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ORIGINAL RESEARCH **PERIOPERATIVE MEDICINE**

Association of neuregulin-1 with hormonal and lipid profile in women with polycystic ovarian syndrome

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ABSTRACT

Background & objective: Polycystic ovarian syndrome (PCOS) is a disorder of the reproductive aged women, which may affect fertility of these women from 14-45 y of age. Neuregulin-1 (NRG-1) is a trophic factor that contains an epidermal growth factor (EGF)-like domain, and has been shown to be associated with the regulation of inflammation and ovulation. We evaluated the role of NRG-1 and its relationship with hormonal and lipid profile in women with PCOS.

Methodology: This was a case-control study which included 60 women, known to be suffering from PCOS and another 60 age-matched women, who had regular menstrual cycle, as a control group. Blood samples were collected from Infertility Clinic/ Al-Yarmouk Teaching Hospital. Hormonal and lipid profiles were measured using standard methods. Enzyme linked immunosorbent assay (ELISA) was used to measure serum level of NRG-1. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of NRG-1.

Results: The median serum level of neuregulin in patients was 2.73 pg/mL (range = 1.13-7.39 pg/mL) which was higher than that of controls (median = 2.1 pg/mL, range = 0.33-7.39 pg/mL) with a significant difference the area under the curve (AUC) was 0.652, 95%CI = 0.545-0.758, P = 0.008. The sensitivity and specificity of the test at cut off value of NRG-1 = 2.25 were 62% and 52%, respectively. Neuregulin-1 displayed a significant negative correlation with anti-Müllerian hormone (AMH) (r = -0.324, P = 0.038).

Conclusions: Serum level of neuregulin-1 is increased in women with polycystic ovarian syndrome, but has a poor diagnostic value, and its negative correlation with anti-Müllerian hormone. However, the diagnostic value of neuregulin-1 is poor and cannot be used in early diagnosis of polycystic ovarian syndrome.

Abbreviations: AMH - Anti-Müllerian hormone; AUC - Area under the curve; EGF - Epidermal growth factor; HDL-C - High-density lipoprotein cholesterol; LDL-C - Low-density lipoprotein cholesterol; NRG-1 - Neuregulin-1; PCOS - Polycystic ovarian syndrome; SG - Stress granules; TC - Total cholesterol; TG -Triglyceride.

Keywords: Infertility; Neuregulin-1; Polycystic ovarian syndrome

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1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a hormonal and metabolic disorder characterized by menstrual irregularities, hyperandrogenism (acne, amenorrhea, alopecia, etc.) and, sometimes, infertility, obesity and severe menstruation disruption (amenorrhea or oligomenorrhea).[1] The family of epidermal growth factor (EGF) like signaling molecules known as neuroregulins, is engaged in cell-to-cell communication and is crucial for the growth, upkeep, and repair of the nervous system, heart, breast, and other organs. A ligand for the oncogene ErbB2 was described by independent investigations. (neu, Her2) and substances that promoted Schwann cell division and acetylcholine receptor production by force. According to Marchionni M., these ligands and factors are basically byproducts of the same gene, known as neuregulin (NRG-1).[2] Few studies have been done on NRG-2, -3, and -4, and it is still not fully understood how they work. On the other hand, it was recently found that NRG-2 is a part of stress granules (SG), which are microscopic aggregates of messenger ribonucleoprotein complexes that are stopped in translation and form in response to direct stress conditions.[3] Moreover, it was demonstrated that astrocyte-secreted NRG-2 coupled to ErbB3 on neurons enhanced neural survival.[4]

The main objective of the study was to evaluate serum neuregulin-1(NRG-1) as a specific biomarker for early diagnosis or identification of hormonal irregularities in women with PCOS.

