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Role of Apelin-13 and Its Relationship with Hormones levels and other Parameters in Iraqi Polycystic Ovary Syndrome patients

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ABSTRACT:
PCOS is an endocrino-pathy that accounts for 75 percent of infertility in women of childbearing age who are not ovulatory. Apelin is a peptidergic hormone extracted from adipose tissue.This study including the relationship of serum apelin-13 with pituitary gland hormone and they linked to the danger cardio-vascular diseases disease in the healthful and patient women with PCOS issue. This study including56 cases women with PCOS, and 34 healthy woman forming control group. The PCOS patients was subdivided by BMI into 2subgroups (the first group was excessive weight Polycystic ovary syndrome with body mass index is equal or more than 30 and the 2^{ed} group was Normal weight Polycystic ovary syndrome PCOS body mass index is less than30). Fasting-insulin levels, HOMA-IR, FSH, LH, testosterone, GST activity, and serum AP-13 levels it was performed for all groups. PCOS Ladies appearedlower concentration of apelin-13 than control (11.21 ± 1.51 (pg/ml) versus 34.90 ± 5.98 (PG/ML), P-value=0.0001), while the glutathione s transferase activity was increase in patients of polycystic ovary syndrome and lower in healthy group (9.70 ± 1.05 (IU/L) versus 4.71 ± 0.71 (IU/L), P-value= 0.0001). APLEN-13 levels are direct proportional with BMI and HOMA IR in patients of polycystic ovary syndrome, but the glutathione s transferase activity levels no significantly correlated negatively withAPLEN-13 inpatients of polycystic ovary syndrome. In addition to, excessive weightpatients of polycystic ovary syndrome showedincreased Apelin-13levels more than Normal weight PCOS (9.42 ± 1.66 (pg/ml) versus 13.29 ± 2.61 (PG/ML), P-value=0.712),While the glutathione s transferase activity show lower in excessive weight PCO cases more than Normal weight PCOS (8.31 ± 1.27 (IU/L) versus 11.31 ± 1.71 (IU/L), P=0.167). The information recommend that Apelin-13level is negatively connected with glutathione s transferase activity in patients group. Apelin 13 does not legitimately fall into the trap of causing PCO disruption, however it may be include as an adipo-kine that influences by the BMI and effected on hormones. Increase antioxidant capacity and alsodecreasedin AP-13level may would be increase the danger of CVD in (PCOS) ladies, notwithstanding referred to hazard factors, e.g. (IR, hypertension, excessive obesity, dyslipidemia).
Key.Words: heart Disease, body mass index (BMI), glutathione s transferase (GST), Polycystic.ovary.syndrome (PCOS),Resistance of insulin (IR).

Introduction

Polycystic ovary syndrome, known as PCOS, is a disorder caused by a hormonal imbalance that affects how a wamans ovaries function. It's a complex condition that was first identified as it is the cause of hirsutism and the chronic anovulation in polycystic ovaries women [1]. The most common signs of PCOS are irregular menstruation, acne, and elevated levels of

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androgenic hormones. (2.).Apelin is a bioactive peptide that was discovered as an endogenous ligand for the G-protein conjugate the APJ-receptor in bovine gastric extracts (3).
apelin and its receptor, which are commonly distributed in centric nervous-system and peripheral-tissues, control the system of cardiovascular , fluid balance, and cells of endothelial (4). Adipokineapelin has recently identified as a new adipo-kinethat is expresses and secreted by the Adipocytes mature in both of humans and mouse (5). Insulin controls, by Vosvatidilinoctol 3-kinase and protein kinase C, the expression abelian in human adipocytes (6).
Obesity is a common result in PCOS women (7), butisn't considered a diagnostic criterion. PCOS isn't just a disease of the reproductive system; it's also been linked to type two diabetes, metabolic syndrome, and, in some cases, disease of cardiovascular. (8)

PCOS's cause is still uncertain (9). A consensus workshop on PCOS in Rotterdam concluded that two out of three factors should be available with the purpose diagnosis PCOS. (10)

Ovulation interruption of chronic, clinical and / or biochemical evidence of excessive androgens, and ultrasound or laparoscopic findings of polycystic ovaries are all examples. Only after ruling out other identified diseases with clinical symptoms that are similar, such as hypothyroidism and elevated prolactin, PCOS has no clear cause, but genetic predisposition appears to play a significant role [11].

