity, menstrual irregularity and an ovular infertility, but the clinical presentation can vary. PCOS is the commonest cause of anovulatory infertility and hirsutism world-wide [3]. The diagnosis of PCOS based on the presence of any two of the following three criteria: (a) polycystic ovaries on ultrasound scan; (b) oligo and/or anovulation; and (c) clinical evidence of hyperandrogenism, provided other etiologist have been excluded. Also the presence of 15 cysts arranged in a single plane, measuring 2 to 10 mm in diameter, and or increase ovarian volume is considered as morphological diagnostic criteria based on ultrasonography [3, 4]. Insulin resistance (IR) has been recognized as important factor in the pathogenesis of the disorder in approximately 65% of women with PCOS [5, 6]. Insulin resistance can be clinically defined as inability of exogenous or endogenous insulin to increase glucose uptake and associated hyperinsulinaemia [7]. Women with PCOS have peripheral insulin resistance affecting skeletal muscle and adipose tissue, although insulin resistance does not affect the ovary, thus enabling the excess insulin to cause ovarian androgen hyper secretion [8]. The consequences of insulin resistance and the additional cell dysfunction include an increased prevalence of impaired glucose tolerance and type 2 diabetes compared to body mass index (BMI)-matched controls [9, 10] IR is frequently observed in lean and obese women with PCOS. Obese women with PCOS are more insulin resistant than lean, suggesting that obesity and PCOS exert independent effects on insulin resistance. But weight loss restores insulin sensitivity only in some [11]. Long term health implications of PCOS includes metabolic disorders, such as obesity, hyperlipidaemia, increased risk of type 2 diabetes, and increased risk of cardiovascular disease There are also defects in pancreatic β-cell function in affected women, these abnormalities are heritable [12, 13]. Polycystic ovarian morphology is a marker of inherited biochemical traits in families with PCOS women, hyperinsulinemia was found to be common between 1st degree relatives of PCOS women in both sexes [12, 14, 15]. Metformin belongs to the class of biguanides, it is widely used to improve insulin resistance in women with PCOS [16]. It acts by reducing the tissue resistance to insulin through increased glucose uptake in skeletal muscle and fatty tissue, decreasing intestinal glucose uptake and decreasing hepatic gluconeogenesis. Furthermore, metformin therapy reduces androgen concentrations, rise release of sex hormone-binding globulin (SHBG) and induces spontaneous ovulation and pregnancy in some patients [17, 18, 19]. Insulin resistance with its compensatory hyperinsulinemia has provided the rationale for off-label use of metformin to treat affected women [16].

**Aim**

The aim of this study was to find if there is an association between PCOS and IR in women patients admitted clinic of infertility in Sebha region, Libya, and to determine the benefit of using metaformin treatment as a treatment of choice in these group of women.

**Methods**

A total of 25 PCOS cases and 19 of age and BMI matched healthy control women are recruited for the study. They are between the ages of 20 and 45 years. Women diagnosed with PCOS were recruited from the clinic of infertility, Sebha, Libya. PCOS was diagnosed according to at least two of the following three features: polycystic ovaries on ultrasound, oligomenorrhea or amenorrhea and clinical or biochemical hyperandrogenism. Questionnaire was field for all volunteers, including the treatment used for PCOS cases. The measurements were conducted in Alafia Clinic, Department of Biochemistry, Sabha, Libya. Anthropometric data – height, weight, body mass index (BMI) was obtained from all the subjects. Ten ml of fasting venous blood was drawn: 5ml in plain tube to obtain serum to estimate insulin concentration. 5 ml in fluoride oxalate tubes to obtain plasma for glucose measurement. Insulin concentrations in serum were estimated using ELISA based kit from ST AIA-PACK IRI. Glucose was measured spectrophotometrically using enzymatic glucose oxidase-peroxidase method (GOD-PAP). HOMA-IR (homeostatic model assessment – insulin resistance) for estimating insulin resistance was calculated mathematically by the formula: HOMA-IR (in mass units) = [glucose (in mg/dl) x insulin (mIU/L)]/405 BMI was calculated as – weight in kg/height in meter square

**Statistical analysis**

Data were analysed statically using Minitab 16. Results are expressed as mean ± SD. Analysis of all continuous variables between PCOS and control groups were done by 2 sample t test. $P<0.05$ was considered to be statistically significant.

