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Original Research Article

Tumor Necrosis Factor Alpha Synergetic with Insulin Resistance Potentially Contributes to the Development of Polycystic Ovary Syndrome.

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Abstract

Introduction: polycystic ovary syndrome (PCOS) is one from record common endocrine disorders, which is complicated in the multi system disease and its etiology is silent not clearly understood. The environment factors and the genetic factors production a crucial role in the pathogenesis of PCOS. The obesity is android in type with greater waist to hip ratio and obese in posterior abdominal wall and mesentery. Due to that (50%) of women with PCOS are fat, additional the possibility of insulin resistance is the development of type 2 diabetes. Aims of the study to estimate the role of TNF-α and insulin resistance in pathogenesis of PCOs and identify the relationship of obesity with IR and TNF-α in PCOs. IR and TNF-α concentration was assessed by competitive ELISA method.

Significant of differences were detected between PCOS patients and controls. Each the PCOS had raised up BMI, WHR, fasting insulin, homeostatic model assessment (HOMA) score, and serum TNF-α when matched with controls ($p<0.05$). The conducted examination indicated the contribution of TNF-α in path mechanism of PCOS being the basis of increase body weight which lead to development of insulin resistance.

Key Words: Polycystic ovary syndrome, Tumor necrosis factor alpha, insulin resistance, body mass index, waist to hip ratio.

عامل نخر الورم ألفا مع مقاومة الأنسولين يمكن أن يساهم في تطوير متلازمة المبيض المتعدد الكيسات

الخلاصة

المقدمة: متلازمة المبيض المتعدد الكيسات هي واحدة من اضطرابات الغدد الصماء الأكثر شيوعا، التي تشارك في مرض متعدد النظام ومسبباته لا يزال غير مفهومة بشكل واضح. ويعتبر حاليا أن العوامل البيئية و العوامل الوراثية تلعب دورا حاسما في التسبب في متلازمة تكيس المبايض. السمنة ترتبط مع زيادة الخصر إلى نسبة الورك والدهون في جدار البطن الأمامي ومساريقي. بسبب أن ٥٠٪ من المرضى الذين يعانون من متلازمة تكيس المبايض هي السمنة، وخطر آخر من مقاومة الانسولين هو تطوير داء السكري من النوع ٢. أهداف الدراسة لتقدير دور عامل نخر الورم الفا ومقاومة الأنسولين في التسبب في مرض متلازمه تكيس المبايض المتعدد وتحديد العلاقة بين السمنة مع مقاومه الانسولين وعامل نخر الورم الفا في منظمات الرعاية الصحية. وتم تقييم مقاومه الانسولين وعامل نخر الورم الفا تركيز من قبل طريقة ELISA تنافسية. وقد لوحظت اختلافات كبيرة بين مرضى متلازمة تكيس المبايض والضوابط. جميع مؤشرات مرضى تكيس المبايض كانت مرتفعة في مؤشر كتلة الجسم ونسبة الخصر إلى الورك وأنسولين الصيام ونموذج تقييم التماثل (HOMA) والمصل عامل النخر الورم الفا بالمقارنة مع الضوابط ($p <0.05$). عامل نخر الورم الفا له سبب في إمراضيه متلازمة تكيس المبايض كونها أساس لزيادة وزن الجسم مما يؤدي إلى تطوير مقاومة الأنسولين.

الكلمات المفتاحية: متلازمة المبيض المتعدد الكيسات، عامل نخر الورم ألفا، مقاومة الانسولين، مؤشر كتلة الجسم، الخصر إلى نسبة الورك.

