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The effect of Clusterin level as a potential marker in women with polycystic ovary syndrome

Hiba Ali Numan[1*], Thualfeqar G.M. Almohanna[2], Mohammed. Q. Almayali3, Rawaa Adday Ali[4], Hanaa Khazal Abdulghareeb Taha1[5], Hanaa Addai Ali[6]
[1,3,5,6]Department of Chemistry, Faculty of Science, University of Kufa, Najaf, 54001, Iraq; hibaa.alameen@uokufa.edu.iq (H.A.N) ikbaliqbalhabdulkareem@gmail.com (M.Q.A) mariamhilla92@gmail.com (H.K.A.T) alimahdi1907@gmail.com (H.A.A)
[2]Department of Chemistry, Faculty of Medicine, University of Kufa, Najaf, 54001, Iraq; engsjs991@gmail.com (T.G.M.A)
[4]Microbiology Department, College of Veterinary Medicine, AL-Qasim Green University, Babylon 51013, Iraq; aalisadigj@gmail.com (R.A.A).

Abstract: An organ with high metabolic activity, adipose tissue secretes a variety of adipocytokines that control the metabolism of fats and carbohydrates and advance insulin resistance (IR). It is currently unclear what pathophysiological mechanism underlies PCOS. In most cases, IR and metabolic abnormalities coexist with PCOS, a chronic endocrine and metabolic illness. Prompt identification and intervention aid in enhancing patients' quality of life while delaying the development of associated issues. Adipokine clusterin (encoded by CLU) is new. Diabetes and obesity-related populations have higher serum clusterin levels. In order to establish a foundation for early PCOS screening, diagnosis, and therapy, the current study examined variations in serum CLU levels in PCOS patients along with their relationships to sex hormones and metabolic markers. A case-control study design consisting of ninety newly diagnosed PCOS patients of ages ranging between (18-42) years have been recruited according to the Rotterdam criteria of PCOS diagnosis. To compare the results, 90 apparently healthy women of age were matched with the patients' group as a control group. Serum clusterin, fasting insulin (FIN), and fertile hormones have been measured in sera using the enzyme-linked immune sorbent assay (ELISA) technique. An independent t-test analysis was performed on the data. Pearson correlation was utilized to evaluate the relationship between the variables. It was found that the PCOS patients had considerably greater serum CLU (41.672± 3.85 vs. 28.5845± 3.01 µg/ml, $P < 0.001$) than healthy women. A multiple stepwise linear regression analysis showed that HOMA-IR was separately linked with BMI, and HOMA-IR were independently associated with CLU ($P < 0.05$). Serum CLU exhibited a positive connection ($P < 0.05$) with BMI, FSG, FINS, and HOMA-IR. Serum CLU in the PCOS group correlated well with TG, CLU, HOMA-IR, FSH, FSG, and FINS. The PCOS women group significantly outperformed the fertile, healthy women group regarding BMI, LH, FSH, FSG, FIN, HOMA-IR, TC, TG, and LDL-C levels. They also had lower levels of HDL-C and QUICKI values. Additionally, serum clustrein levels. 31.68 A cut-off value of CLU as a marker for diagnosing PCOS with a sensitivity of 90.0% and a specificity of 87.5% (AUC: P value = <0.0001, 0.887-1.000.

Keywords: *Clusterin; Fertile hormones, Insulin resistance; Insulin sensitivity; PCOS.*

1. Introduction

Polycystic ovarian syndrome, or PCOS, is a multifaceted endocrine disorder affecting a large number of women worldwide who are fertile (Zhou et al., 2000). Insulin resistance, elevated testosterone levels, enlarged and dysfunctional ovaries, and other conditions are commonly associated with this syndrome (Witchel et al., 2019b). About 10% of women are estimated to have PCOS prior to menopause

* Correspondence: hibaa.alameen@uokufa.edu.iq

and experience its aftereffects (Sadeghi et al., 2022). The signs and symptoms of androgen excess, ovarian dysfunction, and polycystic ovarian morphology on ultrasonography are combined to describe and diagnose it (Nash-Thomas, 2020).

