A study on changes in hormonal disruption in polycystic ovary syndrome with advancing age and body mass index

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ABSTRACT

Introduction and Aim: Polycystic ovary syndrome is a diverse condition that contributes to metabolic problems like insulin resistance and hyperandrogenism which women experience during their reproductive years, and it is closely related to the body mass index. The purpose of this study was to evaluate the clinical, biochemical, and hormonal profiles of PCOS patients and healthy women concerning age and BMI and to correlate insulin with other parameters.

Materials and Methods: The present case-control study was conducted from June 2019-April 2021. 180 PCOS women and 170 age-matched healthy women were enrolled from Mangalore, Karnataka. Anthropometric measurements, biochemical, hormonal profile, and the presence of IR were estimated in all patients and were further subdivided based on age and BMI.

Results: The mean age of patients with PCOS and controls was 25.9± 5.6 years vs 24.7 ± 6.8 years. BMI and WHR had statistical significance (p<0.01) between the groups. TG & HDL showed statistical significance (p<0.05) in both age groups who were underweight and had normal BMI. A significant difference (p<0.05) was also observed in plasma insulin and HOMA-IR in all groups except in women who were obese.

Conclusion: PCOS women were presented with hyperandrogenism and had metabolic risk factors like insulin resistance and low HDL-C levels at budding age and increased BMI. When comparing women with and without PCOS from the south Indian state of Karnataka, our findings revealed that changes in sex hormone levels had no significant impact on age or BMI.

Keywords: Age group; body mass index; insulin resistance; lipid profile; polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) otherwise known as hyperandrogenic anovulation or Stein-Leventhal syndrome is a heterogeneous, multifactorial, and polygenic condition affecting 5%-15% of women of childbearing age worldwide (1). PCOS is associated with clinical/biochemical signs of excess androgen, menstrual irregularities ranging from amenorrhea to menorrhagia, and polycystic ovaries. Risk factors for the onset of PCOS include family history, lack of exercise, and obesity which in turn may lead to a high likelihood of developing CVD, insulin resistance, dyslipidemia, type 2 diabetes mellitus, hypertension, and cancer (2). IR and hyperinsulinemia appear to be important in the pathophysiology of PCOS by affecting the hypothalamic-pituitary-ovarian axis synergistically increasing ovarian androgen production which has been highly debated (3). IR has been observed in non-obese Chinese women with PCOS, indicating hyperinsulinemia independently of obesity. In this case, phenotypic expression differs depending on whether the women are thin, fat, or have higher androgen expression, regardless of their body mass (2). Central obesity has been debated as a key component of several metabolic disorders such as IR, dyslipidemia, and metabolic syndrome. As a result, the mechanism by which obesity influences the pathophysiology of PCOS remains unknown, and thereby, obesity is not considered to be part of the diagnostic criteria(4). Biochemical hyperandrogenism, a criterion in the diagnosis of PCOS, appears to decrease with age, which is an important aspect of clinical practice (5). Insulin resistance, low HDL levels, and high triglyceride levels all contribute to dyslipidemia which is a commonly observed pattern in PCOS although differences have been observed in different geographical regions (6). Because of its high prevalence, and metabolic, reproductive, and cardiovascular consequences, PCOS has received a lot of attention. Initial evidence states that because of various genetic and environmental factors, ethnicity is strongly linked to the PCOS phenotype (7). It remains unknown whether dyslipidemia and sex hormones in PCOS women differ from those in non-PCOS-related infertility, and whether changes in sex hormones are linked to anthropometric measurements, insulin levels,
and lipid profile in PCOS women (4). As a result, the current study's goal is to evaluate the clinical, anthropometric, and hormonal changes observed in PCOS women concerning advancing age and BMI and to correlate the levels of insulin with other parameters in the state of Karnataka, India.

MATERIALS AND METHODS

Study design

This case-control study was conducted at the Obstetrics and Gynecology department, KSHHEMA IVF of Justice KS Hegde Charitable Hospital, and Central Research Laboratory of KS Hegde Medical Academy, Mangaluru, India, from a period of June 2019 to April 2021. 180 women with polycystic ovary syndrome and 170 healthy women within the age group of 18-40 years were enrolled in the present study. The study was reviewed and approved by the institutional Ethical Committee, NITTE University (NU/CEC/2019/0215 dated: 20-02-2019), and written informed consent was obtained from all the participants.

