Study the Effect of Regucalcin on Insulin Resistance and Testosterone Status in Polycystic Ovarian Syndrome

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Abstract

Backgrounds: Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by ovarian dysfunction, elevated androgen levels, metabolic disturbances, and hyperinsulinemia. **Aim of the study:** In this study, we tried to measure whether there is any correlation between serum Regucalcin (RGN) levels with Insulin Resistance (IR) and Testosterone in PCOS patients. **Materials and methods:** This study included 42 patients from the Al-Anbar governorate who were recruited from private clinics, along with 42 healthy individuals who served as controls. Enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of RGN and F. Testosterone (F.Test), while fasting serum glucose (FSG), and fasting serum insulin (FSI) were determined by enzymatic colorimetric methods.

Results: Serum level of RGN (ng/mL) was higher in controls than PCOS patients (P<0.0001), while, FSG, body mass index (BMI), F.Test, LH/FSH, homeostasis model assessment of insulin resistance (HOMA-IR), FSI were higher in PCOS than in controls. The results showed a significant negative correlation between RGN with, FSG, BMI, F. Test, LH/FSH, homeostasis model assessment of insulin resistance (HOMA-IR), FSI (P <0.0001), A non-significant negative correlation with waist/thoracic (W/T) and Rate of pluses (ROP). The studied parameters demonstrated a descending order of the area under the receiver operating characteristic (AUROC) curve: RGN (1), BMI (1), FSG (1), HOMA-IR(1), FSI (0.9977), LH/FSH (0.9819), F.Test (0.9714). The Rreceiver operating characteristic (ROC) curve indicates that RGN, BMI, FSG and HOMA-IR were excellent sensitive markers in the diagnosis of PCOS, while FSI, LH/FSH, and F.Test showed Good discriminatory efficacy between patients with PCOS and healthy individuals.

Conclusion: The study discovered a weak correlation between RGN and IR, as well as testosterone levels. This finding suggests that RGN could be a potential biomarker for detecting PCOS and a useful diagnostic tool for the disease.

Keywords: Androgens, Anthropometric Measurements, Blood pressure, LH, FSH

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Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine condition that affects many women. Its etiology and pathophysiology are intricate. Some names for it include Stein-Leventhal syndrome and hyperandrogenic anovulation (HA). [1,2] Menstrual irregularities, infertility, hirsutism, acne, and obesity are among the multiple symptoms of this chronic illness. [3] PCOS is characterized by an ovarian volume of more than 10 mL and the presence of multiple small cysts in at least one ovary, ranging from 2 to 9 mm in diameter. Although it was previously believed to only affect adult women, recent evidence suggests that it is a lifelong syndrome that can first appear during pregnancy. Although the precise etiology of this complex illness is unknown, a combination of inherited and environmental factors is thought to be the main cause. Hormonal imbalance, chronic low-grade inflammation, hyperandrogenism, and insulin resistance are the key pathophysiological components of PCOS. In addition to impeding folliculogenesis, these factors increase the risk of concomitant conditions such as type II diabetes and endometrial cancer. According to international recommendations, the three main characteristics used to diagnose PCOS are ovarian morphology, anovulation, and hyperandrogenism. [4,5]

Regucalcin (RGN) is a calcium-binding protein that consists of 299 amino acid residues and has a molecular weight of approximately 33 KDa. [6] It was first discovered in rat liver in 1978 by M. Yamaguchi. In humans, the RGN gene is located on

the X chromosome [7, 8] and is composed of seven exons and six introns. The expression of RGN decreases with age in an androgen-independent manner and is also referred to as Senescence Marker Protein-30 (SMP-30). Apart from the brain, lungs, and skeletal muscles, RGN is predominantly expressed in the liver and kidney. The overall structure of RGN protein encompasses 24 stands which form 6 sheets, with the ability to bind Ca^{2+} ions and others. [9] RGN was demonstrated to be a cytoplasmic protein that can go to the nucleus, [10, 11] where it appears to affect DNA fragmentation, as well as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, which are connected to the regulation of cell death and proliferation. Studies that showed a dual function of RGN in regulating both proliferation and apoptosis by altering the expression and activity of crucial regulators of these processes further supported the relevance of RGN in maintaining cell tissue homeostasis. [12-14] Additionally, RGN has been defined as an antioxidant protein that regulates metabolism and oxidative stress. [10, 12] There is extensive evidence indicating that changes in the expression of RGN are associated with the development of metabolic diseases. [15] These changes can lead to the dysregulation of various metabolic pathways, including glucose absorption and metabolism. [16] In *vitro* studies using cloned rat hepatoma H4-II-E cells have shown that increased RGN expression results in enhanced lipid synthesis and glucose utilization, leading to IR. [17]