Since PCOS is one of the conditions that cannot be diagnosed using typical diagnostic techniques like blood tests, cultures, and biopsies, there is no specific test for PCOS diagnosis. The act of narrowing down the pool of potential diagnoses by ruling out relevant disorders based on symptoms is known as differential diagnosis. Based on related research, To establish a differential diagnosis for PCOS, conditions such as adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, and thyroid disorders should be investigated (Di Lorenzo et al., 2023, Witchel et al., 2019a). While past medical history, weight changes, and insulin resistance symptoms may be useful, the most commonly recommended tests include transvaginal ultrasound, a pelvic examination, and hormone testing (Al-Ashou and AL-Saraj, 2023). Thus far, research on both humans and animals has demonstrated a significant correlation between irisin and insulin resistance (Li et al., 2015). It could be regarded as a PCOS early biomarker that enables an early diagnosis of the illness. Its detection may have a significant impact on human physiology and aid in lowering the population's long-term morbidity (Bostanci et al., 2015, Kyritsi et al., 2017).

A heterodimeric glycoprotein called clusterin (CLU) is found in many different organs and bodily fluids and is controlled by a range of environmental stressors. CLU has been linked to several physiological and pathological processes, including the control of the immune system, cell death, cell cycle, DNA repair, tissue differentiation and remodelling, lipid transport, and the advancement of cancer (Pereira et al., 2018, Rohne et al., 2016).

The heterodimeric glycoprotein known as human CLU1 was first isolated from serum and identified as an apolipoprotein (Kirszbaum et al., 1989, De Silva et al., 1990). In the wake of these investigations, CLU was discovered in every human bodily fluid examined (Jenne and Tschopp, 1992). CLU is involved in extracellular or intracellular activities in addition to its role as an apolipoprotein. The classic hydrophobic secretory signal sequence is represented by the first 22 amino acids of the 449 amino acid polypeptide that the CLU gene encodes. Disulfide bonding marks the maturation of the primary translation molecule, which is then transformed into a form of roughly 60 kDa that is associated with the endoplasmic reticulum and high in mannose. The mature secreted heterodimeric CLU protein form, which is roughly 70–80 kDa, is the result of prolonged further N-linked glycosylation and proteolytical cleavage in the trans-Golgicompartments (Trougakos and Gonos, 2002). A different ~55 kDa form of CLU protein, called nuclear CLU (n-CLU55), has been shown to arise from a ~49 kDa primary protein form (c-CLU49) in MCF-7 cells after death (Yang et al., 2000). An alternatively spliced CLU transcript is the source of this c-CLU49 protein variant (Leskov et al., 2003).

2. Materials and Methods

Ninety newly diagnosed PCOS patients with ages ranging from 18 to 42 years old were recruited for a case-control study. Gynaecologists at the Fertility Center and AL-Zahraa Teaching Hospital in the Najaf Governorate identified PCOS in women between December 2021 and April 2022 using the Rotterdam criteria for PCOS diagnosis. Ninety-nine healthy women who matched the sick group's age were included as a control group in order to compare the results. The University of Kufa's Faculty of Science Ethics Committee and the Najaf Health Directorate of the Hospital Administration for Obstetrics and Gynecology authorized the study. By dividing an individual's length in square meters by their weight in kilograms, the Body Mass Index (BMI) was calculated as follows: BMI = (weight in kg) / (height in meters2) (McDougall et al., 2018). Venous blood samples taken during fasting from the patients and the control group were divided. The serum was kept at -20°C until it was time for analysis. Using a kit, the colourimetric approach was used to estimate the serum glucose levels during a fasting inquiry and the levels of lipid profile (TC, TG, LDLC, and HDL-C) for quantitative in vitro diagnostic evaluation. Insulin levels were assessed using the ELISA test (CALBIOTCH Company, USA). The

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Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) was utilized to estimate the Insulin Resistance Index (DeUgarte et al., 2005).

$$Insulin\ \left(\frac{\mu U}{ml}\right) \times\ glucose\ \left(in\frac{mg}{dl}\right) = \frac{HOMAIR}{405} \quad 1$$

$$HOMA\,\beta\,\% = \frac{360 \times insulin}{Glucose - 63} \quad 2$$

Clusterin was determined by ELISA assay (Elabscience, USA)

GraphPad Prism version 5 and the Statistical Package of Social Science (SPSS ver. 21) were used to conduct the statistical analysis. For continuous variables, this formula was the standard deviation (SD) plus or minus the mean. For variables with uneven and equal frequencies, respectively, the Independent t-test and the Paired t-test were used to look for significant differences. Standardized Pearson coefficients were used to evaluate bivariate correlations. Statistically and extremely statistically significant were the designations given to the P values less than 0.05 and 0.01, respectively.