Subjects

Among the 350 participants, 180 PCOS diagnosed women were chosen using the 2003 Rotterdam criteria with the combination of at least two of the following characteristics: (1) oligo/anovulation (2) clinical or/and biochemical signs of hyperandrogenism (hirsutism, acne, and alopecia), and (3) polycystic ovarian morphology on ultrasound. Exclusion criteria for patients included: pregnancy, breastfeeding, other hyperandrogenic conditions like Cushing syndrome, late-onset congenital hyperplasia, androgen-secreting tumors, use of oral contraceptives, or any other medication that may interfere with hormonal and metabolic changes. The control subjects consisted of 170 healthy age-matched women, who had visited the outpatient clinic for regular periodic medical examination. The women in the control group included those who had regular menstruation (25-35 days), no family history of type 2 diabetes mellitus, infertility, and no signs and symptoms of hyperandrogenism.

Anthropometric and clinical measurements

Detailed information regarding the subject's clinical, menstrual, and family history was documented on a pre-designed proforma. Menstrual history like secondary amenorrhea was described as the lack of menstrual periods for more than 6 months, whereas oligomenorrhea was defined as a monthly delay of more than 35 days to 6 months. Diabetes mellitus and hypertension in first and second cousins, menstruation problems, and hirsutism were also noted. Height and weight were measured in indoor attire without shoes for each patient. The BMI was computed by dividing the weight in kilograms by the square of the height in centimeters. which was classified as <18.5 underweight, 18.5-24.9 normal, 25-25.9 overweight, and >30 as obese. The waist-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference at the midpoint between the lower edge of the rib and the iliac crest. The hip circumference was measured at the broadest circumference of the greater trochanter. A WHR <0.85 was considered normal.

Laboratory assays

Blood samples were taken from all the willing participants under fasting conditions by venipuncture from a cubital vein between days 3 and 5 of a natural menstrual cycle and when it came to women who had irregular periods or amenorrhea, it was performed on any day, regardless of the number of days since the last menstrual period. 4 millimeters of whole blood was collected for biochemical and hormonal analysis under aseptic conditions and separated into 2 parts: 3 mL whole blood taken in plain vacutainer tube and 1 mL of blood was collected in fluoride tube. The samples collected in the tubes were centrifuged at 4000rpm for 5 min and serum was separated and stored at -80°C for analysis. A blood chemistry test including blood glucose level and lipid profile (total cholesterol; triglycerides; HDL; and LDL) was done to diagnose dyslipidemia and metabolic syndrome spectrophotometrically by enzymatic colorimetric reaction and were expressed as mg/dL. Hormonal assays including serum follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone (T), prolactin, vitamin D, and levels of insulin were performed by ELISA kits available commercially and an ELISA reader (Spark Tecan) was used to measure the absorbance. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated according to the formula, HOMA IR=fasting insulin (µIU/mL) *[fasting glucose (mg/dL)]/ 405.

Statistical analysis

SPSS (version 16.0, IBM, USA) was used to analyze the data. Values were expressed as mean±SD, and an independent sample t-test was applied for normally distributed data, while the median (interquartile range) and Mann-Whitney U-test were applied for non-parametric data. Correlation analysis was performed by Spearman’s coefficient correlation test. A p-value > 0.05 was considered statistically significant.

RESULTS

The baseline and biochemical characteristics of the women involved in the study are summarized in Table 1. Women with PCOS had greater BMI (24.6±5.6 vs 21.6±3.9) than healthy controls. A significant increase in BMI, WHR, fasting glucose, plasma insulin levels,

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and HOMA-IR status in PCOS patients was observed in comparison with controls. Furthermore, PCOS individuals had significantly higher triglyceride and LDL levels, as well as lower HDL levels. Clinical hirsutism with a history of weight gain was observed in 42 (23%) patients. 52 (29%) patients had signs and symptoms of oligo/amenorrhea and dysmenorrhea. 37 (21%) women were diagnosed with primary/secondary infertility, while the remaining 49 (27%) women showed all the combined effects of PCOS symptoms (Fig 1).