Insulin resistance (IR) is defined as a compromised immune response to insulin stimulation of target tissues, primarily the muscles, liver, and adipose tissue. Due to IR's impairment of glucose elimination, beta-cell insulin synthesis rises in response, leading to hyperinsulinemia[18]. This leads to compensatory hyperinsulinemia. IR and hyperinsulinemia are characteristic features of PCOS. One of the key factors contributing to IR in PCOS is abnormal signaling within the phosphatidylinositol-kinase (PI3-K) pathway after insulin binds to its receptor. [19-21] The accumulation of visceral fat worsens the effects of this pathway because obesity is the main cause of IR. IR activates the hypothalamic-pituitary-adrenal axis, which leads to increased production of adrenal androgens. Additionally, insulin stimulates androgen production in the ovaries by binding to insulin or insulin-like growth factor-1 receptors, resulting in reduced synthesis of SHBG. This leads to higher levels of free Testosterone. Testosterone, in turn, reduces the sensitivity of the hypothalamus and pituitary to the feedback effects of estradiol and progesterone. [22, 23] A recent study found that women with PCOS have higher IR compared to healthy individuals, and the precise reason for IR in PCOS remains unknown. It appears to be associated with altered insulin signaling, increased blood levels of androgens, obesity, inflammation, and genetic and epigenetic modifications. The ovaries are among the several tissues in PCOS that can be specifically affected by infrared radiation in terms of their metabolic or divisional processes. [24]

Many studies conducted in Iraq have explored the association between inflammatory markers and different diseases. [25-27], however, this study is the first to examine how RGN affects IR and testosterone status in Iraqi women with PCOS.

The main goal of the study was to measure serum RGN levels in PCOS patients and healthy individuals to discover the relationship between RGN levels with IR and testosterone. In addition, use ROC analysis to find AUC, sensitivity and specificity.

Materials and methods:

Eighty-four individuals were recruited in this study, and 42 of them received an ultrasound imaging diagnosis of polycystic ovarian syndrome (PCOS) based on the Rotterdam criteria. Based on age, sex, and ethnicity, 42 HCs were matched with PCOS patients as study participants. The responders were all in the age range of twenty to forty. The sample from private laboratories in Fallujah and Ramadi was decided to be conducted between August and November of 2023. On the second day of the menstrual cycle (MC), blood samples were taken following a minimum of eight hours of fasting. The blood was centrifuged at 1500 x g for ten minutes to extract the serum. In eppendorff tubes, the serum was kept cool until it was time for analysis. The concentration of RGN and free testosterone in the samples were determined using ELISA (BT LAB/China) and (DRG, Germany), respectively, while FSH and FSI were determined by enzymatic colorimetric methods. BMI was calculated for all participants by dividing their weight in kilograms by

the square of their height in meters. Waist circumference (WC), thoracic circumference (TC), neck circumference (NC), and hip circumference (HC) were measured for all study participants. Additionally, various ratios including (W/H), (W/T), and (W/N), were determined.

Statistical Analysis:

Graph Pad Software, La Jolla, CA, USA's Graph Pad Prism version 8.02 was used to statistically analyze these data. Consequences were expressed using the mean, standard deviation (SD), and standard error of the mean (SEM). The results were analyzed using an unbiased t-test, and the distinction between HCs and PCOS patients was made using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. P values less than 0.05 were regarded as statistically significant. Cutoff values, specificity, and sensitivity were determined.

Results:

According to the grading criteria listed in Table 1. The results for the patients and the control group are expressed using the mean, SD, and SEM. The average age of the patients was 30.52 years, while the average age of the HCs was 30.19 years, as shown by $P > 0.05$. Serum RGN (ng/mL) was found to be higher in controls than in PCOS patients ($P<0.0001$). Patients diagnosed with PCOS showed higher BMI, waist/neck (W/N), waist/hip (W/H), diastolic blood pressure (DBP), mean arterial pressure (MAP) ($P <0.0001$), W/T ($P = 0.0210$), systolic blood pressure (SBP), and ROP than HCs ($P = 0.0004$, $P = 0.0017$), respectively. On the other hand, PCOS patients' blood levels of FSG, FSI, F. Test., LH/FSH, and HOMA-1R were higher in PCOS patients' serum than in controls.

