ORIGNAL RESEARCH

Evaluation of the Hormonal and Biochemical Changes in Obese and Non-obese Polycystic ovary syndrome (PCOS) Iraqi Women Before and After Vitamin D Supplementation

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ABSTRACT

Vitamin D deficiency is common in women with polycystic ovarian syndrome. Vitamin D plays an important physiologic role in reproductive functions of ovarian follicular development and luteinization through altering anti-müllerian hormone signaling, follicular stimulating hormone activity and progesterone production in human granulosa cells. Vitamin D is precipitated in adipose fat tissues, making it not able to be used for the body as a result; obese people with high body mass index are already highly expected to have low levels of serum vitamin D.

Background: There are associations of Vitamin D deficiency with type 2 diabetes, insulin resistance, metabolic syndrome and cardiovascular disease in polycystic ovarian syndrome women.

Objective: This study aimed to evaluate the association of vitamin D deficiency with sex hormones and metabolic markers, like fasting blood glucose, fasting insulin level and Homeostasis model assessment of insulin resistance. This evaluation was done in obese and non-obese Iraqi women with polycystic ovarian syndrome before and after supplementation with vitamin D.

Methods: Eighty polycystic women were enrolled in this study. Forty of them were obese with body mass index more than 30 and were considered as group A. The other 40 were nonobese women with a body mass index of less than 30 and were considered as group B. Physical examination was performed for all patients including height, weight and waist circumference, and blood pressure measurements. Five ml of blood were aspirated during the follicular phase in the early morning after overnight fasting for measuring follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin, thyroid function test, fasting insulin, fasting sugar and vitamin D3. Then, a supplement of vitamin D3 400 IU was given twice daily for six months to the patients with a low level of serum vitamin D3 and then reevaluated again for biochemical parameters.

Results: There were no significant differences between two groups in hormonal assay before and after treatment with vitamin D3. There were significant differences before and after treatment with vitamin D3 in groups, improvement in vitamin level, decrease in serum insulin level, fasting blood sugar and Homeostasis model assessment of insulin resistance.

Conclusion: Vitamin D plays a role in the improvement of biochemical variables like serum insulin level, fasting blood sugar and Homeostasis model assessment of insulin resistance in both obese and nonobese polycystic ovarian Iraqi women.

Keywords: Body mass index, Polycystic ovarian syndrome, Vitamin D deficiency.

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INTRODUCTION

Vitamin D is a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, phosphate, and magnesium[1] and affects many metabolic functions. Vitamin D3 (cholecalciferol) is the most important compound in the vitamin D group; It's the real vitamin D. The vitamin D deficiency is common in Iraqi women with polycystic ovarian syndrome. Vitamin D plays an important physiologic role in reproductive functions of ovarian follicular development and luteinization through altering anti-müllerian hormone (AMH) signaling, follicular stimulating hormone activity and progesterone production in human granulosa cells.[2] Vitamin D is precipitated in adipose fat tissues, making it not able to be used for the body as a result; obese people with high body mass index BMI are already highly expected to have low levels of serum vitamin D.[3]

PCOS is one of the most common endocrine disorders in women,[4] also called hyperandrogenic anovulation (HA).[5]

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It was affecting approximately 4–18% of women in the reproductive period between the ages of 16–44 years.[6] PCOS associated with many metabolic disturbances like obesity, insulin resistance, hyperinsulinemia, dyslipidemia[7,8] and hypertension. PCOS women may also have an increased risk of vitamin D deficiency (VDD). Approximately 67–85% of women with PCOS have VDD.[9] Also, there are associations of VDD with type 2 diabetes, insulin resistance, metabolic syndrome and cardiovascular disease in PCOS women.[10]

The effect of vitamin D on reproductive and metabolic dysfunctions in women with PCOS was may be intermediated by insulin resistance. The bulk of PCOS women (obese and Non-obese) had hyperinsulinemia and insulin resistance.[11] These high insulin levels make a payment to the defects observed in the hypothalamic-pituitary-ovarian axis. As well hyperinsulinemia increases GnRH pulse frequency, elevated LH over FSH dominance, this will lead to increased ovarian androgen production which leads to decrease follicular maturation and decrease sex hormone-binding globulin (SHBG), the entire these actions will guide to the growth of PCOS .[11]

Also metabolically, hyperinsulinemia and insulin resistance is associated with a high risk of impaired glucose tolerance type 2 diabetes mellitus and cardiovascular diseases.[6,12] Therefore, vitamin D may play a chief role in the development of PCOS.