Table 1: Anthropometric and biochemical assessment among groups

| Parameters          | Case (n=180)       | Controls (n=170) | P value |
|---------------------|--------------------|------------------|--------|
| Age (yrs)           | 25.96±5.64        | 24.75±6.83       | 0.062  |
| Height (cms)        | 155.95±15.49      | 157.81±10.37     | 0.204  |
| Weight (Kg)         | 61.53±15.16       | 54±9.6           | 0.000**|
| BMI<sup>1</sup>     | 24.61±5.10        | 21.6±3.9         | 0.000**|
| WHR<sup>1</sup>     | 0.85±0.05         | 0.80±0.05        | 0.000**|
| FBS (mg/dL)<sup>1</sup> | 90.91±18.77    | 78.23±15.55      | 0.000**|
| TC (mg/dL)<sup>1</sup> | 166.53±39.43     | 162.03±30.84     | 0.245  |
| TG (mg/dL)<sup>1</sup> | 123.21±48.02     | 101.44±40.68     | 0.000**|
| HDL (mg/dL)<sup>1</sup> | 50.16±8.24       | 61.49±10.78      | 0.000**|
| LDL (mg/dL)<sup>1</sup> | 97.50±36.25      | 80.73±28.03      | 0.000**|
| LDL/LDL<sup>1</sup> | 2.02±0.75         | 1.93±0.80        | 0.855  |
| Insulin<sup>2</sup> | 14.28 (6.03-27.14) | 6.00 (2.59-15.08) | 0.000**|
| HOMA-IR<sup>2</sup> | 2.97 (1.01-6.06)  | 1.00 (0.4-3.41)  | 0.000**|

BMI, body mass index; WHR, waist-hip ratio; FBS, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA IR, homeostatic model assessment insulin resistance.

<sup>1</sup>Values are presented as mean± SD; Student t-test;
<sup>2</sup>Median (25<sup>th</sup>–75<sup>th</sup> percentile); Mann-Whitney U test; **p<0.01

![Fig. 1: Signs and symptoms presented by women with PCOS](image)

Serum hormone concentrations of women who participated in the present study are summarized in Table 2. The hormonal profile of subjects in control groups was within the normal range. The concentration of testosterone was significantly higher in the PCOS group, whereas vitamin D levels were low in comparison with the control group which was statistically significant (p<0.01).

Table 2: Hormonal assessment of subjects in study group

| Parameters          | PCOS (n=180) | Controls (n=170) | P value |
|---------------------|--------------|------------------|--------|
| FSH (IU/L)          | 4.62 (3.18-6.19) | 4.63 (3.24-6.33) | 0.885  |
| LH (IU/L)           | 9.02 (5.48-16.41) | 7.34 (4.9-13.69) | 0.122  |
| Testosterone (nmol/L) | 2.75 (1.68-4.64) | 1.81 (1.14-2.95) | 0.000**|
| Estradiol (nmol/L)  | 0.52 (0.39-0.69)  | 0.58 (0.31-0.77)  | 0.116  |
| Prolactin (mIU/L)   | 511.55 (389.34-706.96) | 464.17 (362.93-637.45) | 0.221 |
| Vitamin D (ng/ml)   | 17.4 (13.63-24.11) | 20.76 (15.03-32.72) | 0.002**|

FSH, follicle-stimulating hormone; LH, luteinizing hormone. Values are presented as Median (25<sup>th</sup>–75<sup>th</sup> percentile); Mann-Whitney U test **p<0.01