Table 1: Comparisons of Parameters between Two Studied Groups

Parameter	Healthy Controls			PCOS Patients			p-value
	Mean	SD	SEM	Mean	SD	SEM	
Regucalcin ng/mL	243.2	34.54	5.330	105.9	19.23	2.967	<0.0001
BMI kg/m^2	24.89	1.494	0.2306	31.49	1.779	0.2745	<0.0001
W/H	0.7891	0.0491	0.0076	1.028	0.0619	0.0096	<0.0001
W/T	0.9464	0.0596	0.0092	0.9749	0.0510	0.0079	0.0210
W/N	2.497	0.1339	0.0207	3.024	0.2080	0.0321	<0.0001
DBP mmHg	83.36	3.091	0.4769	86.60	3.231	0.4986	<0.0001
SBP mmHg	123.4	3.901	0.6019	126.2	0.4781	3.098	0.0004
MAP mmHg	96.70	2.666	0.4114	99.81	2.824	0.4357	<0.0001
ROP 1/min	76.67	3.525	0.5439	79.05	3.200	0.4938	0.0017
FSG mg/dL	85.12	6.808	1.051	107.5	3.839	0.5924	<0.0001
FSI µIU/mL	7.067	3.285	0.5068	23.01	4.302	0.6638	<0.0001
LH/FSH	0.5881	0.2983	0.0460	3.461	2.414	0.3725	<0.0001
F. Test. pg/mL	0.3667	0.1215	0.0188	0.7886	0.1893	0.0292	<0.0001
HOMA-1R	0.7787	0.3513	0.0542	2.631	0.4903	0.0757	<0.0001
Age years	30.19	6.102	0.9415	30.52	6.217	0.9592	0.8048

Table 2: Relationship of Regucalcin Studied Parameters.

Parameter	r (Regucalcin ng/mL)	p-value
Regucalcin ng/mL	1	0.000
LH/FSH	-0.624	<0.0001
BMI kg/m2	-0.835	<0.0001
W/N	-0.758	<0.0001
W/T	-0.2061	0.060
W/H	-0.839	<0.0001
DBP mmHg	-0.397	<0.0001
SBP mmHg	-0.395	<0.0001
MAP mmHg	-0.456	<0.0001
ROP 1/min	-0.288	0.008
FSI µU/L	-0.862	<0.0001
FSG mg/d L	-0.855	<0.0001
F. Testosterone pg/mL	-0.752	<0.0001
HOMA2 IR	-0.860	<0.0001

The results indicate that, with P=0.000, HCs had considerably higher serum RGN levels (ng/mL) than PCOS patients. RGN was found to have a significant negative correlation with W/N, FSG, MAP, SBP, ROP, BMI, F. Test, W/H, DBP, LH/FSH, HOMA-IR, FSI (P <0.0001), A non-significant negative correlation with W/T and ROP according to table 2.

Table 3: Area under ROC curve for all analyzed Parameters in PCOS

Parameter	AUC	Positive if COV	Sensitivity٪	Specificity٪	Likelihood Ratio
Regucalcin ng/mL	1.000	< 164.0	100.0	100.0	
BMI kg/m^2	1.000	> 27.77	100.0	100.0	
W/H	0.9994	> 0.9300	97.62	97.62	41.00
W/T	0.6310	> 0.9628	61.90	61.90	1.625
W/N	0.9932	> 2.694	95.24	95.24	20.00
DBP mmHg	0.7684	> 85.50	69.05	76.19	2.900
SBP mmHg	0.7166	> 125.5	69.05	66.67	2.071
MAP mmHg	0.8027	> 98.67	69.05	71.43	2.417
ROP 1/min	0.6956	> 78.50	61.90	66.67	1.857
FSG mg/dL	1.000	> 99.50	100.0	100.0	
FSI µIU/mL	0.9977	> 15.12	95.24	95.24	20.00
LH/FSH	0.9819	> 1.095	95.24	95.24	20.00
F. Test. pg/mL	0.9714	> 0.5350	88.10	90.48	9.250
HOMA-1R	1.000	> 1.659	100.0	100.0	