Introduction

Polycystic ovary syndrome (PCOS) is the more common endocrine dysfunctions in female of generative age with an incidence of approximately 5%-10% worldwide [1]. Researchers and health care providers know that environmental and genetic factors contribute to the development of PCOS. Unknown of the exactly cause of PCOS [2]. A identification of PCOS is based on at least 2 of the following by 3 criteria: oligo ovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovary on ultrasound

assessment (>12 small antral follicles in ovary), with the exclusion of the circumstances such as congenital adrenal hyperplasia, androgen secreting tumors or Cushing's syndrome [2, 3]. Although all female with PCOS have symptom of insulin resistance it is additional pronounced in those with chronic anovulation [4]. Hyper-expression of tumor necrosis factor alpha (TNF-α) in adipose tissues and muscle is involved in the development of insulin resistance in humans, by reducing the tyrosine kinase activity of the insulin receptor [5]. TNF-α is articulated in human body by adipose tissue and that its plasma concentration in overweight subjects is reduced after weight loss [6]. Adipocyte derived TNF-α is thought to function predominantly in an autocuing paracrine way in adipose tissue and has been postulated to play a crucial role in the development of insulin resistance and glucose metabolism abnormalities that relationship fat to type 2 DM [7]. TNF-α promotes IR, causes Hyperandrogenism, and this will of fact the follicular development and, from this time, it has been associated in the pathophysiology of PCOS [8]. TNF-α has the capability to prevent the insulin stimulated tyrosine kinase activity of the insulin receptor and the insulin receptor substrate-1 (IRS-1) via making serine phosphorylation of IRS-1 and thus converting IRS-1 into an inhibitor of the insulin receptor tyrosine kinase in human body [9]. And so, the propose of this study to estimate the title role of TNF-α and insulin resistance in pathogenesis of PCOS and to identify the correlation of obesity with the TNF-α and IR in PCOS.

Materials and Methods

This study includes (100) females, divided in two groups, the first group includes (50) females with PCOs and the second group includes (50) apparently healthy females. The sample were taken from patients attended the Infertility center in Maternity and Children Hospital in Babylon province in Hilla city, and healthy women. The study was conducted from 1st of October 2016 to 1st of February 2017. The useful side of the study was performed in the lab of Biochemistry Dept in College of Medicine/ University of Babylon.

Ethical Issues:

Depends on the following: a-Agreement of scientific committee in College of Medicine (University of Babylon/ Iraq). b-The objectives and methodology was explained to all female included in the current study to gain their verbal acceptance.

Blood collection:

Venous blood samples were drawn from all subjects by using disposable syringe in the sitting position. Subjects will be inquired to come for blood sampling in fasting status, (4 mL) of blood was obtained from each subject by venous puncture and pushed slowly into heparin tube and then centrifuged at 14000 rpm for about 20 minutes then the plasma are divided into three parts and stored at 20˚C until analysis [insulin, TNF-α level) while glucose measured directly before stored.

Methods:

Body Mass Index (BMI) was intended by weight (kg) divided by the square of height (m); weight and height are measured by the same scale for the all sample subjects for determination of obesity.

BMI = Weight (kg) / Square Height (m2).

Insulin Resistance (IR) calculating the homeostasis model assessment insulin sensitivity index (HOMA) [10].

HOMA (mg/dL) = G0 X I0 / 405

Where, G0; the fasting glucose and I0; insulin levels, respectively [11].

Assay of the fasting glucose level by Spectrophotometric technique while assay for fasting insulin level and TNF-α was based on standard sandwich (ELISA) kit. The ELISA kit was provided from Elab science®/USA (Catalog No: E-EL-H0109) and the assay performed depending on the manufactured instructions.

Statistical analysis

The results were analyzed by Student's t-test using Statistical Package for the Social Sciences (SPSS) version 20. All data were expressed as mean ±SD. P-Value < 0.05 was considered significant. Linear regression analysis was carried to study the correlation between variable studied.

Results

Table (1) shows mean differences of study variables including (age, body mass index, glucose level, insulin level, insulin resistance and TNF-α level) according to study group

including (patients with polycystic ovary and control group).

Table (1): The mean differences of study variables according to study group.