Table 3 presents the comparison of biochemical and hormonal parameters in the study population based on age. The age distribution between PCOS patients and non-PCOS controls was grouped as 18-28 years, consisting of 114 PCOS and 119 controls, and another group ranging from 29-40 years, where 66 patients and 51 healthy controls were involved. The biochemical and anthropometric parameters, between both categories, showed significantly higher levels in PCOS women of both age groups in comparison with healthy women. On the other hand, the serum testosterone level was elevated in cases that were also statistically significant in both the age groups, while estradiol and vitamin D levels were significantly on the lower side with advancing age. The metabolic parameters and androgen levels distributed among underweight, normal, overweight, and obese PCOS and control women are illustrated in Table 4. In the overall subjects recruited, PCOS was detected in 180 women of which 15 were underweight, while in 87 women normal BMI was observed. 55 PCOS women were overweight and 23 were obese. In 170 healthy controls, underweight women were 43, 96 women were normal, 24 were overweight and 7 women were obese. A statistically significant difference (p<0.05) was observed in WHR, fasting glucose, and insulin levels in all BMI groups except in women who were obese. Likewise, in obese PCOS and healthy subjects, no significant differences were found in any of the biochemical and androgen levels.
Table 3: Comparison of biochemical and hormonal parameters among women with and without PCOS based on age

| Parameters | 18-28 years | 29-40 years |
|------------|-------------|-------------|
|            | PCOS (n=114) | Controls (n=119) | P value | PCOS (n=66) | Controls (n=51) | P value |
| WHR¹ | 0.84±0.05 | 0.79±0.06 | 0.000** | 0.86±0.04 | 0.81±0.04 | 0.000** |
| BMI¹ | 23.67±4.89 | 20.92±3.87 | 0.000** | 25.94±4.74 | 23.42±3.62 | 0.001** |
| Height (cms)¹ | 155.08±18.92 | 158.42±11.2 | 0.109 | 157.42±6.29 | 156.20±7.32 | 0.362 |
| Weight (kg)¹ | 59.92±16.26 | 53.01±10.14 | 0.000** | 64.32±12.77 | 56.68±9.07 | 0.004** |
| FBS (mg/dL)¹ | 88.81±16.17 | 77.37±16.58 | 0.000** | 94.59±22.29 | 80.58±12.21 | 0.000** |
| TC (mg/dL)¹ | 161.34±36.22 | 158.66±29.1 | 0.535 | 175.67±43.2 | 171.12±33.8 | 0.561 |
| TG (mg/dL)¹ | 120.53±44.95 | 101.35±41.3 | **0.011** | 127.91±53.0 | 101.67±39.3 | **0.006** |
| HDL (mg/dL)¹ | 57.45±8.67 | 62.83±10.68 | 0.000** | 47.9±6.93 | 58.09±6.9 | 0.000** |
| LDL (mg/dL)¹ | 93.72±33.97 | 76.05±24.05 | 0.000** | 104.16±39.3 | 91.97±31.54 | 0.091 |
| LDL:HDL¹ | 1.90±0.67 | 2.01±0.77 | 0.873 | 2.25±0.83 | 1.64±0.66 | 0.003** |
| Insulin (µIU/mL)² | 14.28 (5.67-25.1) | 5.23 (2.25-13.93) | 0.000** | 15.57 (7.82-36.66) | 9.95 (3.03-18.2) | 0.002** |
| HOMA-IR² | 2.8 (0.86-5.6) | 0.94 (0.38-3.2) | 0.000** | 3.01 (1.45-8.1) | 1.75 (0.61-3.73) | 0.003** |
| FSH (IU/L)² | 4.52 (3.09-6.29) | 4.69 (3.3-6.4) | 0.661 | 4.66 (3.40-6.0) | 4.57 (3.05-6.31) | 0.695 |
| LH (IU/L)² | 9.48 (5.6-17.3) | 7.48 (4.9-15.4) | 0.122 | 8.2 (4.87-15.4) | 7.25 (4.60-13.36) | 0.504 |
| Testosterone (nmol/L)² | 2.84 (1.7-4.6) | 2.14 (1.3-3.1) | **0.011** | 2.48 (1.6-4.58) | 1.25 (0.85-1.99) | 0.000** |
| Estradiol (nmol/L)² | 0.53 (0.39-0.6) | 0.56 (0.3-0.7) | 0.591 | 0.51 (0.33-0.68) | 0.65 (0.37-0.84) | 0.046* |
| Prolactin (mIU/L)² | 524.98 (389.6-705.3) | 483.09 (366.6-706.9) | 0.530 | 462.2 (389.3-706.9) | 444.2 (351.2-557) | 0.171 |
| VitaminD (ng/mL)² | 17.2 (13.4-22.8) | 19.66 (14.8-27.5) | 0.074 | 18.44 (13.9-26.4) | 31.4 (18.6-36.5) | 0.000** |

