Vitamin D and Insulin resistance at different body mass index in women with PCOS

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Abstract- Background: Obesity is associated with chronic low-grade inflammation, that may contribute to insulin resistance by the actions of inflammatory adipocytokines. Low 25-hydroxy vitamin D levels are found to be significantly related to insulin resistance in women with PCOS and may exacerbates the disease.

Aim of study: To find the correlation between vitamin D and insulin resistance in women with PCOS.

Methods: A cross sectional study is conducted in Department of Obstetrics and Gynecology at Al-Elwiya Maternity Teaching Hospital from 1st March till 31th October 2018. Including 100 women with polycystic ovarian syndrome attended the outpatient clinic of the hospital seeking for treatment. Diagnosis of PCOS was done according to Rotterdam Criteria. The insulin hormone was measured by enzyme-linked-immunosorbent sensitive assay kit. Blood sugar and serum vitamin D was also measured and insulin resistance (IR) was calculated.

Results: Mean of vitamin D was significantly higher in patients with normal BMI than that among overweighed and obese patients (29.33 versus 20.39 and 15.87 (nmol/L), P= 0.001).

High insulin resistance is seen in 61% of patients. Mean of insulin resistance is significantly higher in obese patients than that among overweighed and patients with normal BMI (5.73 versus 4.34 and 1.88, P= 0.001). No significant correlation is seen between vitamin D level and insulin resistance (r= - 0.193, P= 0.055).

Conclusion: Obesity is a significant risk factor in developing low vitamin D level and high insulin resistance in patients with PCOS.

Index Terms- Polycystic ovary, Vit D, Insulin resistance

I. INTRODUCTION

The disorder can be morphological (polycystic) or predominantly biochemical (hyperandrogenemia). Hyperandrogenism, a clinical hallmark of PCOS, can cause inhibition of follicular development, micro cysts in the ovaries, anovulation, and menstrual changes(2).

Polycyctic ovarian syndrome is due to many genetic and environmental factors (3).Associated conditions with PCOS include type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer(4). Polycyctic ovarian syndrome is the most common endocrine disorder among women between ages of 18 and 44 years old. In 2003 a consensus workshop sponsored in Rotterdam indicated PCOS to be present if any two out of three criteria (Oligo ovulation and/or anovulation, Excess androgen activity and Polycystic ovaries) are met (5).

PCOS is associated with peripheral insulin resistance and hyperinsulinemia,and obesity amplifies the degree of both abnormalities. Insulin resistance in PCOS can be secondary to a post-binding defect in insulin receptor signaling pathways, and elevated insulin levels may have gonadotropin-augmenting effects on ovarian function. Hyperinsulinemia may also result in suppression of hepatic generation of sex hormone–binding globulin (SHBG), which in turn may increase androgen (6).

Vitamin D has a physiologic role in reproduction including ovarian follicular development and luteinization via altering anti-mullein hormone (AMH) signaling, follicle-stimulating

hormone sensitivity and progesterone production in human granulosa cells. The prevalence of vitamin D deficiency in women with PCOS is about 67-85%, with serum concentrations of 25(OH)D <20 ng/ml [(7)].

Low 25-hydroxy vitamin D [25(OH)D] levels may exacerbate PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism, obesity and increase the risk of cardiovascular diseases. Many observational studies found a role of vitamin D in an inverse association between vitamin D status and metabolic disturbances in PCOS [(8)].

Aim of Study is to find the correlation between vitamin D and insulin resistance and BMI in women With PCOS.

II. Patients and Method:

This is a cross sectional study that was conducted in the Department of Obstetrics and Gynecology at Al-Elwiya Maternity Teaching Hospital during the period from 1st of Mar till end of Oct 2018.