3. Results and Discussion

Table 1 displays the study groups' initial set of characteristics. Ninety people with PCOS made up the 180 samples; ninety seemingly healthy women served as the control group. There is no discernible variation in the age variables between the groups under study. WHR and BMI were considerably greater when comparing the patient and control groups. In addition to hyperandrogenism, other symptoms include high LH levels and, as a result, elevated serum LH to FSH ratio, as well as reversal of the peripheral serum estradiol to estrone ratio., and incorrect pituitary gonadotropic hormone outputs. Transcriptional preference for the β-subunit of LH over the β-subunit of FSH is the reason why the LH/FSH ratio increases in PCOS patients. due to increased gonadotropin-releasing hormone secretion frequency (Młotkowska et al., 2020, Malini and George, 2018).

Table 1.
General patient and control characteristics.

Parameters	Groups		P value
	Patients group Mean±SD	Healthy group Mean±SD	
No.	90	90	-
Age(Years)	29.35± 7.67	28.11± 8.04	NS
BMI(kg/m²)	34.3.38 ± 2.10	22.38 ± 0.85	0.001

Participants in this study had greater total antral follicle counts and larger total ovarian volumes when their LH/FSH ratios were higher, which is contrary to other studies' findings (Malini and George, 2018). Table 2 shows the lipid profile levels for both sick and healthy groups.

Table 2.
The lipid profile levels in sick and healthy groups.

Parameters	Groups		P.value
	PCOS patients Mean±SD	Healthy group Mean±SD	
TC (mmol/L)	4.88±1.72	3.41±1.01	0.015
TG (mmol/L)	1.78±0.43	0.81±0.07	0.022
HDL-C (mmol/L)	1.21±0.25	1.36±0.20	0.047
LDL-C (mmol/L)	3.28±0.99	1.92±0.82	0.018
VLDL-C (mmol/L)	0.362±0.07	0.165±0.01	0.01

The present findings indicate that lipid profile alterations in PCOS women may be associated with lipid disruptions and elevated body fat percentage, which are critical metabolic risk factors in PCOS women. Metabolic problems, insulin resistance, impaired glucose tolerance (IGT), diabetic mellitus

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(DM), and an increase in the number of cardiovascular disease risk factors have all been linked to PCOS (Wild et al., 2011).

As a result, a lower blood level of HDL-C may be linked to cell system deficiencies when applying antioxidant and anti-inflammatory defences, which aids in developing atherogenic dyslipidemia in PCOS. In addition to having anti-inflammatory and anti-atherogenic qualities, HDL-C stops LDL particles from oxidizing. According to research, women with PCOS may experience changes in the quality of their HDL-C in addition to a decline in their HDL-C level (Kim and Choi, 2013). Table 3 compares hormonal profile levels in patients and healthy groups, and Table 4 compares the data on glycemic indices and insulin resistance in the patient groups with those in the healthy group.

Table 3.
Comparison of hormonal profile levels in patients and healthy groups.

Parameters	Groups		P.value
	Patients group Mean±SD	Healthy group Mean±SD	
LH (mIU/L)	10.83±1.69	4.25±0.95	0.009
FSH (IU/L)	6.16±2.01	4.29±2.18	0.054

Table 4.
Comparisons between the data of Glycemic indices and insulin resistance in the patient groups with the healthy group.

