Effect of pioglitazone treatment on serum chemerin and vaspin levels in polycystic ovary syndrome.

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Abstract:

Abdominal fat synthesizes a variety of adipokines, including vaspin and chemerin, that affect the resistance to insulin. This research was conducted to demonstrate the effect of pioglitazone, one insulin sensitizer used to decrease insulin resistance, on these adipokines in obese patients with polycystic ovary (PCOS). Twenty-five obese women with PCOS were treated with pioglitazone 15mg/bid for 12 weeks. Modifications in fasting blood glucose (FBG), serum fasting insulin (FSI), chemerin and vaspin serum levels, follicle stimulation hormone (FSH), luteinizing hormone (LH), testosterone (T), and in baseline and post-therapy were assessed. Body mass index decreased without any substantial variance after 12 weeks of pioglitazone therapy ($P > 0.05$). T, FSI, HOMA-IR, LH, and FBG levels have decreased considerably ($P \leq 0.01$, $P \leq 0.05$) after the therapy. No substantial variations were found in FSH ($P > 0.05$). Serum chemerin and vaspin levels were observed no significant difference than before treatment ($P > 0.05$) in obese women with polycystic ovarian syndrome cases.

Key words: Adipokines, PCOS, insulin resistance, pioglitazone.

تأثير علاج بيوجليتازون على مستويات الكيميرين في الدم ومستويات الفاسبين في متلازمة المبيض المتعدد الكيسات

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الخلاصة:

تصنع الأنسجة الدهنية العديد من الأديبوكينات مثل الفاسبين والكيميرين ، والتي لها تأثيرات على مقاومة الأنسولين. صُممت هذه الدراسة لإظهار تأثير بيوجليتازون ، وهو أحد أهم الأدوية المستخدمة لتقليل مقاومة الأنسولين لدى مرضى السمنة المصابين بمتلازمة تكيس المبايض ، على هذه الأديبوكينات. تكونت مجموعة الدراسة من 25 امرأة بدينة مصابة بمتلازمة تكيس المبايض. تم قياس مستويات مصل الهرمونات المختلفة (كميرين , فاسبين والانسولين) في جميع الحالات قبل وبعد العلاج بيوجليتازون. بعد 12 أسبوعًا من العلاج بالبيوجليتازون ، لم يلاحظ أي فرق كبير في مستويات

الكيميرين والفاسبين مقارنة بما قبل العلاج, بينما انخفضت تركيزات الأنسولين بالدم و مقاومة الانسولين بشكل ملحوظ في النساء البدينات المصابات بمتلازمة المبيض المتعدد الكيسات مقارنة بالمستويات ما قبل العلاج .تشير هذه النتائج الى ان علاج بيوجليتازون لم يودي الى اختلاف كبير في مستويات الكميرين و الفاسبين في حالات متلازمة المبيض المتعدد الكيسات السمنة

الكلمات المفتاحية: الأديبوكينات، متلازمة تكيس المبايض ، مقاومة الأنسولين ، بيوجليتازون.

Introduction

Polycystic ovarian syndrome (PCOS) is an insulin resistance associated disorder defined by hyperandrogenicity and menstrual dysfunction [1]. PCOS pathophysiology has many facets. Insulin resistance (IR) and the resulting hyperinsulinemia are among them [2], to this reason, insulin sensitizing medicines have been utilized for many years in women with PCOS, improving metabolism, fertility and ovulatory abnormality in patients considerably [3]. Fatty tissue not only storage large quantities of fat for energy; but also incorporates numerous adipokines, such as vaspin, chemerin, and omentin-1, which affect resistance to insulin. [4]. Chemerin is produced as an inactive precursor called (prochemerin), easily transformed into its active form by proteolytic cleavage, it plays a part in insulin secretion, insulin sensitivity [5], angiogenesis [6], and obesity [7]. Serum chemerin values were reported to be closely linked to metabolic syndrome characteristics For example obesity and IR [8]. Tan *et al* [9] concluded that serum chemerin increased significantly in PCOS patients and indicate that elevated chemerin levels could be a compensatory insulin resistance mechanism in PCOS cases. Visceral adipose derived tissue serine protease (vaspin) has been recently found in obesity Otsuka Long-Evans Tokushima (OLETF) rats. The vaspin content of OLETF rats is high within 30 weeks in their abdominal fat; the amount of serum insulin is also high simultaneously. Even so, vaspin content decreases when these rats become diabetes at 50 weeks of age [10,11]. The latest studies in humans demonstrated a positive relationship between vaspin gene expression in abdominal fat with circulating vaspin values, obesity, and T2DM [12, 13]. Whether humans and OLETF rats are diabetic, the opposite changes in vaspin levels imply that regulation and action of vaspin vary from each species. Since there is insulin resistance, obesity, glucose intolerance, T2DM, and defects in the secretion of steroid hormones from the ovaries and suprarenal glands in several patients suffering from PCOS. This research was aimed at investigating the effects of pioglitazone therapy in women with polycystic ovarian syndrome on serum chemerin and vaspin levels.