The study included 100 women with polycystic ovarian syndrome (PCOS) attended the outpatient clinic of the hospital seeking for management. The data were arranged on a questionnaire paper which was designed for the study. The data collection was done through daily visits. The workup includes:

1. Detailed history including:
   - Demographic data (Age, occupation, marital status with date of marriage).
   - Menstrual history: (Regularity and date of menarche).
   - History of infertility: Primary or secondary
   - Medical , surgical and family history
2. General examination.
3. Body Mass Index (BMI) [(9)]: Is calculated by weight in (kilograms) divided by the square of height in (meters). Weight and height are measured by the same scale for all the women.

BMI = Weight (Kg) / Square height (m^2)

Participants were classified according to their BMI as:

- Normal (≤ 24.99 kg/m^2)
- Overweight (25 - 29.99 kg/m^2)

- Obese (≥ 30 kg/m²)

4. Investigation for Fasting blood sugar, Fasting insulin hormone and Vitamin D.
5. Examination by ultrasound: (Feature of PCOS in U/S).

Diagnosis of PCOS was done according to Rotterdam Criteria as two of the following three criteria are required [(10)]:

Oligo / anovulation, 2. Hyperandrogenism, 3.Clinical (hirsutism or less commonly male pattern alopecia) or Biochemical (raised FAI or free testosterone), 3. Polycystic ovaries on ultrasound.

Five mls of blood was taken from each woman by venipuncture at any day of menstrual cycle since insulin hormone and blood sugar level remains stable throughout menstrual cycle.
Centrifugation done at 3000 RPM for 15 mints and the serum obtained in properly labeled sterilized tube and stored at – 40 C till analyzed. The insulin hormone was measured by enzyme-linked-immunosorbent sensitive assay kit (Insulin ELIZA). Blood sugar and serum vitamin D was also measured.

The insulin resistance (IR) is calculated as:

IR= Fasting blood sugar (mg/dl) * fasting insulin (µU/l) / 405 Any value ≥ 2.6 mmol/dl was considered IR [(11)].
According to committee of the Institute of Medicine, persons are at risk of vitamin D deficiency at serum 25 (OH) D concentrations < 30 nmol/L (< 12 ng/mL). Some are potentially at risk for inadequacy at levels ranging from 30 – 50 nmol/L (12 – 20 ng/mL). [(12)]

III. STATISTICAL ANALYSIS:

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Analysis of variances (ANOVA) (two tailed) was used to compare the continuous variables among BMI levels accordingly. Pearson's correlation test

(r) was used to assess correlation between BMI and both of vitamin D and insulin resistance, also used between vitamin D and insulin resistance. A level of P – value less than 0.05 was considered significant.

Ethical considerations and official approvals:

1. Verbal permission was obtained from each patient prior to collecting data, and information were anonymous. Names were removed and replaced by identification codes.
2. Approval of the scientific committee at Al-Elwiya Maternity Teaching Hospital and The Council of Iraqi Board of medical specialization.

IV. RESULTS:

Age ranges from 16 – 41 years with a mean of 26.83 years and standard deviation (SD) of ± 7.36 years. Half of them are ≥ 30 years. About 4/5 of participants are married and more than half of them are housewives (52%). Regarding number of children, 44% of them are infertile.

Menstrual cycles are irregular in 82% and primary infertility is the main complaint (52%).

Table 1: Distribution of patients by general characteristics

Variable	No. (n= 100)	Percentage (%)
Marital Status		
Single	19	19.0
Married	81	81.0
Occupation		
Housewife	52	52.0
Employee	28	28.0
Student	20	20.0
Number of children		
No children	44	44.0
< 3	22	22.0
≥ 3	34	34.0
Medical history		
No history	72	72.0
Hypertension	14	14.0
Diabetes	8	8.0
Hypertension + Diabetes	6	6.0
Menstrual history		
Regular cycle	18	18.0
Irregular cycle	82	82.0
History of infertility		
No history	37	37.0
Primary	52	52.0
Secondary	11	11.0

Figure 1. shows the distribution of the patients according to BMI. It ranges from 19.48 – 54.43 kg / m^2 with a mean of 31.52 kg / m^2 and a SD of ± 9.74 kg / m^2. It is obvious that the highest proportion of patients are obese (43%).