Analysis of the Receiver Operating Characteristic (ROC) curve revealed which biomarkers were most useful for identifying PCOS patients who had experienced RGN [AUC: 1, Positive if COV: < 164.0, Sen %: 100, Spec %: 100] (Fig. 1-A**).** BMI [AUC: 1, Positive if COV: > 27.77, Sen %: 100, Spec %: 100]. FSG [AUC: 1, Positive if COV: > 99.50, Sen %: 100, Spec %: 100]. HOMA-1R [AUC: 1, Positive if COV: > 1.659, Sen %: 100, Spec %: 100], Shows F. Test., FSI, LH/FSH, W/H, W/N, W/T, MAP, DBP, SBP, ROP, Good discriminatory efficacy between healthy subjects and patients with PCOS. F. Test. [AUC: 0.9714, Positive if COV: > 0.5350, Sen %: 88.10, Spec %: 90.48, Likelihood Ratio (LHR): 9.250] (Fig. 1-C). FSI [AUC: 0.9977, Positive if COV: > 15.12, Sen %: 95.24, Spec %: 95.24, LHR: 20.00] **(**Fig. 1-B). LH/FSH [AUC: 0.9819, Positive if COV: > 1.095, Sen %: 95.24, Spec %: 95.24, LHR: 20.00]**.** W/H [AUC: 0.9994, Positive if COV: > 0.9300, Sen %: 97.62, Spec %: 97.62, LHR: 41.00]. W/N [AUC: 0.9932, Positive if COV: > 2.694, Sen %: 95.24, Spec %: 95.24, LHR: 20.00]. W/T [AUC: 0.6310, Positive if COV: > 0.9628, Sen %: 61.90, Spec %: 97.62, LHR: 1.625]. MAP [AUC: 0.8027, Positive if COV: > 98.67, Sen %: 69.05, Spec %: 71.43, LHR: 2.417]. DBP [AUC: 0.7684, Positive if COV: > 85.50, Sen %: 69.05, Spec %: 76.19, LHR: 2.900]. SBP [AUC: 0.7166, Positive if COV: > 125.5, Sen %: 69.05, Spec %: 66.67, LHR: 2.071]. ROP [AUC: 0.6956, Positive if COV: > 78.50, Sen %: 61.90, Spec %: 66.67, LHR: 1.857], as shown in the table 3.

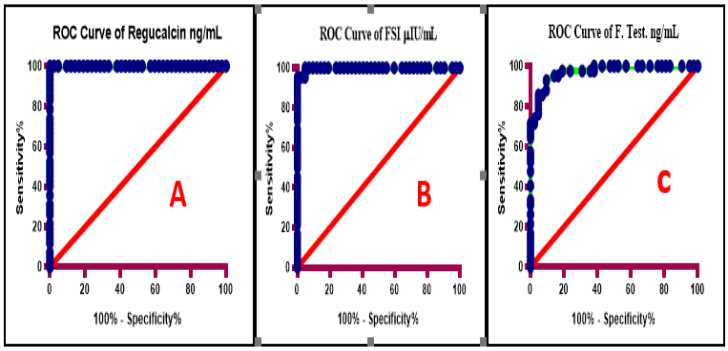

Figure 1: Area under the curve for ROC analysis Test. for Regucalcin, FSI and F.

Discussion:

Polycystic ovarian syndrome (PCOS) is a neurological, metabolic, and reproductive condition that affects 5–18% of women and has long-term repercussions. The etiology is complex and includes factors linked to obesity, insulin resistance, excessive androgen exposure, ovarian and hypothalamic dysfunction, as well as genetic and epigenetic predisposition. Based on the 2003 Rotterdam criteria, the diagnosis can only be confirmed if three criteria are met: irregular cycles, polycystic ovary morphology, and hyperandrogenism, either clinically or biochemically. Due to its limited specificity in teenagers, ovarian morphology is disregarded; instead, hyperandrogenism and irregular cycles are necessary. [28] According to a study conducted by scientists Yamaguchi and Murata, it has been confirmed that RGN is a protein regulated by insulin and plays a crucial role in glucose utilization and lipid metabolism in liver cells. In the case of type 1 diabetes, the level of RGN decreases, indicating a possible link to IR. When the expression of RGN is increased, glucose

utilization and fat production are enhanced, further supporting its involvement in IR. [29] Previous studies have found that RGN overexpression was found to suppress the expression of insulin receptor (Insr) or phosphatidylinositol 3-kinase (PI3K) mRNAs, which are proteins related to insulin signaling, as well as to increase the expression of glucose transporter 2 (GLUT 2) mRNA to enhance glucose utilization in the liver cells. IR in liver cells overexpressing endogenous RGN may be significantly influenced by the suppressive effects of RGN on the expression of Insr and PI3K mRNAs. RGN may also inhibit signal transduction pathways that are involved in the action of insulin in hepatic cells. [16,30] On the other hand, a previous study has shown that IR is one of the causes of non-alcoholic fatty liver disease (NAFLD), and the progression of this disease is associated with changes in RGN levels. Patients with NAFLD were found to have low levels of RGN. Hepatic RGN levels were significantly decreased in NAFLD patients. [31] The results of previous studies support the findings of the current study, which found that patients with PCOS have low levels of RGN, while insulin resistance levels were higher in patients compared to healthy individuals. On the other hand, our study showed a negative correlation between RGN and testosterone. The serum level of these hormones was significantly lower in healthy individuals compared to patients. This can be explained by a study that found hormonal influences, such as testosterone, have been demonstrated to control the expression of RGN mRNA in a variety of tissues and cell types. It has also been demonstrated that pathophysiological conditions linked to hormonal disorders inhibit the production of RGN mRNA. One important molecule that could play a role in hormonal effects and the metabolic diseases they cause is RGN. [32].