¹Values presented as mean± SD, Student ‘t’ test
²Median (25th – 75th percentile); Mann-Whitney U test; **p<0.01; *p<0.05

Table 4: Comparison of metabolic and androgen parameters among women with PCOS and healthy women based on BMI

| Parameters | BMI <18.5 kg/m² | P value | BMI - 18.5-24.9 kg/m² | P value |
|------------|-----------------|---------|-----------------------|--------|
| Age (yrs)¹ | 22.87±4.19 | 0.615 | 25.03±5.16 | 0.702 |
| WHR¹ | 0.79±0.04 | 0.010* | 20.08±5.62 | 0.728 |
| Height (cms)¹ | 148.3±38.9 | 0.078 | 165.19±12.6 | 0.222 |
| Weight (kg)¹ | 42.3±4.57 | 0.225 | 43.9±3.1 | 0.097 |
| FBS (mg/dL)¹ | 89.81±15.54 | 0.000** | 76.0±12.2 | 0.000** |
| TC (mg/dL)¹ | 142.88±28.7 | 0.292 | 150.7±22.9 | 0.836 |
| TG (mg/dL)¹ | 102.31±28.6 | 0.088 | 88.2±26.3 | 0.002** |
| HDL (mg/dL)¹ | 51.9±10.55 | 0.010* | 62.8±10 | 0.000** |
| LDL (mg/dL)¹ | 85.46±26.8 | 0.010* | 67.6±20.1 | 0.024* |
| LDL: HDL¹ | 1.65±0.53 | 0.000** | 1.14±0.39 | 0.707 |
| Insulin µIU/mL² | 9.14±17.3 | 0.005** | 2.8 (1.9-6.3) | 0.024* |
| HOMA-IR² | 2.18±3.9 | 0.002** | 0.48 (0.31-1.3) | 0.034* |
| FSH (IU/L)² | 5 (3.2-5.9) | 0.015 | 4.6 (3.5-6.3) | 0.773 |
| LH (IU/L)² | 8.8 (6.1-15.4) | 0.045 | 7.86 (4.5-13.2) | 0.115 |
| Testosterone (nmol/L)² | 6.3 (0.4-0.9) | 0.060 | 0.55 (0.29-0.65) | 0.170 |
| Estradiol (nmol/L)² | 646.8 (310-966.6) | 0.022 | 480.4 (364-703.3) | 0.289 |
| Prolactin (IU/L)² | 19.8 (14.5-26.2) | 0.612 | 19.5 (15.2-34.5) | 0.139 |
| Vitamin D (ng/mL)² | 0.011* | 0.010* | 0.010* | 0.010* |
Table 4: Continued….