Parameters	PCOS Patients group Mean±SD	Healthy control group Mean±SD	P-value
FSG (mg/dL)	103.61±9.74	85.32±7.34	0.48
FIN (mIU/L)	14.39±6.75	9.24±3.75	0.0001
HOMA-IR	3.97±1.15	1.89±0.62	0.007
QUICKI	0.27.30±0.082	0.48.7±0.085	0.01

The most prevalent metabolic characteristic, insulin resistance (IR), is irrespective of body mass index (BMI) and body fat distribution and is present in approximately 35%–80% of women with PCOS (Pasquali et al., 1994). A pathological condition known as insulin resistance (IR) is typically described as having a diminished sensitivity or response to the metabolic activities of insulin. It has been shown to be a reliable predictor of several illnesses. The onset and persistence of PCOS in women are significantly influenced by their IR status. It is acknowledged to be the cause of numerous metabolic disorders linked to metabolic syndrome (Polak et al., 2017). If aberrant gonadotropin production and insulin resistance are related, several recent investigations have been carried out to explore this possibility (Wang et al., 2022). Banaszewska et al.'s earlier study discovered that there were significant differences in BMI and blood insulin levels between PCOS individuals with an LH/FSH ratio >2 and those with a ratio <2. In addition, Kurioka et al. found that hyperinsulinemia was present in most participants in the group with a ratio <2 (Banaszewska et al., 2003, Kurioka et al., 2007). Table 5 shows the clusterin levels in patients and healthy groups, and Figure 1 shows the ROC for clusterin.

Table 5
Comparison of clusterin levels in patients and healthy groups.

Parameters	Groups		P.value
	Patients group Mean±SD	Healthy group Mean±SD	
clusterin (pmol/L)	41.672± 3.85	28.5845± 3.01	0.001

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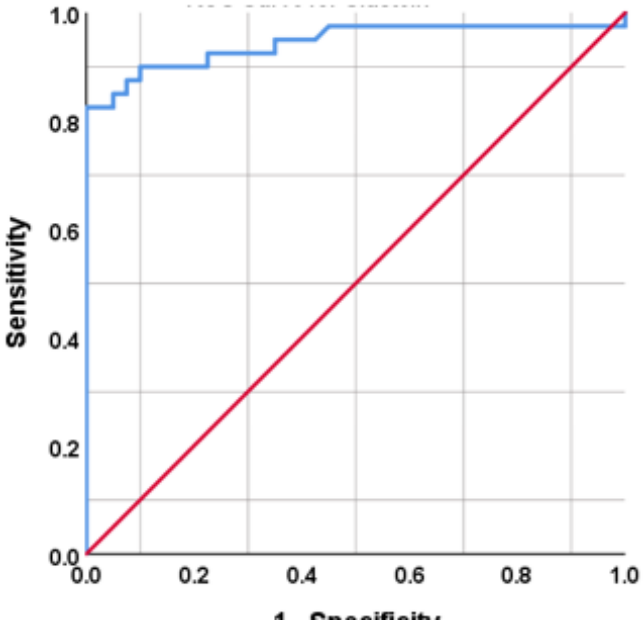

Figure 1.
Receive operating characteristic curve (ROC) for clustering.

Molten globule domains, three large intrinsically disordered regions of clusterin, are capable of stabilizing strained protein structures. It was determined twenty years ago that a discernible increase in clusterin expression was a hallmark of Alzheimer's disease (AD). It was eventually shown that clusterin could bind to amyloid-β peptides, preventing them from fibrillizing. By binding to megalin receptors and facilitating their endocytosis within glial cells, clusterin helps to eliminate amyloid-β fibrils and peptides. Clusterin functions as a complement inhibitor, which can lessen complement activation observed in AD. Clusterin, which regulates lipid and cholesterol levels, is also present in lipoprotein particles (Nuutinen et al., 2009). In summary, CLU seems to be a molecule involved in a number of internal processes in addition to acting as an effective extracellular chaperone or apolipoprotein. It most likely belongs to one of the several (unrelated) molecules in the vast family that coordinate the immediate cellular response to any kind of insult and control the ratio of cellular growth to arrest or death to survival. This hypothesis is supported by the numerous regulatory elements as well as the CLU gene promoter's remarkable sensitivity and responsiveness to a wide range of cytokines, growth factors, stressors, and apoptosis-inducing substances (Jones and Jomary, 2002). There are some studies that indicate that women with polycystic ovary syndrome are more susceptible to developing some types of cancer, such as endometrial cancer and breast cancer. Table 6 shows the correlations between clusterin and studied variables in women with polycystic ovary syndrome patients.

Table 6.
The correlations between clusterin and studied variables in women with polycystic ovary syndrome patients.