2. METHODOLOGY

This is a case-control study which included a total of 60 women with PCOS who were attending national infertility clinic – Al-Yarmouk Teaching Hospital Baghdad, Iraq, during the period from February 2023 to November 2023. PCOS was diagnosed relying on Rotterdam Diagnostic Criteria. The determination was made when at least two criteria were met (oligo/anovulation, hyperandrogenism, or polycystic ovaries by ultrasound) after ruling out various causes of androgen excess. On the other hand, subjects with hypertension, diabetes, and body mass index (BMI) >35 kg/m^2 were excluded from the study. Other age-matched 60 women with regular menstrual cycle were enrolled as a control group.

Demographic characteristics of the study population including age, weight and height (form which BMI was calculated) and family history of PCOS were collected.

2.1. Blood sample collection

Five mL venous blood was taken from all women on days 2-3 of their menstrual cycles after overnight fasting. Sera were isolated from coagulated blood, and lipid profile; i.e., total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) were measured by Rochel/HitachCobas device C311.

2.2. Hormonal profile

The serum levels of prolactin, anti-Müllerian-hormone (AMH), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, estradiol, progesterone and prolactin were all measured by ELISA technique using ready commercial kits.

2.3. Serum level of NRG-1

Serum level of NGR-1 was measured by using ELISA techniques (HumanNRG-1, ELK, China, Cat:ELK2232) according to the manufacturer's instructions. The kit has a detection range: 0.16-10 ng/mL.

2.4. Statistical analysis

Statistical analysis was performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were subjected to normality test (Shapiro Wilk test). Data with normal distribution were presented as mean and standard deviation, and analyzed with Student's t-test. Data with non-normal distribution were presented as median and range and analyzed with Mann Whitney U test Categorical variables were expressed as numbers and percentages and analyzed with Chi-square test. Receiver operating characteristic curve (ROC) was used to evaluate NRG-1 in the context of discrimination between patients and controls. Spearman's correlation test was used to explore the possible correlation of NRG-1 with other variables. A $P < 0.05$ was considered statistically significant difference.

3. RESULTS

3.1. Demographic characteristics

Table 1 shows the demographic characteristics of the study population. The mean age of women with PCOS was 26.98 ± 7.22 y, which was very close to that of controls (25.07 ± 6.39 y) with no significant difference. Likewise, the two groups were comparable in terms of weight, height and BMI with no significant differences. Family history of PCOS was very common among patients (46.67%) compared with controls (5%) with a highly significant difference. The mean duration of the PCOS in affected women was 4.18 ± 2.33 y.

Table 1: Comparative demographic data of the study population

Variables	Controls (n = 60)	Patients (n = 60)	P- value
Age (y)	26.98 ± 7.22	25.07 ± 6.39	0.126
Weight (kg)	70.43 ± 6.64	72.84 ± 7.72	0.070
Height (cm)	163.57 ± 3.51	164.17 ± 4.84	0.438
BMI (kg/m^2)	26.33 ± 2.39	27.01 ± 2.54	0.132
Family history of PCOS	3 (5%)	32 (53.33%)	< 0.001

Data presented as Mean ± SD or n (%)

Table 2: Reproductive status of the study population

Variables	Controls (n = 60)	Patients (n = 60)	P-value
Gravida			
None	15 (25)	26 (43.33)	**0.002**
≤3	33 (55)	33 (55)	
>3	12 (20)	1 (1.67)	
Parity			
None	15 (25)	33 (55)	**< 0.001**
≤3	35 (58.33)	26 (43.33)	
>3	10 (16.67)	1 (1.67)	
Abortion			
None	45 (75)	49 (81.67)	0.507
1-2	15 (25)	11 (18.33)	