Variable	Study groups	N	Mean ± SD	Range	P-value
Age (years)	**PCOS**	50	22.44 ± 3.20	19-26	0.148
	Controls	50	23.34 ± 2.95	20-26	
BMI (kg/m^2)	**PCOS**	50	27.70 ± 5.07	18.35-38.8	<0.001*
	Controls	50	24.39 ± 2.28	22.11-26.67	
Glucose level (mg/dl)	**PCOS**	50	119.19 ± 24.11	52.5- 171	<0.001*
	Controls	50	104.3 ± 12.1	92.2- 116.4	
Insulin level (ng/ml)	**PCOS**	50	(10.76 ± 2.86)	6.88- 18.34	< 0.001
	Controls	50	(6.99 ± 1.92)	6.38- 7.62	
Insulin resistance	**PCOS**	50	(3.18 ± 1.14)	1.06- 6.46	< 0.001
	Controls	50	(1.79 ± 0.54)	1.53- 2.07	
TNF- α (pg/ml)	**PCOS**	50	(23.19 ± 3.95)	13.34- 28.05	< 0.001
	Controls	50	(14.63 ± 1.62)	9.25- 20.01	

*p value ≤ 0.05 was significant

Correlation between Insulin Resistance and Body Mass Index:
Figure (1) shows the correlation between insulin resistance and BMI (kg/m^2). There was a significant positive correlation between two study variables (r=0.244, P=0.015).

Correlation between Insulin Resistance and TNF-α: Highly significantly **(r=0.543, P<0.001)** positive correlation were found between TNF-α and insulin resistance as in figure (2).

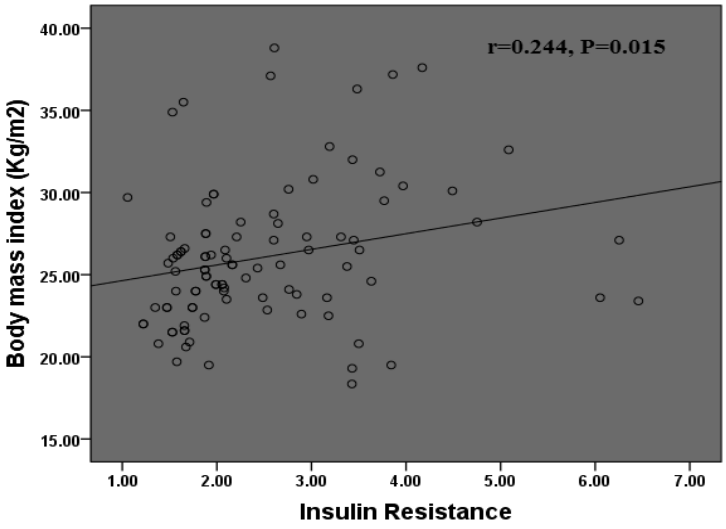

Figure (1): Correlation between insulin resistance and BMI for PCOS patients.

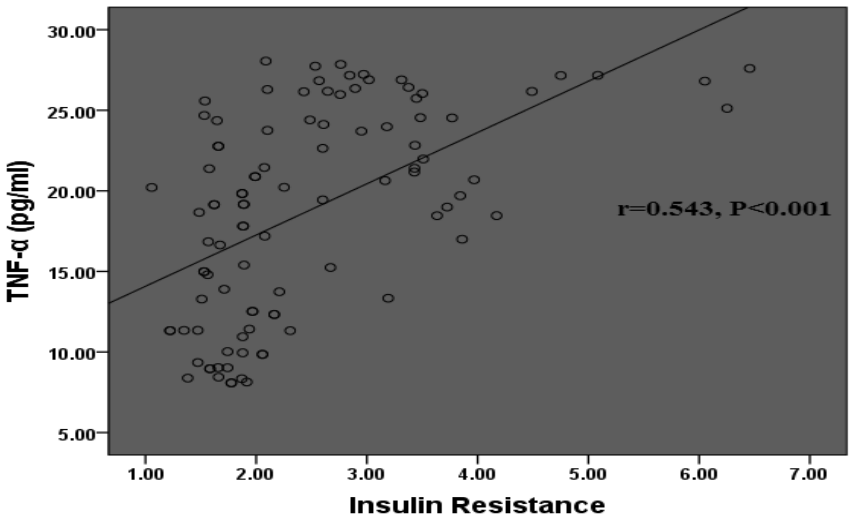

Figure (2): Correlation between insulin resistance and TNF-α for PCOS patients.

