



## Genetic Polymorphisms Study of Polycystic Ovary Syndrome Associated with *Omentin-1V109D* Gene in Iraqi Women

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### Abstract

Polycystic ovary syndrome (PCOS) is the most frequent endocrinological disorder, occurring in young women at reproductive age. This study was carried out to investigate the association between the fat mass and obesity associated gene (Omentin-1V109D gene) polymorphism with some physiological and biochemical Parameters. The present study indicates to the association between PCOS patients and control groups according to the hormonal profile and there is a link between obesity and pathogenesis of hyperprolactinemia, our data showed highly significantly difference. This study shows demonstrated the comparison of the mean of selected Lipid profile between PCOS patients and control group involving (T. Cholesterol, Triglyceride, HDL, LDL and VLDL). The mean value of serum total cholesterol (T.C), Triglyceride, HDL, LDL and VLDL are highly significantly increased ( $p < 0.01$ ) in PCOS patients group compared with healthy group (control). It was found highly significant association ( $P \leq 0.01$ ) of serum-FSH, serum-LH, testosterone and prolactin hormones. It was found the mean value of serum total cholesterol, triglyceride, HDL, LDL and VLDL are highly significantly ( $P \leq 0.01$ ) increased in PCOS patients. The *Omentin* gene (V109D rs2274907A) polymorphism have a significant association with hyper LDL, in women with PCO, and may represent as a risk factor for PCOS incidence.

### 1. Introduction

Polycystic Ovary Syndrome (PCOS) is the most common heterogeneous complex endocrine disorder. It approximately affects 6-15% of the women in their reproductive age and is one of the leading cause's female poor fertility [1]. It was initially described as the association of anovulation and clinical and/or biological hyperandrogenism [2].

In 2003, the Rotterdam Consensus Conference introduced polycystic ovaries on ultrasound (corresponding to a follicle number per ovary  $\geq 12$  and/or an ovarian volume  $\geq 10$  mL) as a supplementary, not mandatory, diagnostic criterion [3]. Thus, PCOS diagnosis currently requires the presence of at least two of these three criteria:

Oligo/anovulation, hyperandrogenism, and polycystic ovaries morphology (PCOM) [4]. The patients affected by this syndrome may show an increased prevalence of obesity, insulin resistance, hypertension, dyslipidemia, metabolic syndrome, insulin tolerance, diabetes mellitus, gestational diabetes mellitus, hyperandrogenism (hirsutism, acne, and alopecia), oligomenorrhea, amenorrhea, anovulation and infertility, high BMI (weight gain), and high Luteinizing hormone: Follicle-stimulating hormone ratio (LH:FSH ratio). Diagnosis is made by physical and medical history and blood tests to check the hormones levels and ultrasound [5].

Some types of genetic studies and methods such as (candidate gene approach, connection analysis, family studies, and genome-wide association studies) have been utilized so far to investigate the genetic background of PCOS [6]. Omentin (also known as intelectin: ITLN) is one of the most major visceral fat adipokines expressed by genes 1 and 2. [7]. There are many references showing a positive correlation between Omentin and the levels of adiponectin and high-density lipoprotein (HDL) [8]. It has been demonstrated in the literature that A326T (rs2274907) single nucleotide miss-sense polymorphism in the exon-4 of the Omentin 1 gene, which substitutes valine instead of aspartate at position 109 (Val109Asp or V109D), can lead to PCOS. A number of studies have shown that Omentin enhances glucose uptake in human adipocytes by increasing insulin sensitivity [7]. In addition, some studies indicated that plasma Omentin 1 level is inversely correlated with BMI, waist circumference, and insulin resist IR as measured by homeostasis model assessment (HOMA). Moreover, there are data showing a positive correlation between Omentin and the levels of adiponectin and high-density lipoprotein (HDL) [7], [8]. It has been demonstrated in the literature that A326T (rs2274907) single nucleotide miss-sense polymorphism in the exon-4 of the Omentin 1 gene, which substitutes valine instead of aspartate at position 109 (Val109Asp or V109D), could be accompanied by T2D and obesity, [9, 10]. Structurally, position 109 is located outside the fibrinogen domain of Omentin protein. Therefore, Val109Asp and other sequence variations can lead to a real disease-causing mutation [9].