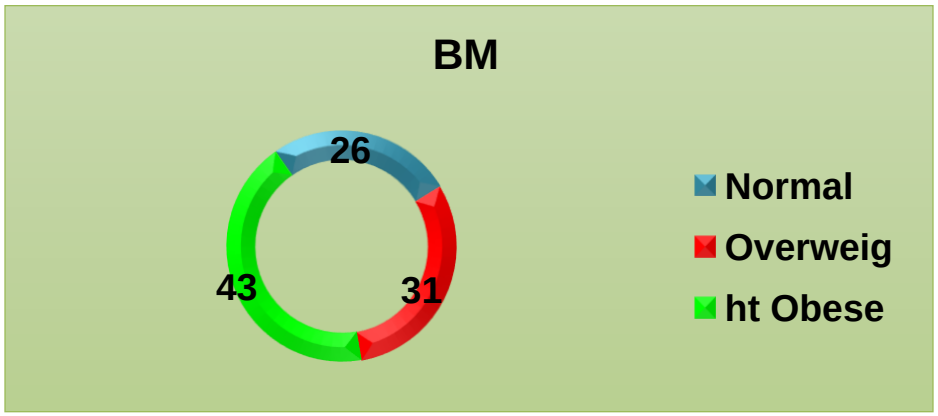

Figure 1: Distribution of patients according to BMI

Distribution of patients according to vitamin D level is shown in figure (2). Mean vitamin D level is ranging from 6.8 – 39.4 nmol/L with a mean of 20.77 nmol/L and SD of ± 11.38 nmol/L and 69% of patients have vitamin D level deficiency.

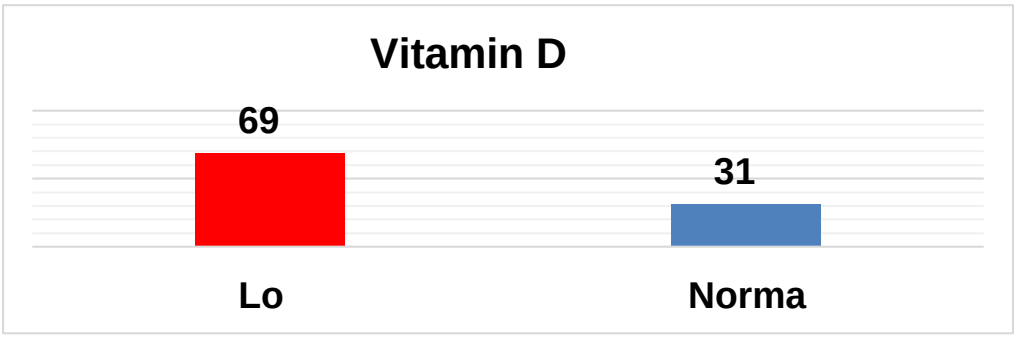

Figure 2: Distribution of patients by vitamin D level

Vitamin D level according to different BMI is demonstrated in table (2). Mean of vitamin D was significantly higher in patients with normal BMI than that among overweighed and obese patients (29.33 versus 20.39 and 15.87(nmol/L), P= 0.001).

Table 2: Vitamin D level according to different BMI

BMI	**Vitamin D (nmol/L)** **Mean±SD**	**P-Value**
Normal	29.33 ± 7.81	**0.001**
Overweight	20.39 ± 10.16	
Obese	15.87 ± 11.19	

Correlation between BMI and vitamin D level is shown in figure(3). A statistically significant