Study limitation:

To provide more support for the use of RGN in PCOS patients, a larger sample size and controlled, multi-center clinical study should be conducted to examine the safety and efficacy of the drug. The meta-analysis used a relatively limited sample size.

Conclusion:

The study discovered a negative correlation between RGN and HOMA-IR, as well as free testosterone levels. Notably, the levels of RGN in the blood were higher in healthy individuals compared to those with PCOS. This intriguing finding suggests that RGN might serve as a promising biomarker for the detection of PCOS. Additionally, it has the potential to be utilized as a reliable diagnostic tool for this condition.

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دراسة تأثير الريكوكالسين على مقاومة الانسولين وهرمون التستوستيرون في مرضى متلازمة تكيس المبايض

الخلفية : متلازمة تكيس المبايض (PCOS) هي اضطراب شائع في الغدد الصماء يتميز بخلل في المبيض وارتفاع مستويات الأندروجين واضطرابات التمثيل الغذائي وفرط أنسولين الدم.

هدف الدراسة: في هذه الدراسة، حاولنا قياس إذا كان هناك أي ارتباط بين مستويات ريكوكالسين (RGN) في الدم ومقاومة الأنسولين (IR) والتستوستيرون لدى مرضى متلازمة تكيس المبايض.

الاسلوب: شملت هذه الدراسة ٤٢ مريضاً من محافظة الأنبار تم اختيارهم من العيادات الخاصة، بالإضافة إلى ٤٢ فرداً سليماً كانوا بمثابة مجموعة ضابطة. تم استخدام اختبار الامتصاص المناعي المرتبط بالإنزيم (ELISA) لتحديد مستويات مصل الريكوكالسين وهرمون التستوستيرون الحر (F.Test)، بينما تم تحديد الجلوكوز في مصل الصائم (FSG)، والأنسولين في مصل الصائم (FSI) باستخدام الطرق اللونية الأنزيمية.

النتائج: كان مستوى مصل الريكوكالسين أعلى في الاصحاء مقارنة مع المرضى ($P < 0.0001$)، بينما الجلوكوز في مصل الصائم ومؤشر كتلة الجسم (BMI) وهرمون التستوستيرون الحر و نسبة الهرمون الملوتن الى الهرمون المنبه للجريب (LH/FSH) ومقاومة الانسولين (HOMA-IR) والأنسولين في مصل الدم الصائم كانوا أقل في الافراد الاصحاء بالمقارنة مع المرضى . أظهرت النتائج وجود علاقة سلبية بين الريكوكالسين ،FSG، BMI، F.Test، LH /FSH، (HOMA-IR، FSI ،) ($P < 0.0001$) و ارتباط سلبي مع نسبة الخصر الى الصدر (W/T) ومعدل النبض(ROP). أظهرت المتغيرات المدروسة ترتيبا تنازليا للمسافة الواقعة تحت خاصية تشغيل المستقبل AUROC :RGN(1)، BMI(1)، FSG(1)، HOMA-IR(1)، FSI (0.9977)، LH/FSH (0.9819)، F.Test (0.9714) .اشار منحنى تشغيل المستقبل الى ان RGN ، BMI، FSG ، HOMA-IR،كانت علامات ممتازة في تشخيص متلازمة تكيس المبايض، بينما أظهرت FSI، LH/FSH، F.Test ،علامات جيدة بين مرضى متلازمة تكيس المبايض والافراد الاصحاء. اكتشفت الدراسة وجود علاقة ضعيفة بين RGN وIR، وكذلك مستويات هرمون التستوستيرون. تشير هذه النتيجة إلى أن RGN يمكن أن يكون علامة حيوية محتملة للكشف عن متلازمة تكيس المبايض وأداة تشخيصية مفيدة للمرض

الكلمات المفتاحية: الاندروجينات ، القياسات الجسدية، ضغط الدم، هرمون الجسم الأصفر، الهرمون المنبه للجريب