There is a difficult connection between vitamin D and sex hormones because it is partially compensated by several mechanisms like low serum vitamin D level by calcium recruitment due to high parathyroid hormone (PTH) level.[3,13]

The most important point is that vitamin D deficiency is an important feature of obesity especially due to the storage of (25OHD) vitamin D in adipose tissue because of the lipophilic features leading later on to compensatory increase in PTH.[3,14]

This study aimed to evaluate the association of vitamin D deficiency with sex hormones and metabolic markers, like fasting blood glucose, fasting insulin level and HOMA-insulin resistance (HOMA-IR) in obese and non-obese Iraqi women with PCOS before and after supplementation with vitamin D.

PATIENTS AND METHOD

This study was a prospective interventional study conducted in the outpatient department (OPD) of AL-Yarmouk Teaching Hospital which is a tertiary referral center in Baghdad from the period of 1st of January 2017 to February 2019. The protocol of the study was approved by the Ethical Research Committee of Obstetrics and Gynecology. Eighty polycystic women were enrolled in the study. Forty of them were obese with body mass index (BMI) more than 30 and they were assigned as group A and the other forty patients were not obese with BMI less than 30 were assigned as group B. Informed consent was taken from all participants. The polycystic ovarian syndrome was diagnosed based on Rotterdam criteria.

Inclusion Criteria

- PCOS patients with Rotterdam criteria.
- Age between 18–42 years old.
- Normal thyroid function and normal prolactin level.

Exclusion Criteria

- Any medical or endocrine diseases such as thyroid diseases and hyperprolactinemia.
- Recent history of vitamin D supplementation within the last 4 months.

A detailed history was taken from all participants. Physical examination was performed for all patients including height, weight and waist circumference measurements. The BMD was calculated by the standard equation as weight in kilograms divided by the square of height in meters (kg/m2). Blood pressure was measured in both groups. Five ml of blood were aspirated by the standard venipuncture method during the follicular phase of the menstrual cycle. The collection of blood was done early in the morning after overnight fasting. The collected blood was placed in plane tubes and allowed to clot for 10 minutes and then centrifuged for 20 minutes. The resultant serum samples were stored at –8 Co till the time of analysis. The samples sent to measure FSH, LH, serum testosterone, serum prolactin, thyroid function tests, fasting insulin, fasting sugar levels and 25(OH)D. Six months course treatment with vitamin D3 400IU twice times a day was prescribed to the patients who had low vitamin D levels and reevaluated at the end of this period by history asking about menstrual regularity and looking for any hormonal or biochemical improvement. No other treatment was given to the patients, only advised them to change lifestyle for diet and exercise.

Statistical Analysis

Statistical Package for Social Sciences (SPSS 25)* was used for data analysis. Continuous data represented by mean, standard deviation and range. The differences between groups for continuous data were measured using Student's t-test and paired t-test was used for comparison of changes in the levels of the parameters affected by treatment with vitamin D. Alpha level ≤ 0.05 was considered significant.

- *IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. (New-York, USA) IBM Company.

RESULTS

The demographic data of both groups were compared as shown in Table 1 which demonstrates that the difference was statistically not significant regarding the age while it was significant regarding waist circumference, BMI and systolic blood pressure.

Regarding diastolic blood pressure; though it does not reach statistical difference still it was higher in obese than non-obese patients.

The difference in the hormonal changes between the study groups was statistically significant regarding LH and FSH, but the difference was not significant regarding serum testosterone and serum prolactin while the difference between the study groups regarding serum insulin level, FBS, HOMA-IR, and vitamin D which were statistically significant.