| Parameters          | BMI - 25-29.9 kg/m² | BMI >30 kg/m² |
|---------------------|----------------------|---------------|
|                     | PCOS (n-55) | Control (n-24) | PCOS (n-23) | Control (n-7) | P value |
| Age (yrs)¹          | 27.68±5.73 | 27.63±8.62 | 0.977 | 27.63±6.62 | 30.4±7.6 | 0.419 |
| WHR¹                | 0.86±0.05 | 0.83±0.05 | **0.015** | 0.88±0.05 | 0.85±0.02 | 0.304 |
| Height (cms)²       | 156.41±5.72 | 153.2±21.9 | 0.366 | 159.66±7.81 | 157±5.47 | 0.602 |
| Weight (kg)¹        | 66.23±5.32 | 66.5±6.36 | 0.834 | 86.42±8.97 | 79.4±10.5 | 0.139 |
| FBS (mg/dL)²        | 94.37±18.77 | 81.2±19.8 | **0.008** | 97.72±24.62 | 82.8±8.04 | 0.198 |
| TC (mg/dL)¹         | 175.43±33.46 | 177.6±26.1 | 0.778 | 176.05±41 | 178.2±16.9 | 0.910 |
| TG (mg/dL)¹         | 126.2±38.85 | 122.9±57.4 | 0.776 | 133.23±58.9 | 114.4±34.2 | 0.501 |
| HDL (mg/dL)¹        | 48.46±7.07 | 57.7±11.3 | **0.000** | 49.63±9.74 | 50.8±2.7 | 0.796 |
| LDL (mg/dL)¹        | 108.42±35.47 | 95.5±22.9 | 0.122 | 102.9±28.3 | 104.3±21.6 | 0.912 |
| LDL: HDL¹           | 2.29±0.66 | 1.69±0.56 | **0.000** | 2.12±0.66 | 2.06±0.32 | 0.824 |
| Plasma insulin      | 18.9 (11.6-37.3) | 8.29 (3.7-15.1) | **0.001** | 24.3 (13.1-40.7) | 6.83 (3.0-26.27) | 0.105 |
| (µIU/mL)²           |            |            |            |              |              |      |
| HOMA-IR²            | 3.6 (1.5-8) | 1.7 (0.7-3.7) | **0.012** | 5.6 (2.2-9.5) | 1.25 (0.6-5.85) | 0.105 |
| FSH (IU/L)²         | 4.52 (3.4-6.1) | 3.94 (3.2-6.57) | 0.540 | 4.8 (2.9-5.9) | 5.27 (2.3-13.3) | 0.662 |
| (IU/L)²             |            |            |            |              |              |      |
| LH (IU/L)²          | 7.3 (4.8-15.9) | 8.19 (4.3-15.03) | 0.815 | 9.4 (4.4-13.4) | 6.17 (5.0-22.1) | 0.660 |
| Testosterone        | 2.78 (1.8-4.6) | 1.46 (1.09-2.2) | **0.001** | 4.1 (2.1-6.3) | 1.8 (1.2-4.12) | 0.126 |
| (nmol/L)²           |            |            |            |              |              |      |
| Estradiol           | 0.52 (0.3-0.6) | 0.69 (0.26-0.79) | **0.041** | 0.51 (0.2-0.8) | 0.77 (0.65-1.28) | 0.088 |
| (nmol/L)²           |            |            |            |              |              |      |
| Prolactin           | 451.6(332.3- | 454.9(409.3-590.4) | 0.857 | 569.4 (400.4-703.5) | 369.8 (252.2-757.5) | 0.588 |
| (mIU/L)²            | 674.3)     |            |            |              |              |      |
| Vitamin D           | 18.9 (13.3-23.1) | 29.8 (19.8- | **0.005** | 14.4 (12.0-18.2) | 18.17 (10.0-26.3) | 0.965 |
| (ng/ml)²            | 40.09)     | 40.09)     |            |              |              |      |

¹Values presented as mean ± SD, Student ‘t’ test
²Median (25th - 75th percentile); Mann-Whitney U test
**p<0.01; *p<0.05

Table 5: Relation between plasma insulin and HOMA-IR with other parameters in PCOS and control women