Patients and Methods

The present study was carried on 25 women with PCOS (mean age 23.72± 4.04, mean body mass index 30.30± 1.64 kg/m2) who had been followed in the Department of Obstetrics and Gynaecology at Al-Haj Jalal Hospital, Wasit, Iraq . PCOS was diagnosed based on the updated Rotterdam Criteria (2003) [14, 15]. The Local Research Ethics Committee approved the study, and all patients involved gave their informed consent. Patients with systemic disorders were excluded from the research (hypertension, diabetes mellitus, hyperprolactinemia, thyroid diseases, cardiovascular and hepatic diseases). Any patient with a background of consuming any other treatments, such as oral pills for

contraception, ovulation products, and antidiabetics, was also "any patient"omitted during the previous three months. Samples collected of all patients have been obtained between the 2nd and fourth day of the follicular menstrual cycle. After 8-12 hours of fasting the plasma levels of chemerin, vaspin, glucose, total testosterone, LH, FSH, and insulin were measured. All samples were obtained with centrifugation and the serum separated into two parts: the 1st part was used to measure blood glucose, insulin, and hormones, and the 2nd part was stored at ˉ80 degrees C before the assessment of chemerin and vaspin.

Laboratory analyses

The concentration of chemerin was calculated with an enzyme-linked immunosorbent test (ELİSA); a Chemerin (Human) (Catalog No: E1435Hu Biotechnology, Shanghai, China) kit.

VASPIN (Visceral Adipose Specific Serine Protease Inhibitor) was calculated with an enzyme-linked immunosorbent test (ELISA); a vaspin (Human) (Catalog No: MBS763334, Mybiosource, USA).

Hormonal parameters such as luteinizing hormone (LH), follicle-stimulating hormone (FSH) were analyzed by sandwich-type method, and total testosterone was analyzed by competition principle. Fasting insulin was analyzed by an immunoenzymometric method, and glucose was measured using ACCU-CHECK Active meter.

The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as follows: HOMA-IR = insulin (μU/mL) x glucose (mg/dL) / 405 [16].

Statistical analysis

The Statistical Analysis System- SAS (2012) program was used to detect the effect of different factors in study parameters. Continuous variables were presented as (Means ± SD). A paired t-test was used to compare means for paired reading. A p-value of ≤ 0.05 was considered significant.

Results

Table (1) displays characteristics, biochemical and hormone levels before and after pioglitazone treatment. After pioglitazone treatment, the values of fasting serum insulin, total testosterone, HOMA-IR, LH, and fasting blood glucose were significantly decreased (P≤0.01, P≤0.05) relative to the values before treatment. BMI, FSH, and LH/FSH ratio values were found with no statistically significant difference after 12 weeks of pioglitazone relative to pre-treatment values (P>0.05).

Table (1): Characteristics, biochemical and hormone levels before and after pioglitazone therapy

Variables	PCOS before (n=25)	PCOS after (n=25)	P-value
Age (years)	23.72±4.04	23.72±4.04	-
BMI (kg/m^2)	30.30± 1.64	29.32 ±0.94	0.0955 NS
Glucose/ (mg/dl)	102.30 ±15.52	96.88 ± 11.32	0.0367 *
Fasting insulin/ (μU/mL)	29.84 ± 8.21	22.05 ± 7.03	0.0085 **
HOMA-IR	7.54 ± 0.14	5.26 ± 0.09	0.0047 **
FSH(IU/l)	5.917±1.54	5.748 ±1.28	0.669 NS
LH (IU/l)	10.66 ± 2.69	9.76± 3.40	0.0455 *
LH/FSH ratio	1.904 ± 0.65	1.758 ± 0.67	0.0887 NS
Total testosterone(ng/ml)	0.746 ±0.09	0.553 ±0.07	0.0026 **

Data are presented as mean ± SD; Number of patients (n); NS: No significant differences (P>0.05), * significantly different (P≤0.05); ** highly significant difference (P≤0.01)

Table (2) displays serum chemerin and vaspin in pre-and post-pioglitazone women with PCOS. There have been no statistically significant variations in serum chemerin and vaspin levels in PCOS women pre and post 12 weeks of treatment, (222.0 ± 39.05 vs 246.6 ±42.43 ng/L and 2.42 ± 0.37ng/mL vs 2.47± 0.31, respectively).