poor negative correlation is detected between BMI and vitamin D level (r= -

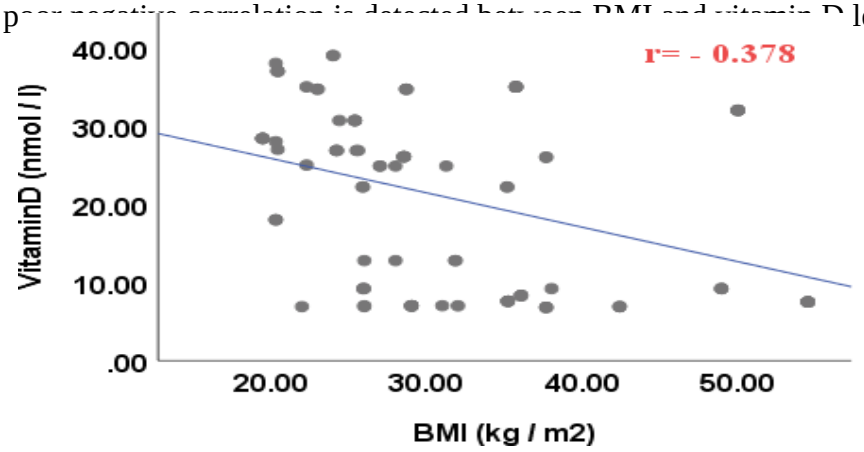

Figure 3: Correlation between BMI and vitamin D level

Distribution of patients by insulin resistance status is shown in figure (4). Mean of insulin resistance ranges from 0.97 – 12.8 with a mean of 4.3 and SD of ± 2.86. High insulin resistance is seen in 61% of patients.

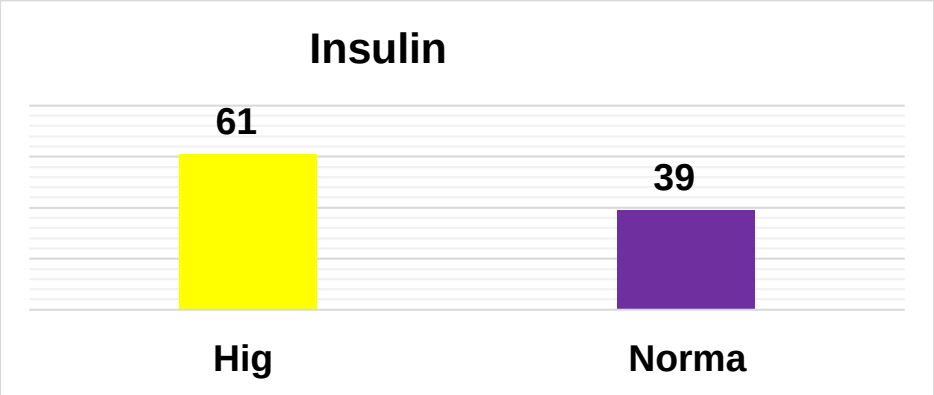

Figure 4: Distribution of patients by insulin resistance status

Comparison in mean of insulin resistance according to different BMI is demonstrated in table (3). Mean of insulin resistance is significantly higher in obese patients than that among overweighed and patients with normal BMI (5.73 versus 4.34 and 1.88, P= 0.001).

Table 3: Comparison in insulin resistance by BMI

BMI	**Insulin Resistance** **Mean±SD**	**P-Value**
Normal	1.88 ± 1.37	**0.001**
Overweight	4.34 ± 2.75	
Obese	5.73 ± 2.66	

Correlation between BMI and insulin resistance is shown in table and figure (5). A moderate positive correlation is detected between BMI and insulin resistance (r= 0.592) and this correlation is statistically significant (P= 0.001).