Variable	Cut-off concentration	Sensitivity%	Specificity%	AUC	95% CI of AUC	p-value
Clusterin (pmol/L)	31.68	90.0	87.5	0.944	0.887-1.000	<0.0001

Table 7 illustrates the correlation and *P* value between Clustein and biochemical parameters in women with polycystic ovary syndrome patients.

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Table 7.
Correlation between clustein and studied variables in women with polycystic ovary syndrome patients.

Variables	r	P-Value
Age (Years)	0.28	0.057
BMI (kg/m^2)	0.34	0.03
TC (mmol/L)	0.30	0.05
TG (mmol/L)	0.42	0.01
HDL-C (mmol/L)	-0.37	0.01
LDL-C (mmol/L)	0.31	0.05
VLDL-C (mmol/L)	0.21	0.062
LH (mIU/L)	0.47	0.01
FSH (IU/L)	0.32	0.05
FSG (mg/dL)	0.25	0.056
FIN (mIU/L)	0.36	0.02
HOMA-IR	0.33	0.03
QUICKI	-0.25	0.056

Where SD is the standard deviation, BMI is the body mass index, FSG is the fasting serum glucose, HOMA-IR is the Insulin Resistance Homeostatic Model Assessment, LH is the luteinizing hormone, FSH is the follicle-stimulating hormone, FAI is the fasting insulin, TT is total testosterone, FT is free testosterone and FAI free androgen index, TC is the total cholesterol, LDL-C is the low-density lipoprotein cholesterol, HDL-C is the high-density lipoprotein cholesterol, and TG is the triglycerides.
It can be seen from Table 7 that The level of HDL-C has a significant negative correlation, and it can also be seen that BMI, TC, TG, LDL-C, LH, FSH, FIN, and HOMA-IR have significant positive correlations and are significant with P value ($P<0.05$) with the serum clusterin level.

To the best of our knowledge, this study is the first to investigate clusterin's possible involvement in the onset of polycystic ovarian syndrome. According to our research, ovarian syndrome can result in hormonal abnormalities, irregular menstruation periods, elevated testosterone levels, and ovarian cysts. Pregnancy might be challenging when menstrual cycles are irregular, as this is typically accompanied by a lack of ovulation. Infertility is primarily caused by ovarian syndrome. Ovarian syndrome's medical and psychological repercussions, especially those linked to obesity, body image, and infertility, can lead to social stigma and mental health issues. Luteinizing hormone ("LH"), an ovarian hormone that stimulates the formation of the uterine lining, and estrogen, an ovarian hormone that regulates hair growth, may be present in high concentrations in women with polycystic ovary syndrome (Polak et al., 2017). Our results show that this gene is highly expressed in lymph node metastasis and that its up-regulation is closely related to the various stages of breast tumour development from normal tissue to breast lesions that are premalignant and malignant. Since there is a positive link between clusterin expression and tumour size, Overexpression of clusterin may be an acquired phenotypic trait that promotes the local invasion and spread of breast tumour cells. Consequently, clusters may play a significant role in the diagnosis of polycystic ovarian syndrome (Redondo et al., 2000). Overexpression of clusterin was substantially linked with negative progesterone and estrogen receptor status. Furthermore, three aggressive carcinomas that did not express progesterone or estrogen receptors were found to have nuclear clusterin. In recurrent androgen-independent tumour cells, nuclear clusterin staining was seen in a prior work (Akakura et al., 1996). These scientists hypothesize that clusterin's presence in the nucleus may inhibit the early stages of the apoptotic process.

4. Conclusion

Clusterin seems to be a protective protein that could change its isoform and location to maintain cellular survival. Consequently, adjusting it seems like a very promising approach to treating, curing, or

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avoiding a lot of diseases. First, it could be used as a biomarker for diseases related to the nervous system or addiction. Control of inflammatory illnesses like obesity and treating muscular atrophy in conditions like osteoporosis is needed to guarantee the effectiveness of cancer treatments; clusterin expression may be reduced, either directed or regulated. Additionally, taking supplements containing it could be a target to lessen neuropathic pain or a neuroprotector for conditions including Alzheimer's, α-synucleinopathies, and ischemic brain injury.

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