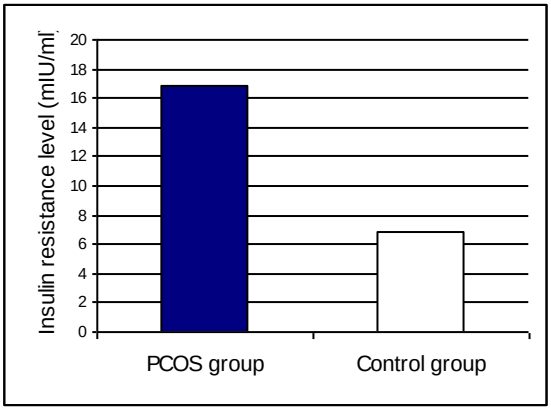
**Results and Discussion**

The results showed no significant difference between the two groups in term of age, BMI (table 1). PCOS patients had significantly higher values of fasting insulin and HOMA-IR. No significant difference in glucose concentrations between the two groups, data were represented in figures (1a, b &2).

**Table 1: Clinical parameters in healthy (control) and PCOS groups represented as mean ± SD.**

| Parameters | PCOS group | Control group | P value |
|---|---|---|---|
| No | 25 | 19 | |
| Age (years) | 31.4 ± 6.3 | 33.5 ± 5.3 | 0.2 |
| BMI (kg/m2) | 32.3 ± 4.9 | 33.0 ± 5.8 | 0.7 |

A.




B.

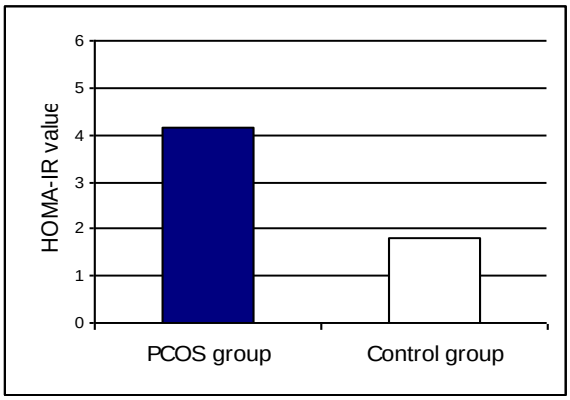



**Fig.(1):** (1a). Insulin resistance level, (1b). HOMA-IR value in PCOS and control women

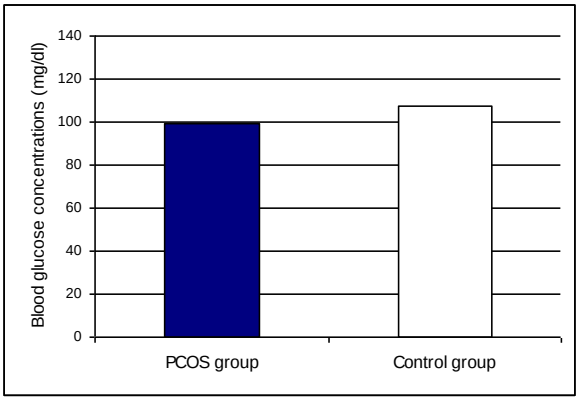
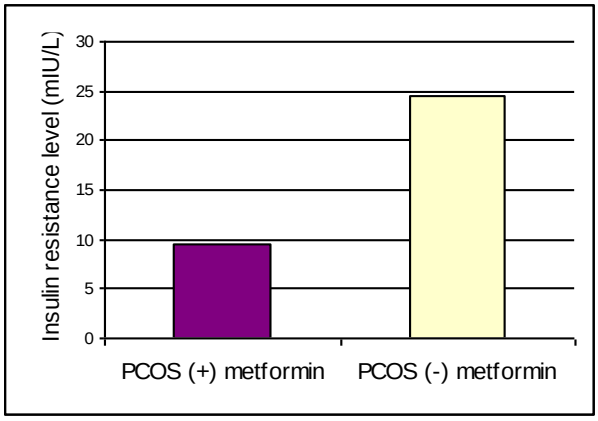