Table 1: Comparison between study groups regarding demographic, hormonal and biochemical changes.

	PCOS patients Mean ± Standard deviation (Minimum – Maximum)		
Variables	*Non obese (n = 40)*	*Obese (n = 40)*	*p value*
Age (years)	24.72 ± 4.78 (16 – 36)	26.1 ± 5 (18 – 36)	0.209
Waist circumference (cm)	67.78 ± 5.57 (60 – 78)	96.57 ± 13.71 (75 – 120)	<0.001**
BMI Kg/cm^2	22.03 ± 1.64 (18 – 24)	28.53 ± 3.23 (23 – 35)	<0.001**
Systolic Blood Pressure	123.25 ± 8.59 (110 – 140)	133.25 ± 10.23 (110 – 150)	<0.001**
Diastolic Blood Pressure	77.5 ± 8.4 (60 – 90)	78.5 ± 8.34 (60 – 90)	0.595
Luteinizing Hormone iu/l	12 ± 2.52 (8 – 17)	13.36 ± 2.61 (7 – 18)	0.02*
Follicular Stimulating Hormone iu/l	4.91 ± 1.59 (2.1 – 7.5)	7.55 ± 2.02 (5 – 12)	<0.001**
Serum Testosterone ng/l	0.78 ± 0.78 (0.06 – 2)	0.91 ± 0.73 (0.06 – 2.03)	0.446
Serum Prolactin ng/l	18.05 ± 8.47 (7 – 30)	18.63 ± 6.74 (6 – 30)	0.736
Serum Insulin level before treatment Miu/l	25.82 ± 2.55 (22 – 32)	26.96 ± 2.34 (21 – 30)	0.04*
Fasting Blood Sugar before treatment mmol/l	5.77 ± 0.25 (5.3 – 6.2)	5.91 ± 0.27 (5 – 6)	0.02*
HOMA–IR before treatment	6.32 ± 0.69 (5.28 – 7.96	6.78 ± 0.73 (5.32 – 7.87)	0.005**
Vit. D before treatment ng/l	13.92 ± 4.73 (6 – 23)	11.43 ± 5.63 (7 – 30)	0.036*

*<0.05, **<0.001 significant, Student t-test

Table 2: Comparison between study groups regarding hormonal parameters before and after the treatment by vitamin D, according to the study group

	Variables	*Before Treatment*	*After Treatment*	*p value*
Non-Obese group (N=40)	Luteinizing Hormone iu/L	12 ± 2.52	11.7 ± 2.37	0.564
	Follicular Stimulating Hormone iu/L	7.55 ± 2.02	7.25 ± 2.26	0.534
	Serum Testosterone ng/l	0.78 ± 0.78	0.76 ± 0.81	0.91
	Serum Prolactin ng/L	18.05 ± 8.47	17.96 ± 8.29	0.962
Obese group (N=40)	Luteinizing Hormone iu/L	13.36 ± 2.61	13.29 ± 2.54	0.903
	Follicular Stimulating Hormone iu/L	4.91 ± 1.59	4.84 ± 1.57	0.843
	Serum Testosterone ng/L	0.91 ± 0.73	0.90 ± 0.70	0.95
	Serum Prolactin ng/L	18.63 ± 6.74	18.59 ± 6.63	0.979

Paired t-test

Table 2 was shown the difference in the hormones between the study groups before and after the supplementation by vitamin D which was statistically not significant.

Table 3 demonstrates the difference in biochemical parameters between the two groups before and after vitamin D which was statistically significant for all parameters.