Omentin-1 (*OME-1*) has been identified as a significant visceral (omental) fat secretory adipokine. This adipokine may act as an endocrine factor affecting muscles, liver, and omental adipose depot; it enhances insulin sensitivity and glucose metabolism. It has been suggested that serum omentin-1 is elevated in patients with fatty liver diseases and represents an independent predictor for hepatocyte ballooning in these patients. Omentin-1, also known as intelectin-1, is a recently identified novel adipocytokine of 313 amino acids, expressed in visceral (omental and epicardial) fat and mesothelial cells, vascular cells, airway goblet cells, small intestine, colon, ovary, and plasma [11].

The aim of this study to determine relationship between genetic variations of *Omentin-1*V109D gene for women that have PCOS with hormonal parameters LH, FSH, Prolactin, Testosterone and, Lipid profile.

## 2. Materials and Methods

### 2.1. Ethics Statement

This study was reviewed and approved by the Institutional Research Ethics Committee of the Al-Razi Center for Research & Medical Kits Production, Corporation of Research and Industrial Development (Baghdad), Iraq. Written informed consent was obtained from all participants, including both patients and apparently healthy individuals. Participants were informed of the study objectives, the confidentiality of their data, and their right to withdraw at any stage without penalty.

### 2.2. Participant Recruitment and Sample Collection

This study was conducted during the period from November 2022 until June 2023. The patients diagnosed with PCOS under the supervision of a specialist doctor in a private clinic in the district of Al-Imameen Al-Kazimin medical city in the Baghdad and Fertility Centre Al-Imameen Al-Kazimin. The current study was approved by Al-Razi Center for Research & Medical Kits Production/ Corporation of Research and Industrial Development (Baghdad) as well as the subject information was collected using special question on other hand writing information consents were obtained for all patients and apparently healthy groups. Blood samples were collected from women with PCOS (n=40) and apparently healthy group (n=40), and their age ranged was 20-40 years. There are genetic and environmental factors contribute to this hormonal imbalance in PCOS. Patients are identified if they are between the ages of (20 – 40) and have at least two of the following characteristics: they have a medical history consistent with PCOS, PCOS was first detected by ultrasound scan, and they experienced oligomenorrhea,

amenorrhea, or highly irregular menses. Ultrasounds can detect PCOS on follicular phase days 3, 4, and 5, patients and healthy controls gave eight ml venous blood samples, five ml of this blood was coagulated at 37°C for 30 minutes in a vacuum sterile glassware gel tube before centrifugation.

### 2.3. DNA Extraction

DNA was extracted from the all (PCOS cases and controls) blood samples by taking 5ml whole blood that placed in EDTA tubes for molecular studies using DNA purification kit (Genaid/Korea). Detection of concentration and purity of DNA by measuring using a Nano-Drop spectrophotometer.