The multigene family of glutathione S-transferases (EC number 2.5.1.18) catalyzes the formation of linkers between glutathione (GSH) and various xenobiotic substrates. There are 16 cytosolic GST genes in humans, which are divided into (6) classes: (Alpha, Mu, Omega, Pi, Theta, and Zeta). In common, GSTs that are grouped inside a class share more than 60% personality though those with under 30% character are sorted into isolated classes. Nonetheless, an arrangement of GSTs did not depend only on series of arrangements, but also immunological connections, substrate active properties, and protein structure correlations. GSTs can be classified as biosynthetic-or the detoxification-type by known elements of these proteins, which are normally gotten from biochemical investigations (12).
The study's aim: Is asses' serum concentration of apelin-13 and pituitary gland hormone and their relationship to the danger of cardiovascular illness. In healthfull ladies and patients' ladies with PCO disorder.

Materials and Methods:

This study including 54 patients with PCOS (their ages ranging from (15-40) years subdivided by Body mass into normal weight: BMI <30 (kg)/ (m2) (n= 22) and also Sub-group excessive weight: BMI ≥ 30 (kg)/ (m^2) (n= 32)), also34 of woman health their ages ran from (19-30) years, was carried out in Kamal Al- samarae Hospital, From January to June 2020. Were enlisted for this investigation after their endorsement. The ladies with PCOS were identify depended on the 2003 criteria of Rotterdam (19(with at the least 2 of the accompanying highlights biochemical hyper-androgens clinical or and amenorrhea, oligomenorrhea, and PCOS on ultrasound. Avoidance criteria including: metabolic, untimely ovarian disappointment, neoplasia of ovarian, acromegaly, or cardiac disease linked condition or other simultaneous medicinal ailment (e.g diabetes mellitus), ladies who are meaning to begin an eating regimen or a particular program of physical action. Weight Index (BMI) was determined utilizing the accompanying recipe: weight (kg) /tallness (m^2). Waist circumference, which refer to the obesity central, was estimated between the costal edge and iliac peak alignment of the umbilical pivot,

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while the Hip circuit was estimated by the hip circumference was measured to the buttocks. WHR demonstrated of the distribution fat.
This survey was approved through the Committee of the Scientific in College also a verbal consent form was obtained from each participant enrolled in the study.

Laboratory methods: -

In this research, 5 mL of venous blood was drawn through a Vacutainer from each woman (patient and healthy), then the blood was placed in a gel tube during the early follicular stage (days 2–5) of the menstrual cycle, then left to coagulate, then separated by centrifuged at three thousand (rpm) for ten minutes to obtain serum. The collected serum was used to check the concentration of FBS as well as the lipid profile measured manually using a kit (human, Germany), the hormonal profile measured using a VIDAS analyzer (Biomerieux, France), and the serum that was left over was stored and preserved frosty at -40°C for the diagnosis of insulin hormone at fasting using ELISA (Demeditec, Germany), apelin-13 by ELISA, and GST Activity measured using a kit (human and GST Activity measured manual using GSH (Sigma chemicals, U.S.A).

Statistical analysis: -

The data was managed and analyzed using version 23. The number and percentage of categorical variables, as well as the mean±SD of continuous variables, were used to perform descriptive statistics.

Results:

FSH and apelin-13 levels in the blood were significantly decrease in PCOS patients compared to healrhygroupat(P values ≤ 0.01), while LH, LH/FSH, testosterone, insulin, HOMO-IR and GST activity levels were significantly higher in PCOS patient than in controls at (P values ≤ 0.01) as shown in table (1).