| Parameters          | INSULIN | Control | HOMA-IR | Control |
|---------------------|---------|---------|---------|---------|
|                     | PCOS | P | PCOS | P | PCOS | P | PCOS | P |
| Age (yrs)           | 0.240 | 0.001** | 0.263 | 0.001** | 0.281 | 0.000** | 0.252 | 0.001** |
| WHR                 | 0.215 | 0.007** | 0.034 | 0.674 | 0.231 | 0.004** | 0.075 | 0.347 |
| BMI                 | 0.327 | 0.000** | 0.249 | 0.002** | 0.307 | 0.000** | 0.247 | 0.002** |
| FBS (mg/dL)         | 0.580 | 0.000** | 0.585 | 0.000** | 0.724 | 0.000** | 0.695 | 0.000** |
| TC (mg/dL)          | 0.303 | 0.000** | 0.107 | 0.181 | 0.315 | 0.000** | 0.148 | 0.063 |
| TG (mg/dL)          | 0.297 | 0.000** | 0.057 | 0.475 | 0.317 | 0.000** | 0.098 | 0.220 |
| HDL (mg/dL)         | -0.122 | 0.108 | -0.325 | 0.000** | -0.170 | 0.024* | -0.329 | 0.000** |
| LDL (mg/dL)         | 0.227 | 0.002** | 0.204 | 0.010* | 0.247 | 0.001** | 0.248 | 0.002** |
| Insulin (µIU/mL)    | -      | -      | -      | -      | 0.989 | 0.000** | 0.988 | 0.000** |
| FSH (IU/L)          | -0.007 | 0.926 | 0.119 | 0.134 | 0.029 | 0.705 | 0.110 | 0.166 |
| LH (IU/L)           | 0.030 | 0.690 | 0.343 | 0.000** | 0.060 | 0.429 | 0.352 | 0.000** |
| Testosterone (nmol/l) | 0.059 | 0.433 | -0.239 | 0.002** | 0.052 | 0.493 | -0.251 | 0.001** |
| Estradiol (nmol/l)  | 0.094 | 0.240 | -0.066 | 0.434 | 0.117 | 0.143 | -0.026 | 0.756 |
| Prolactin (mIU/L)   | 0.004 | 0.964 | 0.117 | 0.163 | 0.022 | 0.783 | 0.118 | 0.159 |
| VitaminD (ng/ml)    | -0.165 | 0.028* | -0.169 | 0.055* | -0.189 | 0.012 | -0.167 | 0.057* |
| HOMA-IR             | 0.989 | 0.000** | 0.988 | 0.000** | -      | -      | -      | -      |

r = Spearman’s correlation test; **p<0.01; *p<0.05

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Correlation between plasma insulin and HOMA-IR with the anthropometric, biochemical, and hormone profile in PCOS and healthy controls are illustrated in Table 5. Insulin alone was weakly correlated with FSH in PCOS women and in the case of controls both insulin and IR showed a weak correlation with testosterone and estradiol. However, in the case of HDL and Vitamin D, both insulin and HOMA-IR were negatively correlated in both patients and controls.

**DISCUSSION**

PCOS is frequently linked to weight gain, obesity, and the development of metabolic syndrome, which includes insulin resistance and dyslipidemia. The incidence of obesity in women with PCOS is typically higher in comparison with healthy women (8). In this context, the current case-control study investigated the potential changes in anthropometric and hormonal features in PCOS women with progressing age and body mass index and associate the levels of insulin with other parameters. We compared a representative group of PCOS patients up to the age of 40 to normal cycling women without PCOS. Our findings in this study support previous findings that biochemical and hormonal levels in PCOS patients vary depending on age and BMI status.

The incidence of central obesity in PCOS is typically higher than in healthy controls (8). All anthropometric parameters tended to deteriorate with increasing age and body mass index in women with PCOS. Among controls, slight variations in body weight, BMI, and WHR were observed (Table 2). PCOS women had higher fasting glucose levels than controls in all age groups and the current study's BMI stratification is also consistent with previous research. (5). The prevalence of lipid abnormalities has been reported as high as 70% in women with PCOS (9). Lipids are vital components of the body's physiological systems. The lipid composition of cellular membranes determines their structural integrity and functional balance. Lipids are also important in cellular signaling, acting as secondary messengers and hormones. (10). Dyslipidemia in PCOS is generally characterized by an increased level of LDL with high triglyceride levels and low levels of HDL. There was a statistically significant link between polycystic ovarian syndrome and high blood TG, LDL, and low HDL in our study, but not in the case of high cholesterol when compared to the control group. Results of other studies have also documented similar findings consistent with ours suggesting that PCOS women were hyperlipidemic with higher cholesterol, TG, LDL levels, and lower levels of HDL than healthy controls (11,12). When the data were separated based on age group, substantial variations in average blood triglycerides and HDL were found in both groups, although LDL levels were not statistically significant in women aged 29 to 40. Differences observed in patterns of dyslipidemia might be attributed to the effect of body mass index. Prior studies had reported findings stating that all levels of serum lipids were higher in PCOS but no significant associations were found in the levels of cholesterol in the subgrouping stage of BMI which was consistent with our findings (6,13). A study conducted in Egypt showed that PCOS women had an atherogenic lipoprotein profile characterized by increased cholesterol, LDL, and TG, especially in the obese group (14). In this study, BMI had a statistically significant impact on HDL and LDL particularly in underweight and normal PCOS women. However, it appears that different studies have reported contradictory results because of factors such as race, genetics, lifestyle, and geographical region.