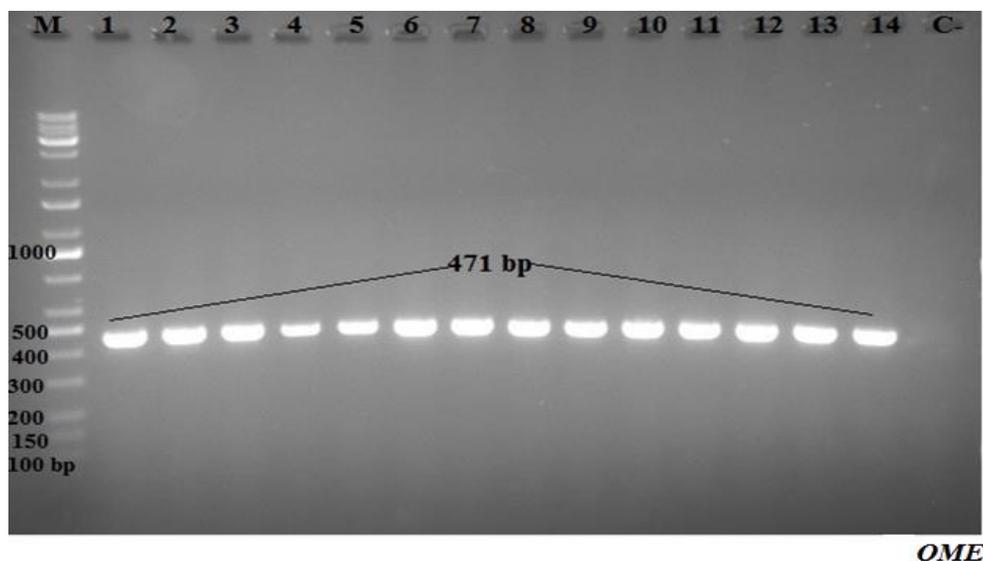
By Polymerase chain reaction (PCR), amplification were detecting in a total volume of 25µl involved (50ng/µl Template DNA, 9.5µl Deionized water, 12.5µl Go Taq G2 promeg , 1µl Forward primer (10 pmol/µl) and 1µl Reverse primer (10 pmol/µl). The *Omentin-1 (OME-1) gene* regions were amplified using the forward primer 5'-GAGCCTTTAGGCCATGTCTCT-3' and the reverse primer was 5'-CTCTCCTTCTTCTCCAGCCCAT-3' [10], [11]. Below the a temperature profile for an *Omentin-1 (OME-1) gene* program, which begins with a 5-minute denaturation at (96°C) and continues with (35 cycles) of denaturation at (94°C) for 1 minute, annealing at (55 °C) for 48 seconds, and elongation at (72°C) for 1 minute. The PCR result was detected by electrophoresis on a 1.5% agarose gel, where the DNA band (265 bp) was visualized and documented using a gel documentation system. Following PCR amplification, PCR products could be consumed using *Omentin-1 (OME-1)* restriction enzymes from thermo scientific , Lithuania, and enzyme buffer (RFLP), the *Omentin-1 (OME-1)* PCR were incubate at room temperature for 24 hours before being electrophoretically separated on a 2% agarose gel for use in determining *Omentin-1 (OME-1)* polymorphisms.

The Statistical Analysis System [12] program was used to detect the effect of difference factors in study parameters. T-test and Least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significant compare between means. Chi-square test was used to significant compare between percentage (0.05 and 0.01 probability). Estimate of Odd ratio and CI in this study.

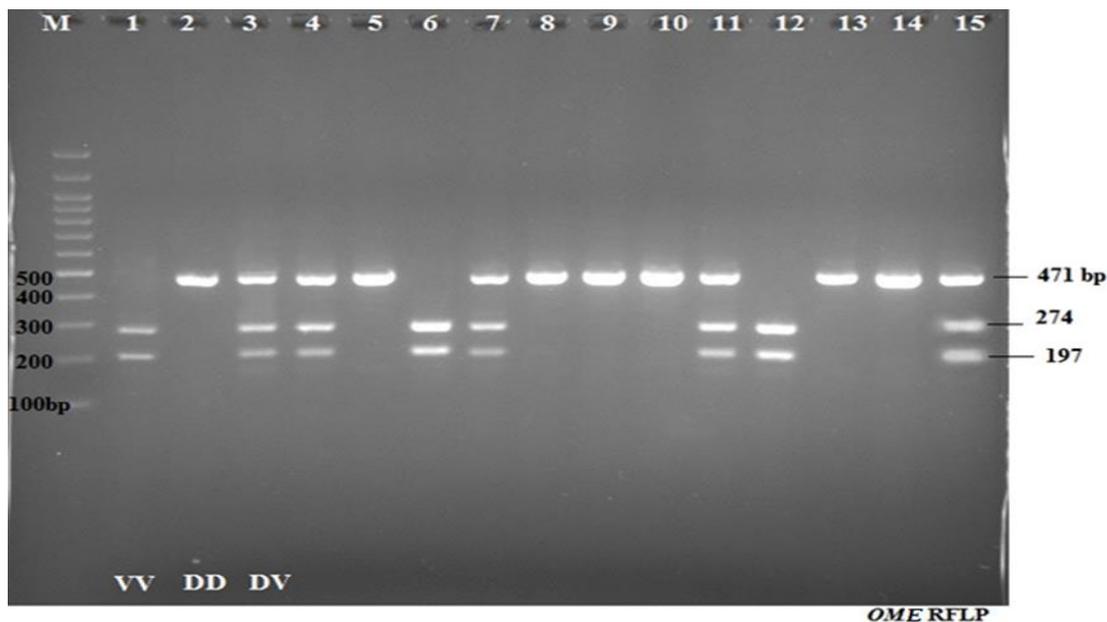
## 3. Results and Discussion

### 3.1. Results

Figure (1) shows the electrophoresis of the (*OME* gene) at 471bp. PCR product of omentin gene was digested overnight at room temperature and electrophoresed on a 2% agarose gel, yielding bands of heterozygous variant type (DV) (471 bp and 274bp,197bp), homozygous wild type (DD) (471bp) and homozygous variant genotype (VV) (274 bp,197bp). Digestion of *OME* gene by XmiI enzymes (Thermo Scientific) is shown in Figure (2).