**Fig. (2):** Blood glucose concentrations in PCOS and control women.

Insulin resistance is common in PCOS patients and accompanied by hyperinsulinaemia [20], altered ovarian function also important [11] independent of obesity [21]. Our study suggested a strong association of PCOS with insulin resistance in Sabha region, Libya. This finding was in agreement with other studies [21, 22, 23]. As they illustrated that PCOS patient from different areas are insulin resistance. The cause of hyperinsulinemia among women with PCOS can be due to increase phosphorylation of insulin receptor proteins, which decreases its protein tyrosine kinase activity leading to abnormal insulin secretion [24]. Increased insulin levels can affect ovary which is described in women with PCOS, insulin resistance, diabetes mellitus and obesity. Insulin acts on the normal ovary by a receptor mediated stimulation of steroidogenesis [11]. Insulin resistance in PCOS is more prominent in anovular women than similar hyperandrogenaemic women with regular menses [25]. The efficacy of metaformin as insulin sensitising agents in the treatment of PCOS supports this hypothesis [19]. PCOS group divided into two groups according to their use of the metaformin treatment. Group one contain 13 PCOS cases treated by metaformin and the second group contain 12 PCOS cases did not receive any treatment. Significant differences were present between the two groups in case of insulin levels and HOMA- IR. No significant difference was found in glucose concentrations between the two groups as showed in figures (3a, b & 4).

A




B

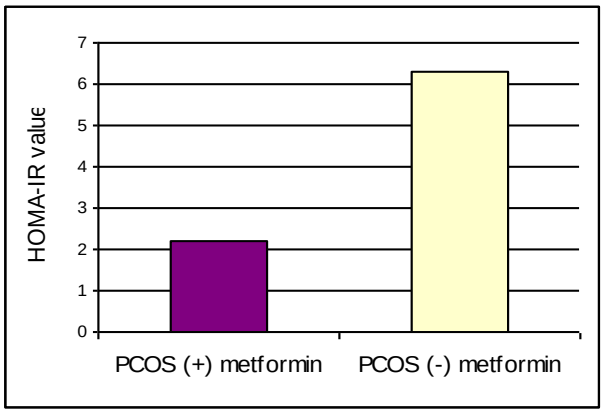



**Fig. (3)** 3a. Insulin resistance level, 3b- HOMA-IR value for PCOS women receive metformin treatment (PCOS (+) metformin) and PCOS women did not receive any treatment (PCOS (-) metformin).

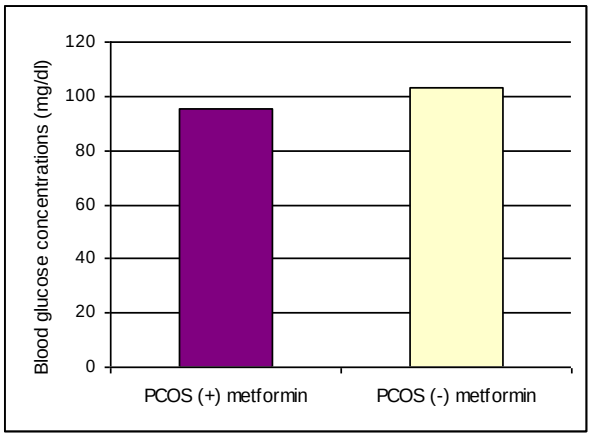



**Fig. (4)** Blood glucose concentrations for PCOS women receive metformin treatment (PCOS (+) metformin) and PCOS women did not receive any treatment (PCOS (-) metformin).

Our study demonstrated positive effect of using metaformin treatment on insulin concentration and IR. Metformin treatment of women with PCOS results in a decline of insulin concentration. Several studies findings demonstrated that metformin therapy improves insulin sensitivity in PCOS women with insulin resistance [18, 26, 27] leading to significant improvement of clinical manifestations of hyperandrogenism. The response to metformin is related to both the severity of hyperandrogenemia and adrenal function [17]. Unfortunately, not all women with PCOS respond to metformin treatment with improved ovulation or decreased Androgen levels [28]. Identifying the subsets of patients who will respond to and benefit from metformin therapy remains a challenge. Some other studies illustrated that metformin has no effect on insulin sensitivity in the absence of weight loss in PCOS women [26, 29]. Therefore, it may not be useful in all women with PCOS and insulin resistance who have been considered the primary candidates for therapy. Importantly, metformin may not improve insulin sensitivity, recent studies confirmed the usefulness of metformin in the treatment of PCOS-related infertility [30].

**Conclusion**

PCOS women are insulin resistant; they had significantly higher values of fasting insulin and HOMA-IR. Metformin treatment of women with PCOS results in a decline of serum insulin concentration; therefore it could be the choice of treatment in PCOS.

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