Data presented as n (%); P < 0.05 considered as significant

Table 3: Hormonal profile in PCOS patients and controls

Variables	Controls (n = 60)	Patients (n = 60)	P- value
FSH (mIU/mL)	6.65 (3.18- 48.80)	8.2 (1.13-18.20)	**0.010**
LH (mIU/mL)	5.75 (2.40-11.02)	7.25 (3.10-20.0)	**< 0.001**
Testosterone (nmol/L)	0.44 (0.16-1.55)	0.65 (0.16-1.40)	**0.008**
AMH (ng/mL)	5890 (5038.36-7858.80)	1167.85 (386-1664.90)	**< 0.001**
E2 (pg/mL)	174.3 (97.97-422.44)	43.19 (13.03-78.58)	**< 0.001**
Progesterone (nmol/L)	29.4 (1.8-46.8)	35.4 (13.2-92.5)	0.111
Prolactin (µg/L)	23.0 (5.08-47.88)	18.13 (3.70-84.68)	0.113
TSH (µU/mL)	2.79 (0.95-4.55)	2.44 (0.36-16.77)	0.457

Data presented as Median (Range); P < 0.05 considered as significant

3.2. Reproductive characteristics

Control group had more common >3 gravida and >3 parity (20% and 16.67%, respectively) than patients (1.67% for both) with highly significant differences. In contrast most included patients and controls had no abortion (81.67% and 75%, respectively) with no significant difference (Table 2).

3.3. Hormonal profile

Data regarding hormonal profile were found to be non-normally distributed. Therefore, these data were expressed as median and, and non-parametric Mann

Table 4: Lipid profile in patients and controls

Variables	Controls (n = 60)	Patients (n = 60)	p- value
TC (mg/dL)	165.42 ± 36.14	173.94 ± 38.14	0.247
TG (mg/dL)	120.38 ± 48.67	172.05 ± 177.31	**0.038**
HDL (mg/dL)	49.55 ± 9.86	43.94 ± 8.52	**0.002**
LDL (mg/dL)	98.22 ± 26.22	109.63 ± 29.11	**0.042**
VLDL (mg/dL)	25.67 ± 13.36	24.34 ± 11.58	0.597