Table 1: Demographic Apelin -13, GST Activity and hormones (FSH, LH, T, insulin) of ladies with PCOS and controls

GroupsParameters	Polycystic ovary syndrome (PCOS) No. (56)	Healthy control No. (34)	P value
LH	6.82 ± 2.20 (1.99 – 12.32)	3.27 ± 1.02 (2.1 - 6.4)	*0.0001
FSH	3.69 ± 1.71 (0.6 - 8.52)	6.24 ± 1.21 (3.5 – 8.5)	*0.0001
LH/FSH ratio	2.25 ± 1.44 (0.65 -9.83)	0.52 ± 0.11 (0.30 - 0.40)	*0.0001
Testosterone	0.67 ± 0.21 (0.2 - 1.3)	0.34 ± 0.20 (0.1 – 0.7)	*0.0001
Insulin	35.64 ± 25.19 (2.05 - 94.96)	24.23 ± 15.00 (0.9 – 62.15)	*0.008
HOMO-IR	0.46 ± 0.33 (0.02 - 1.22)	0.25 ± 0.14 (0.01 – 0.56)	*0.0001

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Apelin-13	11.21 ± 1.51 (3.02- 22.92)	34.90 ± 5.98 (3.87 – 120.26)	*0.0001
GST activity	9.70 ± 1.05 (1.56 – 34.37)	4.71 ± 0.71 (1.04 – 17.18)	*0.0001

In this study found a Lower,insulin, and HOMA IR in Normal weight PCOS when compared to excessive weight PCOS, while higher AP-13 levels, GST activity levels in Normal weight PCOS when compared to excessive weightcontrol as shown in table (2).

Table 2: Hormonal profile, insulin, HOMA IR, apelin-13 and GST activity of the studied groups.

Groups / Parameters	Normal weight polycystic ovary syndrome (PCO) Groupe (1)	excessive weight polycystic ovary syndrome (PCO) Groupe (2)	P value
Apelin-13	13.29 ± 2.61 (5.02 - 67.95)	9.42 ± 1.66 (2.16 - 46.71)	0.712
GST activity (IU/L)	11.31 ± 1.71 (1.56 - 34.37)	8.31 ± 1.27 (1.56 - 30.20)	0.167
Insulin (µIU/mL)	35.50 ± 26.22 (2.05 - 94.96)	35.76 ± 24.71 (5.68 - 81.46)	0.970
HOMA-IR	0.44 ± 0.34 (0.02 - 1.15)	0.47 ± 0.33 (0.07 - 1.22)	0.759

In the present study, researchers discovered that Apelin-13 levels in PCOS patients were substantially and positively associated with BMI, Insulin, and HOMA IR ($P \leq 0.05$), and AP-13 levels weresignificantly and negatively correlated with FSH and LH Levels in PCOS group ($P \leq 0.05$) as shown in table (3).

Table 3: correlation between apelin-13 and some variables

		Apelin-13 Polycystic ovary syndrome (PCOS) No. (56)
Age (years)	R	-0.023
	P	0.867
BMI (Kg/m2)	R	0.312*
	P	0.019
WHR	R	-0.109
	P	0.423
LH	R	-0.291*
	P	0.030
FSH	R	-0.290*
	P	0.030
LH/FSH ratio	R	0.042
	P	0.758
Testosterone	R	-0.028
	P	0.838
Insulin	R	0.485**
	P	0.0001
HOMO-IR	R	0.521**
	P	0.0001
GST activity	R	-0.005
	P	0.969

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Discussion: -

PCOSisgeneralendo-crinopathy an ecting (6-13 present) of ladies of reproductive age and is one of the majore causes lead to the poor fertility in womenthat affects up to 10% ofwomen.It is a common state with a scope of clinical characteristic that effects ladies in reproductive age. These reproductive characteristics involve oligo anovulation (diminished ovulation), irregular menstrual cycles and hyper-androgenism, insulin resistance (IR), hirsutism, excess weight, and infertility are all symptoms of PCOS. (13).