DISCUSSION

To date, PCOS represents one of the commonest endocrine-metabolic disorders with a great impact on women's fertility. The etiology of this syndrome is multifactorial with the environmental and genetic factors being the main one.[8,15] Its prevalence is increasing especially among adolescent and young aged women and till now there is a debate on the opportunity of understanding the pathogenesis and the management of PCOS. Many recent studies highlighted the potential role of obesity in the development of PCOS in an adolescent.[3,7] It is thought that there is an association between vitamin D and obesity through the effects of vitamin D on hormonal modulation and gene transcription that influence the metabolism of insulin.[16]

Table 3: Comparison between study groups regarding biochemical parameters before and after the treatment by vitamin D, according to the study group

Variables		*Before Treatment*	*After Treatment*	*p value*
Non-Obese group (N = 40)	Vit. D ng/L	13.92 ± 4.73	25.12 ± 5.84	<0.001**
	Serum Insulin level Miu/L	25.82 ± 2.55	17.98 ± 2.27	<0.001**
	FBS mmol/L	5.77 ± 0.25	4.81 ± 0.54	<0.001**
	HOMA-IR	6.32 ± 0.69	3.85 ± 0.69	<0.001**
Obese group (N = 40)	Vit. D ng/L	11.43 ± 5.63	29.07 ± 4.78	<0.001**
	Serum Insulin level Miu/L	26.96 ± 2.34	18.78 ± 2.75	<0.001**
	FBS mmoL/L	5.91 ± 0.27	5.02 ± 0.47	<0.001**
	HOMA-IR	6.78 ± 0.73	4.17 ± 0.67	<0.001**

**<0.001 significant, Paired t-test

The current study was designed to compare the effect of vitamin D levels in slim and obese PCOS patients, and to evaluate the hormonal and biochemical changes before and after vitamin D supplementation. The study shows that there was no significant difference between the study groups regarding the age as they were matched to minimize the effect of age on the levels of vitamin D. While the difference was statistically significant regarding waist circumference, BMI and systolic blood pressure because we were dealing with obese and slim patients. Velika-Ašimiet al in 2014 found the same results in his study comparing obese and non-obese PCOS patients.[3] Regarding diastolic blood pressure though it does not reach statistically significant difference it still higher in obese PCOS patients.

In our study the hormonal changes between the two groups before vitamin D supplementation were statistically significant regarding the levels of FSH and LH only but not for serum testosterone and serum prolactin; on the other hand, the difference was statistically significant regarding all biochemical parameters involving in the study. Velika-Ašimi et al. in 2014 found that the difference was statistically significant regarding LH but not significant regarding FSH, serum testosterone, serum prolactin. They concluded that vitamin D level was lower in overweight people and this may be because vitamin D mainly deposit in the adipose tissue making it unavailable for body use[3,9] though its level does not reach statistical significance which disagrees with the result in our study as the difference in vitamin D level here was significant.

Ghadimi R et al. in 2014 found that there was no difference between obesity and the degree of vitamin D deficiency. Also, they concluded that there was no association between the fasting insulin level, HOMA-IR and glucose level, and BMI which disagreed with the findings of our study.[16]

Our study found that there was no significant association between vitamin D treatment and hormonal parameters while the difference was statistically significant with biochemical variables this disagrees with a study done by Ardabili et al. in 2012 who studied the relation between vitamin D supplementation and HOMA-IR and they concluded that there was no significant association between them[17] but they did not involve the hormonal parameters. Wehr et al in 2011 observed a significant improvement in insulin resistance and lowering in fasting insulin level and androgen level following vitamin D treatment[18] which is agreed in part to the results of our study. Seyyed et al in 2018 and Asemi et al in 2015 found a significant improvement in HOMA-IR and fasting insulin level after vitamin D supplementation but not for gonadotropin or sex hormones.[19,20] Regardless of all the discrepancies of the above studies but most of these studies found a positive effect of vitamin D supplementation on biochemical but not the hormonal parameters in patients with PCOS.

The importance of this subject is that vitamin D deficiency is associated with multiple health problems including ischemic heart disease, diabetes, cerebrovascular accident and even depression,[3,19,20] and for this reason comes the importance of performing future studies involving large and different population to support the results of this study.

CONCLUSION

In the current study, vitamin D plays a role in the improvement of biochemical variables like serum insulin level, FBS and HOMA-IR in both obese and nonobese PCOS Iraqi women. So that recommended giving vitamin D3 supplementation to PCOS female with low-level vitamin D.

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