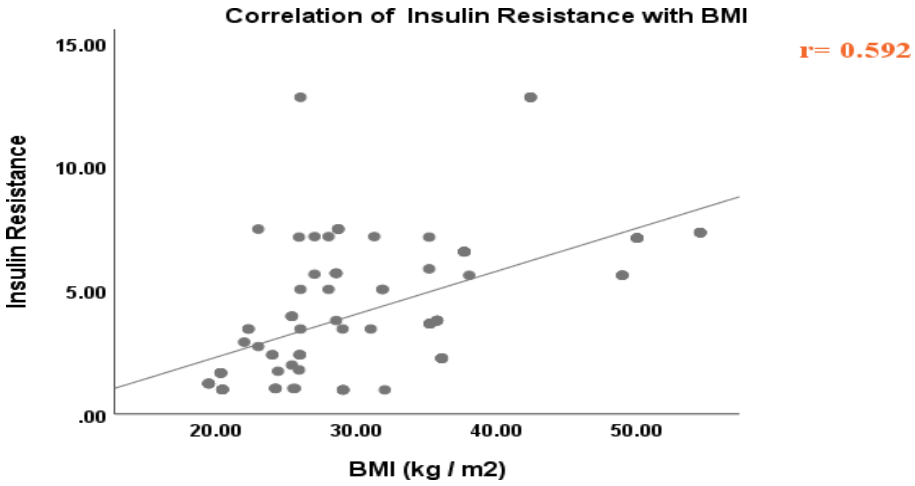

Figure 5: Correlation between BMI and insulin resistance

Correlation between vitamin D level and insulin resistance is shown in figure (6). No significant correlation is seen between vitamin D level and insulin resistance (r = - 0.193, P= 0.055).

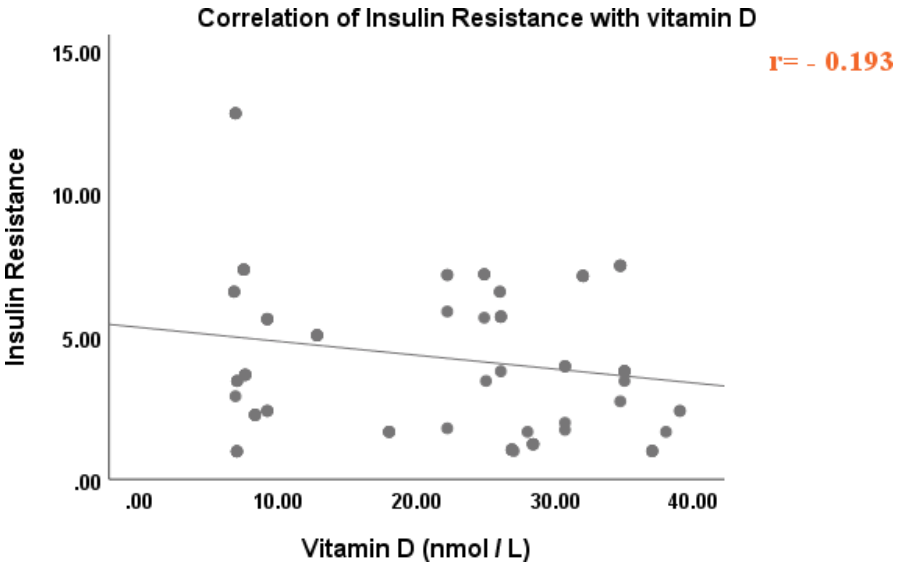

Figure 6: Correlation between vitamin D level and insulin resistance

V. DISCUSSION

Polycystic ovary syndrome is an endocrine-metabolic disorder characterized by multiple hormonal imbalances, had a manifestation of hyperandrogenism, which generate short and long term consequences on female health [(5)].

In the current study, the mean and standard deviation (SD) of vitamin D was 20.77 ± 11.38 nmol/L ranging from 6.8 – 39.4 nmol/L. in which more than two third of study patients had vitamin D deficiency (69%). Level of vitamin D at different study, showed that mean of vitamin D significantly higher when BMI level compared to overweighed and obese patients (29.33 versus 20.39 and 15.87 (nmol/L), P= 0.001). A poor negative correlation was detected between BMI and vitamin D (r= - 0.378).

These results are comparable to Joham et al study in 2016, when found that Vitamin D levels were significantly lower in overweight women with PCOS compared with overweight controls (31.6 and 46.1 nmol/L, respectively, p = 0.01) [13].

Furthermore, a study done by Tsakova et al in 2012, showed that 2/3 of the women with PCOS and obesity appeared to be Vit D-deficient. Obesity accompanied with a significantly lower levels of 25(OH)D when compared to lean [14]. In Yildizhan et al study in 2009, serum 25-OH-Vit. D mean levels were 56.31% lower in the obese and there was an association of increased BMI with decreased 25-OH- Vit. D level in the obese patients. They concluded that low serum Vit. D result from the presence of obesity and insulin resistance. Hypovitaminosis D should be kept in mind while managing obese women with PCOS [15].