**Figure (1):** Gel electrophoresis of the PCR product (*OME* gene) by (1.5%) (1h/90v). Lane M: DNA marker (100bp), Lane C- negative control, Lanes (1-14) are samples.



**Figure (2):** The (*OME*) gene after enzyme digestion (*XmiI*) and electrophoresis on (2%) agarose gel. Lane M (100BP) DNA marker, lane (3,4,7,11, 15) heterozygous variant type (DV) (471 bp and 274bp,197bp), lane (2, 5,8,9,10,13,14) homozygous wild type (DD) (471bp) and lane (1,6,12) homozygous variant genotype (VV) (274 bp,197bp).

Our results show the mean value of age for patients and control group were ( $26.52 \pm 1.21$ ) yr., ( $28.45 \pm 1.16$ ) yr. respectively as shown in Table (1) explained the Comparison between mean value of PCOS patients and controls groups in Age and BMI. Also in the same table, the results of the mean value of BMI for PCOS patients and controls group were ( $34.94 \pm 1.33$ ) and ( $25.93 \pm 1.10$ ) respectively showed highly significant difference ( $P < 0.01$ ) between these groups, these result because of the choice of age group No significant association between Iraqi women with polycystic ovary syndrome.

**Table (1):** Comparison between PCOS patients and controls groups in Age and BMI.

Group	Mean $\pm$ SE	
	Age (year)	BMI (kg/m <sup>2</sup> )
PCOS Patients	$26.52 \pm 1.21$	$34.94 \pm 1.33$
Control	$28.45 \pm 1.16$	$25.93 \pm 1.10$
T-test	3.346 NS	3.450 **
P-value	0.255	0.0001
** ( $P < 0.01$ )		

### Hormonal Profile

Data in Table (2) demonstrated that the Mean  $\pm$  SE of FSH, LH, LH/FSH, Testosterone and Prolactin hormones in the PCOS patient group and Control. The present study indicates to the association between PCOS patients and control groups according to the Hormonal profile it was found highly significant association of serum-FSH and serum-LH. Al-Juaifari (2019) showed highly significant in E2 hormone level in the PCOS women.

There is a link between obesity and pathogenesis of hyperprolactinemia our data showed highly significantly difference. A previous study was conducted on a group of women in south India with PCOS by Naghshband and Malini they found BMI and WC, waist circumference LH, LH/FSH ratio, and testosterone levels were significantly higher in the PCOS group. Higher levels of other metabolic parameters such as BP $\geq$ 130/85 mm Hg, cholesterol, LDL, fasting glucose levels, insulin, were observed, whereas there was a significant reduction in HDL when compared with the control group [17].

**Table (2):** Comparison between PCOS patients and control groups according to the selected Hormonal profile.

Group	Mean $\pm$ SE				
	FSH (mIU/mL)	LH (mIU/mL)	LH/FSH	Testosterone (ng/mL)	Prolactin (ng/mL)
PCOS Patients (N=40)	4.40 $\pm$ 0.32	8.36 $\pm$ 0.30	2.53 $\pm$ 0.40	1.187 $\pm$ 0.18	32.13 $\pm$ 1.79
Control (N= 40)	5.99 $\pm$ 0.26	4.76 $\pm$ 0.17	0.846 $\pm$ 0.04	0.416 $\pm$ 0.03	13.90 $\pm$ 1.09
T-test	0.820 **	0.693 **	0.805 **	1.990 **	4.176 **
P-value	0.0002	0.0001	0.0001	0.0001	0.0001
** (P $\leq$ 0.01)					