Discussion:

Age: There was no significant difference in age (as mean) between control and PCOS group in present study. This age matching helps to eliminate differences in parameters results that may originate due to the significant variation in age [12]. The value of BMI between patients (women with PCOS) and control group was significant, as shown in table (1). Elevated adiposity in PCOS may not be related to adverse lifestyle behaviors [13]. Overweight, Obesity and elevated BMI are clinical types of PCOS that may constitute a major impediment for successful fertility treatment in female diagnosed with PCOS [14]. A positive significant relationship between insulin resistance and BMI, was form in this study which correlation with Maleedhu *et al* study [15, 16]. There were significant differences between means of insulin level, as shown in table (1).

Hyperinsulinemia also may be due to weakening in hepatic insulin extraction in abdominal obesity and mediated in part by increased androgen activity [17].

Really, present 48% of population with PCOS had insulin resistance similar to the outcomes of Chae *et al* (2008). Correspondingly Carmina and Rogerio (2004) found the prevalence of insulin resistance using HOMA-IR to be 77% of PCOS patients [18]. In addition, TNF-α has been shown to affect ovary function, ovulation, fertilization, and implantation in females suffering from PCOS [19]. Current study revealed that TNF-α increase scientifically in PCOS when compare with controls, PCOS patients have been found to have higher serum and follicular fluid concentrations of TNF-α than women without this condition [20]. Increase TNF-α level is a known mediator of insulin resistance by causing enlarged serine phosphorylation of insulin receptor substrate-1 (IRS-1) in insulin sensitive tissues. This leads to decreased expression of GLUT4. This is a key point in the PCOS pathogenesis [21, 22]. As shown in figure below.

Conclusion:

The conducted study indicated the contribution of TNF-α in path mechanism of PCOS being the basis of increase body weight which lead to development of insulin resistance.

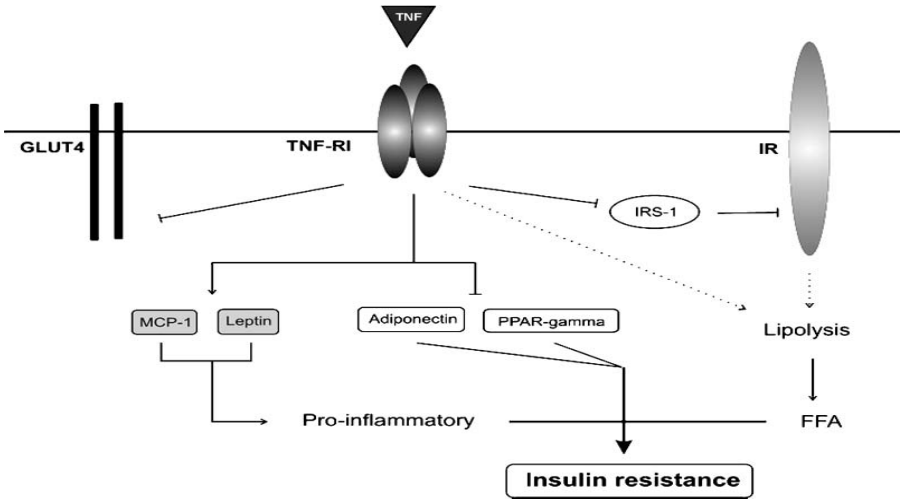

Figure (3): Mechanisms used by TNF-α to exert its effects on glucose metabolic pathways.

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