A study done by Velija-Asimi in 2014, showed that more than 2/3 of patients had Vit. D deficiency but without significant association with BMI and concluded that insulin resistance and vitamin D deficiency significantly predicted the obesity risk in PCOS women. [16]

Yılmaz et al study in 2015 showed that 25-OH D levels were lower in both in the overweight and normal weight PCOS women than in normal weight healthy, and 25(OH)D3 levels were lower in overweight than in the normal weight women with PCOS, though the difference was not significant [17].

The discrepancies observed among studies might have attributed to: vitamin D is fat soluble, a higher proportion of vitamin D may be sequestered in adipose tissue in obese individuals, which might lower serum levels [18], the sample size participated in each study and the presence of other potential confounding factors, such as outdoor times or dietary patterns which could affect the serum vitamin D levels.

In the current study, the mean and SD of insulin was 4.3 ± 2.86 (ranging 0.97 – 12.8). A high insulin resistance was noticed in 61% of study patients. Additionally, obese patients had a significantly higher mean of insulin resistance than those noticed among patients had overweighed and normal BMI level (5.73 versus 4.34 and 1.88, P= 0.001). A moderate positive correlation in this study was detected between BMI and insulin resistance (r= 0.592) which was statistically significant (P= 0.001).

In Chiware et al study (2013), only 34% of patients were insulin resistance, also increasing BMI and insulin resistance were strongly correlated, with an r value of 0.82. Furthermore, a BMI < 29 kg/m^2 had a negative predictive value for insulin resistance of 97% [19].

Additionally, Stepto et al found in their study in 2013, that insulin resistance was present in 62% of overweight controls and 95% of overweight PCOS. Also, found that lean controls were less insulin resistance than lean PCOS, overweight controls and overweight PCOS. There was no significant difference in insulin resistance between lean PCOS women and overweight controls and overweight women with PCOS were significantly more insulin resistant than all groups including overweight controls [20]. Rabøl et al found in their study in 2011, that insulin sensitivity decreased with PCOS and increasing body weight [21].

No significant correlation was found between vitamin D and insulin resistance (r= - 0.193, P= 0.055). In Joham et al study in 2016, Vitamin D is associated with insulin resistance in women with PCOS, and Vitamin D was not associated with insulin resistance after adjustment for confounders; Further analysis by PCOS status revealed that vitamin D was significantly associated with insulin resistance in the PCOS group (p = 0.03), but not in the non-PCOS group [13].

In Ghadimi et al study in 2014, low level of vitamin D was common in PCOs but there was no correlation between vitamin D deficiency and its severity with obesity and insulin resistance, also their results showed that no significant correlations found between Vit D levels and fasting blood glucose [22]. Finally, in Tsakova et al study in 2012, no significant correlation found between Vit D levels and indices of glucose metabolism (fasting blood glucose and immunoreactive insulin (IRI) and after oral glucose tolerance test) [14].

Clinicaly, Hirsutism was noticed in two third of study patients (67%), which was higher than results observed in Ramanand et al study in 2013, in which only 12.5% had abnormal hair growth; clinically only 44.16% women had hirsutism [23], and Zandi's et al study in 2010, in which hirsutism found in 13% of patients [24]. Hirsutism incidence varied in different parts of
the world. The differences observed in the prevalence of national and international studies are possibly due to racial differences and differences between age groups of the sample.

Regarding BMI level, mean and SD was 31.52 ± 9.74 kg / m^2 (range 19.48 -54.43 kg / m^2), with the highest proportion of study patients was obese (43%). In 2017, Kumar et al study, found that mean of BMI was equal to 30.4 kg/m^2 [25].

VI. Conclusion

1. Vit D level showed a significant negative relation with BMI level.
2. Insulin resistance is significant elevated when body weight increased.
3. No significant relationship seen between Vit D level and insulin resistance.

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