Our study as shows in Table (3) demonstrated the comparison of the mean of selected Lipid profile between PCOS patients and control group involving (T. Cholesterol, Triglyceride, HDL, LDL and VLDL). The mean value of serum total cholesterol ( T.C ) , Triglyceride, HDL , LDL and VLDL are highly significantly increased ( p<0.01) in PCOS patients group (190.98  $\pm$ 6.58) , (158.76  $\pm$ 9.87), (33.45  $\pm$ 1.10) , (124.56  $\pm$ 3.99 ) and (31.75  $\pm$ 1.97) (mg/dL ) respectively compared with healthy group (control )( 89.52  $\pm$ 3.64) ,( 82.33  $\pm$ 2.54) , (50.13  $\pm$ 3.01), (43.47  $\pm$ 1.22), (16.46  $\pm$ 0.51) (mg/dL ) respectively ( p=0.0001), were Similarly, to study by Jahanfar *et al* .which aimed at evaluating the genetic and environmental factors affecting lipids among twins, found no significant differences between women with and without PCOS in serum total cholesterol[14]. Previous study by (Naghshband and Malini was the first to investigate the *FTO* gene variant rs9939609 association with PCOS susceptibility in South Indian women.[17] Our findings indicated that *FTO* SNP rs9939609 was a significant association of *FTO* polymorphism with hyperandrogenemia, fasting glucose levels, and BMI as in South Indian women with PCOS.

The Association between genotype and allele of OMN-1 gene Polymorphism in results indicated in Table (4) show a significant relationship between Genotype and allele frequency of Omentin gene in patients with PCOS and control groups. (OR=18.13; 95%, C.I. =0.99-329.28), while the recessive model of inheritance allele was no significantly different in both groups, and was not associated with the increased risk to PCO (OR=1.0; 95%, C.I. = 0.01-51.63).

**Table (3):** Comparison between PCOS patients and controls according to the selected Lipid profile.

Group	Mean $\pm$ SE				
	T. Cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
PCOS Patients (N=40)	190.98 $\pm$ 6.58	158.76 $\pm$ 9.87	33.45 $\pm$ 1.10	124.56 $\pm$ 3.99	31.75 $\pm$ 1.97
Control (N=40)	89.52 $\pm$ 3.64	82.33 $\pm$ 2.54	50.13 $\pm$ 3.01	43.47 $\pm$ 1.22	16.46 $\pm$ 0.51
T-test	14.979 **	20.301 **	6.370 **	8.325 **	4.060 **
P-value	0.0001	0.0001	0.0001	0.0001	0.0001
** (P $\leq$ 0.01)					

**Table (4):** Genotype and allele frequency of Omentin gene in patients and control groups.

Genotype/ Omentin gene	Patients No. (%)	Control No. (%)	Chi-Square ( $\chi^2$ )	P-value	O.R. (C.I.)
DD	9 (22.50%)	28 (70.00%)	9.75 **	0.0018	Ref. =1
DV	17 (42.50%)	11 (27.50%)	1.285 NS	0.256	0.208 (0.13-0.78)
VV	14 (35.00%)	1 (2.50%)	11.27 **	0.0008	1.35 (0.92-2.24)
Total	40 (100%)	40 (100%)		--	
P-value	0.289 NS	0.0001 **		--	
Allele	Frequency				
D	35 (0.44)	67 (0.84)	P-value = 0.0015 **		
V	45 (0.56)	13 (0.16)	P-value = 0.0001 **		
** (P $\leq$ 0.01), NS: Non-Significant					

The results of this study as listed in the Table (5) showed non-significant ( $P > 0.05$ ) when compared Omentin gene polymorphism and patients' group according to the selected Lipid profile, Only LDL shown significant difference ( $P=0.05$ ).

**Table (5):** Relationship between Omentin gene polymorphism and patients group according to the selected Lipid profile.

Genotype/ Omentin gene	Mean $\pm$ SE				
	Cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
DD	197.27 $\pm$ 9.92	163.24 $\pm$ 18.39	34.09 $\pm$ 2.49 a	124.11 $\pm$ 6.81	32.65 $\pm$ 3.67
DV	187.42 $\pm$ 10.33	144.03 $\pm$ 12.68	34.33 $\pm$ 1.53 b	126.12 $\pm$ 5.36	28.80 $\pm$ 2.53
VV	191.21 $\pm$ 13.03	173.76 $\pm$ 20.56	31.41 $\pm$ 1.56 b	132.67 $\pm$ 8.64	34.75 $\pm$ 4.11
LSD value	34.69 NS	52.19 NS	5.381 NS	18.022 *	10.438 NS
P-value	0.854	0.391	0.15	0.050	0.434
<p>Means having with the different letters in same column differed significantly,  ** (<math>P \leq 0.01</math>). * (<math>P \leq 0.05</math>)</p>					