Table (2): Serum chemerin and vaspin in pre and post pioglitazone women with PCOS

Variables	PCOS before (n=25)	PCOS after (n=25)	P-value
Chemerin/ (ng/L)	222.0 ± 39.05	246.6 ± 42.43	0.0852 NS
Vaspin / (ng/ml)	2.42 ± 0.37	2.47± 0.31	0.541 NS

Data are presented as mean ± SD; Number of patients (n); NS: No significant differences

Discussion

PCOS is a condition that is controversial in etiology. It is also observed with hyperandrogenism, IR, and enhanced type 2 DM in women mostly during the reproductive period. Since the discovery of the hormone leptin in 1994, it has been established that fatty tissues not only control the body's energy but also produce numerous of biological substances known as adipokines that contribute to peripheral insulin sensitivity. Adipokines have been very attractive in pathogenesizing essential characteristics of a polycystic ovarian syndrome like IR and central obesity. Studies are currently taking place on the impact and benefits of drugs used to treat this condition concerning the reduction of insulin resistance. In the present study, pioglitazone 15 mg twice daily therapy for 12 weeks has resulted in a minor but no substantial decrease in BMI in obese PCOS patients, which was consistent with results from studies that were done by Shahebrahimi. K et al. and Romualdi *et al* [17,18]. Besides, serum FSH was not affected, this result was in agreement with the result of both Stabile *et al*. and Ota *et al*. did not notice a significant change in the level of serum FSH in women with PCOS after pioglitazone treatment [19,20]. Also found that pioglitazone significantly improves fasting blood glucose and this was in line with Sohrevardi's previous research, which found a significant reduction in the fasting glucose level (p=0.018) for 12 weeks after the treatment of pioglitazone [21], On the contrary, Yuanyuan *et al* and Ortega-Gonza' lez, *et al*, did not demonstrate any noticeable improvement in fasting plasma glucose after pioglitazone therapy [22, 23]. Regarding the effects on insulin levels and HOMA-IR, where a highly significant decrease in these values was produced with the use of pioglitazone, these findings are consistent with the results of several studies, such as Sohrevardi, *et al*, and Cho LW, *et. al* showing PPARs successful in decreased insulin resistance, decreased blood insulin concentration, and HOMA-IR activation by PPARs, in particular gamma form [21,24,]. Thiazolidinedione efficacy for insulinemia has been verified in clinical trials for troglitazone, pioglitazone, and rosiglitazone in obese PCOS patients, irrespective of glucose intolerance [25,26]. There were no BMI changes in the current study after treatment for pioglitazone, which indicated that improving insulin sensitivity was not dependent on adiposity.

Pioglitazone regulates resistance to insulin in peripheral tissues and decreases the release of insulin. Esteghamati *et al*. performed research that examined the connection between treatment with pioglitazone and serum chemerin [27]. This study observed that serum chemerin declining was not altered by pioglitazone in patients with type 2 diabetes after 3 months, similar to that observed in our study, which did not notice a significant difference in chemerin levels following 12 weeks of treatment for obese patients with PCOS. Some of the earlier studies rejected the relation between chemerin and IR variables [6,28]. Conversely, Tang *et al* who observed that troglitazone or metformin decreases the chemerin release from adipose tissue in conjunction with increased insulin sensitivity and decreased body mass index in women of PCOS [29]. Studies of PCOS vaspin levels provided some controversial findings. Women with PCOS often display elevated levels of vaspin. Authors have indicated that obesity and insulin resistance in these patients could be the cause of these elevated vaspin levels. [30,31]. Studies of vaspin levels in patients with PCOS have also found contradictory results after insulin sensitizer therapy. In the previous study, the levels of serum vaspin significantly increased following 24 months of pioglitazone treatment in lean hyperinsulinemic women with androgen increase [32], as in the present study, serum vaspin levels no significant difference after12 weeks of pioglitazone treatment in obese patients with PCOS [33]. Finally, previous research has shown that pioglitazone raises circulating levels of vaspin in diabetic rats and hyperinsulinaemic normal-weight women [34,35]. On contrary, another study displayed lower levels of serum vaspin either after metformin monotherapy or metformin + rosiglitazone combination therapy [36]. The above disparity, firstly, creates the possibility of species variations in TZD and metformin in vaspin and chemerin regulation. Another possible reason is the variations in the underlying conditions (T2DM, polycystic ovary syndrome), medication period and dosage, and baseline body mass index on human vaspin and chemerin values. As a result, chemerin and vaspin functions in IR and PCOS pathophysiology remains controversial.

Conclusion:

Pioglitazone can effectively improve insulin sensitivity, glucose, and LH of obese PCOS patients. Adipocytokines (chemerin, and vaspin) are not considered regulators of insulin metabolism, which may be not involved in the pathogenesis of insulin resistance in PCOS. Pioglitazone treatment can decrease plasma glucose levels and improve insulin sensitivity regardless of improving the profiles of adipocytokines.

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