Apelin is a polypeptide known as the APJ G-coupled protein receptor ligand. There are many active forms of apelin likes AP- 36,apelin 13, apelin17, and AP-13 in its pyroglutamated form. The central nervous-system, especially the.hypothalamus, and some peripheral tissues express Apelin and APJ (14, 15).

In the present examination, AP-13 levels were decrease in patient's woman with PCOS, when contrasted with healthy woman (16), and lower levels of apelin-13 in excessive weight patients when contrasted with normal weightPCO.These outcomes were in concurrence with Ibrahim NA, et al., (18) who announced decrease in AP-13 level in excessive weight patients PCOS and increase in normal weight PCOS patient's, suggesting.a compensating mechanism for insulin resistance (IR) metabolic effects.

Our results were in disagreement with Bongrani A, et al. (17)Who found that normal weight PCOS has a lower AP-13 level than excessive weight PCOS.

Also,these outcomes were indisagreement with Roche J et al., (18) who announced increased in AP-13 level in excessive weight patients PCOS when contrasted with normal weight PCOS patients. Yet, GST Activity were.rise in PCOS cases.when contrasted with.control gathering.

In.the present study,as compared to the healthy groups, there was a substantial declin in hormone FSH and LH increase in the PCO syndrome group (P-value equal 0.01), and there wasn't significant differences between the regular and excessive weight PCOS sub – groups and these findings were consistent with those of Malini NA., (19) who found a statistically significanttlydeclin in hormone FSH and LH increase in PCO syndrome subgroups as compared to healthy group. These findings support the notion that PCOS is characterized by a high degree of LH and a relative lack of FSH.In the current study testosterone (T) levels in PCOS were.significanthigher.than in the control.group (P-value ≤ 0.05). The cause of excessive LH secretion in women with PCO syndrome may be an increased sensitivity of the pituitary gland to (GnRH) or changes in the secretion patterns of (GnRH). It appears to be the product of the hypothalamic pulse generators acquired reduced sensitivity to the adverse reactions to estrogen and progesterone in PCO syndrome, likely as a result of chronic exposure to estrogen.

There was non-connection between AP-13 and, testosterone, LH/FSH proportion in PCOS subgroups as shown in (Table-2). In the present examination and in concurrence with Tekin S, et al., (20) there are a positive correlation have been watch between AP-13 serum levels and both of (BMI), insulin, and HOMO-IR in PCOS gathering, and negative correlation with LH and FSH levels. Our results were in disagreement with Chang CY. (21)And Choi YS.(22)Which found no connection between Apelin-13 levels,insulin,homeostatic model assessment for insulin resistance, and body mass index. This might be related to the reason that HOMA-IR is focused primarily on fasting.glucoseand.levels of insulin, and apelin enhances inmetabolism of glucose by raising the use of glucose in insulin-sensitive tissue, probably in an insulin.independent way rather than through glucose inhibition production in the liver (22). The connection between AP-13 levels and HOMA-IR could be explained by these details.

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Discrepant discoveries among distributed examinations might be credited to the distinctions in ethnicity, age, ponder structure, hereditary attributes of populaces and survey implied technique. In this manner, further investigations are required in bigger companions with various hereditary foundations.

Conclusion

In this study we found: -

- High levels of the insulin and HOMA-IR, AP-13, in the excessive weight patients' than normal weight patient.
- Depending on our results that obtained during this study, apelin-13 isn't legitimately ensnared in the PCOS pathogenesis, yet they might be included as (an adipokines) influenced through BMI and insulin.hormone.
- High levels of the insulin, HOMO-IR, LH level, and GST activity in PCOS groups than the control groups.
- In Iraqi women with PCOS, serum apelin-13 is inversely correlated with age, indicating a trend of change in adipokine homeostasis as the age advances. Lower levels of apelin possibly effect on insulin resistance development (IR) in patients of PCOS.
- High level of GST activity may share to rise the hazard of illnesses of CVD in pcos women.

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