### 3.2. Discussion

The results of this study were consistent with a study which reported that PCOS is the most common endocrine disorder among women between the ages of between (20-40) years .Our results similar to previous study by [13] there were no significant differences in age, residence, and education between the cases and the controls. While our results contradicted with study by [15] which found an association between body mass index and PCO. Our results revealed that the number and percentage of patients higher in age group (25-40 yr.) and (BMI) group were (Overweight  $>$  23).

The result of our study were agree with previous several study they found the women with PCOS showed significant increase in LH and Testosterone level compared to healthy control women also showed significant increase in the LH level in women with PCOS compared to healthy women [14], [16].

The present study indicates to the association between PCOS patients and control groups according to Testosterone Hormone show highly significantly difference, these results are similar to previous study in Iraq by Abdulla which found the women with PCOS showed significant increase in LH and Testosterone level compared to healthy control women.

Our study demonstrated the comparison of the mean of selected Lipid profile between PCOS patients and control group involving (T. Cholesterol, Triglyceride, HDL, LDL and VLDL). The mean value of serum total cholesterol (T.C), Triglyceride, HDL, LDL and VLDL are highly significantly increased ( $p < 0.01$ ) in PCOS patients group ( $p = 0.0001$ ), were Similarly, to study by Jahanfar *et al* .which aimed at evaluating the genetic and environmental factors affecting lipids among twins, found no significant differences between women with and without PCOS in serum total cholesterol [14]. Previous study by (Naghshband and Malini was the first to investigate the *FTO* gene variant rs9939609 association with PCOS susceptibility in South Indian women.[17] Our findings indicated that *FTO* SNP rs9939609 was a significant association of *FTO* polymorphism with hyperandrogenemia, fasting glucose levels, and BMI as in South Indian women with PCOS.

Previous study on Iranian population contracted by Khoshi *et al* revealed Omentin V109D and *FTO* rs9939609 genetic variations may change insulin metabolism and have key roles in developing T2D through insulin resistance. [11] Thus, the evaluation of these polymorphic regions may be helpful for predicting type 2 diabetes. A meta-analysis in 2017 focusing on circulating Omentin levels in women with PCOS showed significant low levels of Omentin in patients with PCOS, and numerous studies have demonstrated the role of Omentin in the pathological processes of inflammatory state, IR, and steroid hormone production in PCOS. [18]. Also, when compared *FTO* gene polymorphism of patients group with selected Hormonal profile which included FSH, LH, Testosterone we found no correlation ship with them ( $p > 0.05$ ), our results disagree with showed there are significance association between *Omentin* gene polymorphism of patients PCOS when compared with Hormonal profile which found *Omentin* in the pathological processes of inflammatory state, IR, and steroid hormone production in PCOS. Naghshband and Malini, showed that patients carrying allele *FTO* gene polymorphism were no significant difference was observed with mutant genotype when compared with Hormonal profile. In other study conducted on Iraqi population by (Mohsen, *et al* listed the distribution of metabolic profile of the PCOS group depending on different genotypes DD, DV, and VV *Omentin* gen. The results showed statistically significant differences in FBG and BMI in different genotypes of the PCOS group ( $p$ -value  $< 0.05$ ) [10], [19]. But no statistical difference in TG, TC, LDL, and HDL levels ( $p$ -value  $> 0.05$ ).

#### 4. Conclusions

This study indicated to the significance association of PCOS patients and controls groups with BMI. Obesity exacerbates the hormonal and clinical features of PCOS in women suffering from PCOS have a high risk of obesity. The present study indicates to the association between PCOS patients and control groups with the Hormonal profile, it was found highly significant association of serum-FSH, serum-LH, Testosterone and Prolactin Hormone. The Omentin (V109D rs2274907A) genes polymorphism have a significant association with hyper LDL, in women with PCO, and may represent as a risk factor for PCOS incidence.

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**Conflict of Interest:** The authors declare that there are no conflicts of interest associated with this research project. We have no financial or personal relationships that could potentially bias our work or influence the interpretation of the results.

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