PCOS women may have an underlying pathological condition that might be associated with long-term risk of coronary heart diseases such as elevated insulin levels or insulin resistance (14). Lipid abnormalities have been linked to insulin resistance in the absence of obesity, (3). According to a study report, insulin levels at baseline are higher in women with PCOS, especially after the age of 25 to 30. (15). Other studies, on the other hand, denied the fact that insulin levels in PCOS rise over time, particularly in women with stable BMI and WHR. (16,17). A drop in androgens and a rise in fat distribution will probably affect insulin levels over time. Furthermore, contradictions between research could be explained by differences in populations or study criteria. Our findings also revealed that IR increased with age in the PCOS group between the ages of 29 and 40. (Table 3). HOMA-IR score was reported to be higher in PCOS women than in controls (Table 2). When plasma insulin and HOMA-IR score were compared based on BMI (Table 4), the levels were gradually on the upper limit depending on the body mass index which was consistent with other studies (5). Statistically, a significant association was found in all BMI subgroups, except in obese PCOS women. IR may worsen because of body fat accumulation. A study conducted by Jahromi et al., (18) presented a positive correlation with BMI which was like our results. Therefore, although PCOS is a contributing factor for IR, changes in BMI are also suggested to be much more evident.

Androgen excess, a key hallmark of PCOS, has been linked in studies as a potential developmental component to the syndrome's etiology throughout fetal life, as well as an independent exacerbating factor of metabolic abnormalities in adolescence and adulthood. (19). The current study found a statistically significant decrease in androgen levels concerning aging and BMI. Our study showed a significant rise in serum LH, testosterone, and prolactin levels while levels of serum FSH, estradiol, and vitamin D were low when compared with controls which were consistent with previous studies (20,21), while others have stated a rise in the levels of serum FSH in comparison with
healthy women (2,14). Adrenal androgens have decreased over time in PCOS patients in prior studies (16,22) and in the present study older age group had significantly lower testosterone and estradiol levels than the younger age group. FSH levels increased in older age groups suggesting relative estrogen resistance and decreased LH levels. However, we found no significant associations between LH and FSH concerning BMI in both PCOS and control women. LH stimulates ovarian androgen production which may explain our findings of lower testosterone levels in higher age groups. Though serum testosterone was higher in PCOS women than in controls, their concentration concerning age tended to decrease (Table 3) and their levels increased with growing body mass index which was statistically significant, particularly in normal and overweight women (Table 4). After 30 years of age, testosterone levels in PCOS patients have been found to drop by 20 to 50 percent. (5). Despite these findings, some studies found no reductions or significant changes in serum testosterone levels in PCOS women under or over the age of 30 (5,23). Prolactin levels were higher in PCOS regardless of age and BMI but tend to decrease as age advances which was consistent with previous reports (24). A significant decrease in vitamin D levels was observed in PCOS patients, which corresponded with a study conducted in northern India (25). However, serum 25(OH)D was drastically reduced in women who were obese and more than 30 years of age. The majority of evidence suggests that as women age, androgen production decreases significantly, but not as dramatically as in non-PCOS women. However, excess insulin and androgens, on the other hand, may contribute to the development of PCOS and metabolic syndrome in obese women. This is largely attributed to the decreased function and number of theca cells of the ovary.

CONCLUSION

According to our findings, most study participants under the age of 29 had normal BMI. However, PCOS women had higher BMI and WHR than healthy women. Cholesterol levels were not significant concerning rising age and increasing BMI but showed a positive and significant correlation with IR. There were no significant associations between the biochemical and androgen levels in obese women with and without PCOS but remained elevated in comparison with other BMI subgroups. IR showed a positive correlation with BMI and was negatively correlated with vitamin D in all study participants. Further studies must be conducted to determine whether dietary intake or lifestyle habits are associated with PCOS morbidity, particularly in IR cases, to reduce the impact of BMI and hyperandrogenism.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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