Data presented as mean ± SD; P < 0.05 was considered as significant

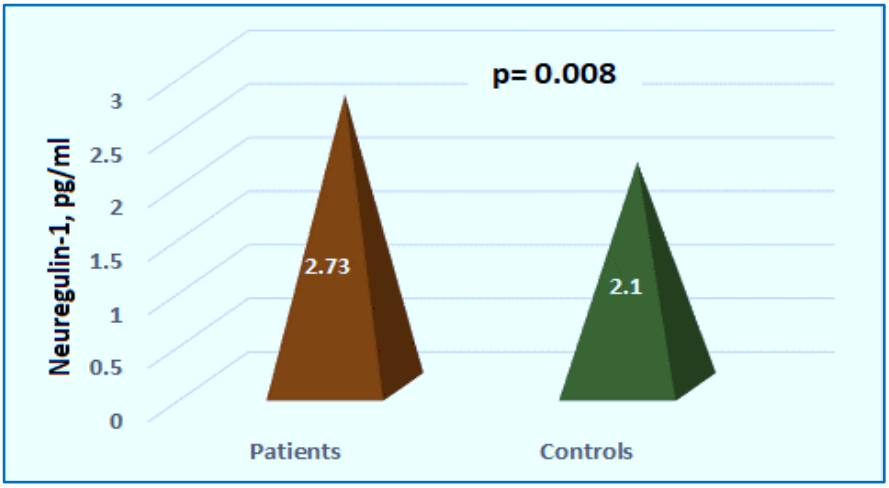

Figure 1: Median serum level of neuregulin-1 in patients and controls

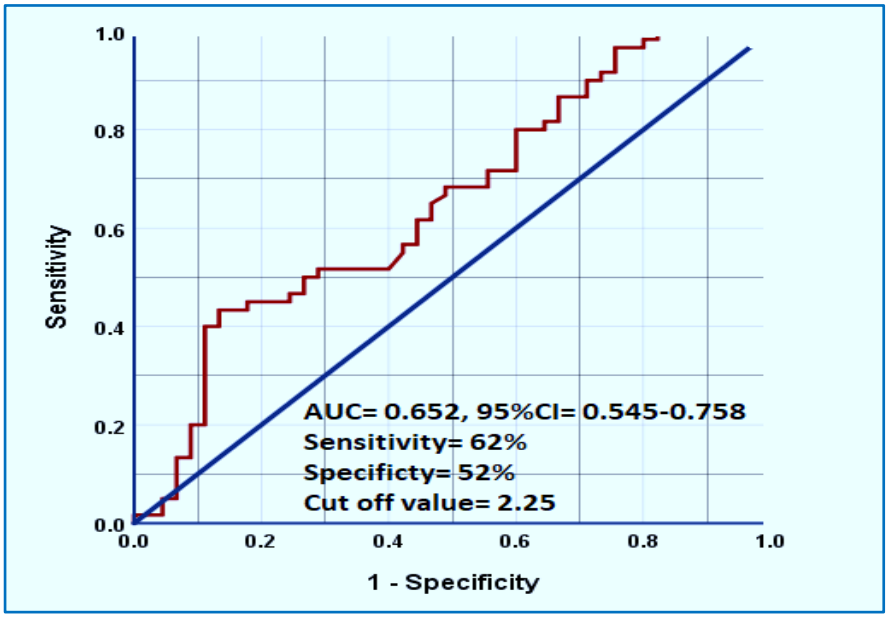

Figure 2: Receiver operating characteristic curve of neuregulin-1 in the context of discrimination between PCOS and healthy women

Whitney U test was used to compare the groups of patients and controls (Table 2). The median serum level of FSH and LH in women with PCOS was 8.2 mIU/mL and 7.25 mIU/L, respectively, which was higher than that of controls (6.65 mIU/mL and 5.75 mIU/mL, respectively) with significant differences. Likewise, the median serum levels of E2, AMH and testosterone were higher in patients (0.65, 1167.85 and 43.19, respectively) than controls (0.44, 5890 and 174.3, respectively) with highly significant differences.

In contrast, healthy women demonstrated higher median serum levels of progesterone than PCOS women (174.3 nmol/L vs. 43.19 nmol/L), although the difference was not significant. The two groups were comparable in terms of prolactin and TSH with no significant differences (Table 3).

3.4. Lipid profile

The two groups were comaparable regarding serum level of TC and VLDL with no signifcant differences. However, patients demonstrated higher levels of TG and LDL than controls (P = 0.038 and P = 0.042 respectively) with significant differences. In contrast, patients had lower HDL than controls with a significant difference (P = 0.002) (Table 4).

3.5. Serum level of neuregulin-1

The median serum level of neuregulin in patients was 2.73 pg/mL (range = 1.13-7.39 pg/mL) which was higher than that of controls (median = 2.1 pg/mL, range = 0.33-7.39 pg/mL) with a significant difference (Figure 1).

3.6. Diagnostic value of neuregulin-1

Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of neuregulin-1 in the context of discrimination between PCOS and healthy women. The area under the curve (AUC) was 0.652, 95% CI = 0.545-0.758, P = 0.008. The sensitivity and specificity of the test, at cut off value of REG-1 = 2.25, were 62% and 52%, respectively (Figure 2).

3.7. Correlation of neuregulin with other variables in PCOS

Spearman's correlation test was used to explore the possible correlation of neuregulin with other parameters in patients and controls. Neuregulin-1 displayed a significant negative correlation with AMH (r = -0.324, P = 0.038) as shown in Table 5, Figure 3.

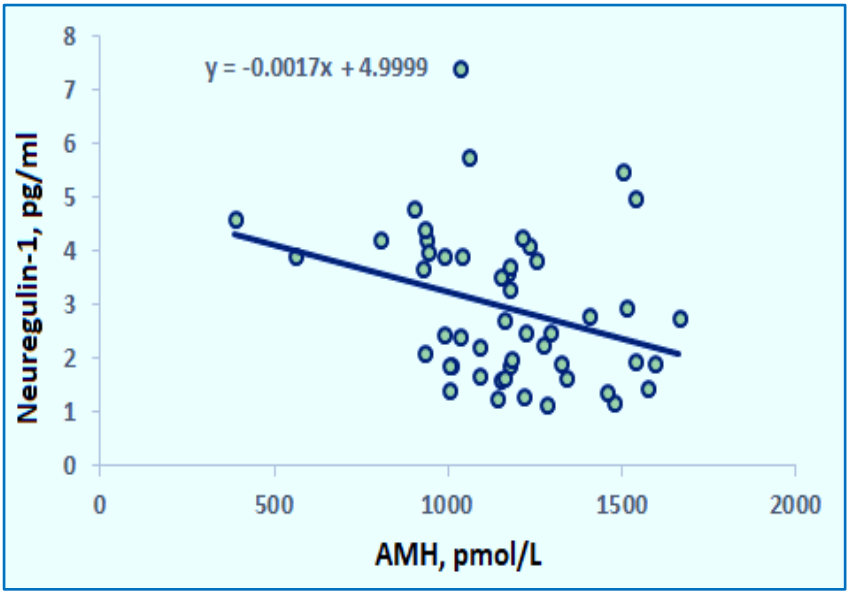

Figure 3: Scatter plot and regression line between AMH and neuregulin-1 in women with polycystic ovarian syndrome (PCOS)

Table 5: Spearman's correlation of neuregulin-1 with other variables in women with PCOS.

Variable	NRG-1	
	Coefficient	P-value
Age	0.020	0.877
Weight	-0.242	0.063
Height	0.018	0.894
BMI	-0.236	0.069
Prolactin	0.181	0.235
HbA1C	0.079	0.548
FSH	-0.054	0.684
LH	0.074	0.574
Testosterone	0.077	0.563
TC	-0.134	0.358
TG	0.053	0.707
HDL	0.034	0.813
LDL	-0.230	0.112
vLDL	-0.090	0.539
AMH	-0.324	0.022
E2	0.109	0.450
Duration	-0.055	0.674

4. DISCUSSION

The results of the study showed that 53.33% of the patients had a family history of PCOS disease, compared with controls (5%) with a highly significant difference. Much evidence has indicated that PCOS is a complex genetic disease. Previous researchers have proven the role of genetic and environmental factors in the pathogenesis of PCOS, as there are several genes responsible for the appearance of its clinical symptoms such as the state of excess androgens, obesity, hyperinsulinemia, the emergence of insulin resistance, heart disease, type-2 diabetes mellitus, and even cancer.[5] Kahsar-Miller et al. found that among 93 women with PCOS, 40% were sisters.[6] In another study by Legro et al. they concluded that 24 of the women with PCOS appeared to have a state of hyperandrogenism with a regular menstrual cycle, while the male hormone level was high for all sisters.[7] Therefore, the prevalence of polycystic ovary syndrome among first-degree relatives is a positive risk factor in providing information about the development of PCOS.[8]

The serum level of FSH in PCOS group was higher than healthy group with a significant difference (P = 0.01). It is consistent with the results of a previous study that found higher levels of FSH in PCOS.[9,10,11] One of the main hormones controlling the menstrual cycle is FSH. The typical hormonal balance is frequently upset in PCOS, which may have an impact on FSH levels.[12] FSH levels may be normal or even high in a large number of PCOS cases. This may seem contradictory because

anovulation, or the absence of ovulation, is frequently linked to PCOS and may indicate decreased FSH levels. However, the hypothalamic-pituitary-ovarian (HPO) axis's disrupted feedback mechanisms are usually the cause of high FSH levels in PCOS.[13]

For testosterone level, the results show that the median concentration of testosterone increased significantly in patients than controls which is consistent with many researches in this regard.[14-16] Hyperandrogenism is the term for the condition when people with PCOS have higher-than-normal levels of testosterone due to an imbalance. High testosterone levels have been linked to the development of symptoms that are frequently linked to PCOS, including irregular menstrual periods, acne, and hirsutism (excessive hair growth).[17]

Estradiol in women with PCOS was higher than control group, which agrees with several previous works,[18,19] but does not agree with others,[20,21] that found a higher level of estradiol in PCOS. Lower levels of estradiol (E2) are frequently seen in PCOS patients as compared to non-PCOS women. PCOS frequently causes irregular or absent ovulation, and lower levels of estradiol can be from disturbances in ovulation.[22] Low estradiol levels are the result of the effect of androgens on metabolism and natural production of estradiol in the ovaries, so its level is decreased.[23]

Serum level of LH in women with PCOS was higher than that of the controls, a result which agrees with earlier researchers,[10,16] who found raised levels of LH in PCOS. LH contributes to hormonal imbalance and reproductive dysfunctions and thus has an important role in PCOS. To control ovulation and the menstrual cycle, LH is essential. It causes the final maturation of the dominant follicle, which results in ovulation, and stimulates the ovarian follicles to create estrogen. Elevations of LH or changes in the LH to FSH ratio are frequently observed in PCOS. The normal ovulatory process may be deactivated with by this increase in LH levels.[24]

The current study shows low levels of AMH in the PCOS group than the control. There are several mechanisms that support a negative correlation between BMI and AMH levels, which has been supported by a number of theories. The primary cells that make up adipose tissue are called adipocytes, and they store fat. Leptin, a hormone well-known for suppressing appetite, is produced by these cells. It has been demonstrated in *in vitro* experiments that leptin inhibits granulosa cell production of AMH.[25]

Serum levels of NRG-1 is increased in the PCOS group compared to the control group, with a significant difference. This is in agreement with Tawfeq and Sarhat, who found elevated levels of NRG-1 in women with PCOS,[26] but does not agree with the study of Arpaci, who found a lower level of NRG-1 in the PCOS group.[27] NRG-1 plays a crucial role in tissue development and homeostasis by controlling cell proliferation, differentiation, and survival.[28] Many studies have shown change in the expression and functionality of NRG-1 and its receptors in women with PCOS than healthy women. For instance, it was discovered that women with PCOS, especially those who also had insulin resistance and hyperandrogenism, had considerably higher serum levels of NRG-1.[29] These results imply that the hormonal and metabolic abnormalities linked to PCOS may be exacerbated by dysregulation of NRG-1 signaling.

It is currently unclear how NRG-1 influences the precise processes that lead to the onset and progression of PCOS. However, several potential options have been proposed. One theory is that NRG-1 stimulates abnormal follicular growth and steroidogenesis, which may disrupt ovarian function. NRG-1 signaling has been shown to increase the synthesis of androgens, which are increased in PCOS, and promote ovarian granulosa cell proliferation. Furthermore, by regulating insulin signaling and glucose metabolism, both of which are dysregulated in PCOS, NRG-1 may have indirect effects on ovarian function.[30] The ever-increasing data connecting NRG-1 to PCOS suggests that treatment intervention may have to target this pathway. Medication that specifically alters NRG-1 signaling, including small molecule inhibitors or monoclonal antibodies, may help PCOS patients' metabolic parameters and restore normal ovarian function. Targeting NRG-1 signaling related downstream effectors, such as androgen or insulin receptors, may also provide different approaches to treating PCOS.[31]

5. CONCLUSION

The results of this study indicate the increased level of neuregulin-1 in women with polycystic ovarian syndrome and its negative correlation with anti-Müllerian hormone. However, the diagnostic value of neuregulin-1 is poor and cannot be used in early diagnosis of polycystic ovarian syndrome

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgement

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8. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

9. Authors' contribution

OTZ: writing the manuscript

RJA, FJA: conduction of the study work and manuscript editing

QSA: Samples collections

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