Conference Paper

Vitamin D Levels in Women with Polycystic Ovary Syndrome

Elida Sidabutar[1], Binarwan Halim[2], Muhammad Fidel Ganis Siregar[2], Delfi Lutan,[2] Ichwanul Adenin[2], and Yostoto Kaban[2]

[1]Pirngadi General Hospital, Department of Obstetrics and Gynecology, Jl. Prof HM Yamin SH no. 47 Medan, Indonesia
[2]Adam Malik General Hospital, Department of Obstetrics and Gynecology, Jl. Bunga Lau no. 17 Medan, Indonesia

Abstract

Introduction. Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. There is some evidence suggested that vitamin D played a role in the incidence of PCOS. Previous research has found vitamin D deficiency in the pathogenesis of PCOS and cohort studies showing the relationship of obesity with decreased levels of 25-hydroxy vitamin D. Therefore, we aim to conduct a study on vitamin D levels in women with polycystic ovary syndrome. **Objective.** To determine the difference of the levels of vitamin D in women with and without polycystic ovary syndrome. **Methods.** This study is a comparative analytical study on two unpaired population by using cross-sectional study design. The study was conducted in Halim Fertility Clinic Medan starting in November 2014 through April 2015. Blood samples were taken from 23 women PCOS and 23 non-PCOS women. Further data were tabulated and analyzed. **Results.** Vitamin D levels are lower in women with PCOS compared to controls. In the PCOS group, the levels of vitamin D were lower in obese women. Vitamin D levels were also lower in PCOS women with WHR > 0.85. **Conclusion.** This study showed a significant lower level of vitamin D in PCOS patient.

Keywords: PCOS, Vitamin D, 25 (OH) D

Corresponding Author: Elida Sidabutar; email: elidars@yahoo.com

Received: 24 August 2016
Accepted: 25 September 2016
Published: 4 October 2016

Publishing services provided by Knowledge E

Selection and Peer-review under the responsibility of the ASPIRE Conference Committee.

1. Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS is a complex disorder, which results in a defect in reproduction and metabolism [1,2]. Previous studies found vitamin D deficiency in the pathogenesis of the metabolic syndrome, and a cohort study demonstrated association of obesity with decreased levels of 25-hydroxy vitamin D in patients with polycystic ovarian syndrome (PCOS) [3,4].

There are many causes of vitamin D deficiency, including reduced skin synthesis and absorption of vitamin D and acquired and heritable disorders of vitamin D metabolism and responsiveness. Use of sunscreen, presence of pigment in the skin, patients with skin grafts for burns will cause a reduction in the synthesis of vitamin D. Obesity can cause decreased bioavailability due to reduced availability of vitamin D. The presence of liver failure and kidney disease will also interfere the metabolism of vitamin D [5].

Allegedly, serum vitamin D levels were low in people with excess weight (overweight) because vitamin D is stored in adipose tissues, making it unavailable for use [6,7]. Several observational studies identified an inverse correlation between serum 25(OH)D concentrations and BMI or insulin resistance. Other studies revealed an association of vitamin D concentration and hyperandrogenism and menstrual disturbances in women with PCOS [8]. Studies regarding vitamin D status in patients with PCOS show an inverse correlation between vitamin D levels and metabolic risk factors such as insulin resistance, BMI, waist-to-hip ratio (WHR), triglycerides, total testosterone and DHEAS, and a positive correlation with insulin sensitivity [9].

In an observational study on 25 women with PCOS and 27 controls, Li et al reported an inverse correlation between the 25(OH)D levels and BMI, 72% of women with PCOS had vitamin D deficiency, of which 44% with severe deficiency (<25 ng/ml) [10].

The same association was observed by Wehr et al in an observational study involving 206 PCOS women with 72% of the population showed the evidence of vitamin D deficiency (25(OH)D serum < 30 ng/ml) and noted the existence of an inverse association between 25(OH)D levels and BMI [3].

2. Material and Methods

This is a comparative analytical study on two unpaired population by using a cross-sectional study design. This study was conducted in Halim Fertility Center Medan from November 2014 to April 2015. 23 women who had been diagnosed with PCOS based on Rotterdam criteria (2003), were included to this study. This criteria consists of different clinical manifestations of both oligo-ovulation or hyperandrogenism (clinical or laboratory), including hirsutism, acne, elevated testosterone, as well as morphologic view of PCOS in ovarian sonography. Inclusion criteria for this study were women aged 18-45 years, married, do not presence of any endocrine disorders (thyroid, parathyroid, diabetes mellitus, Cushing syndrome, congenital adrenal hyperplasia, hyperprolactinemia), virilizing tumors, renal or liver diseases, had never been treated with calcium or vitamin D preparations, and women who are exposed to sunlight. All participates provided a signed informed consent. As control, 23 women without PCOS were included in this study. The damaged blood sample and can not be tested were excluded from the study.

Data consisting of characteristics and anthropometric indices were gathered through an interview conducted by a trained researcher. Weight was measured in light indoor clothing and barefoot and height was measured in stand up position. Then, using the following formula to calculate the body mass index: BMI = kg/m^2. Based on BMI findings, we divided the participants into four following groups: less than 18,5 kg/m^2 as underweight, 18,5-22,9 kg/m^2 as normoweight, 23-24,9 kg/m^2 as overweight and 25 kg/m^2 or more as obese.

To calculate waist-to-hip ratio (WHR), waist circumference measurement was obtained just above the iliac crest and exactly under navel by a tape meter, while hip circumference measurement was obtained when the tape meter was positioned horizontally around the maximum circumference of the buttocks.

Characteristic	PCOS		Without PCOS	
	N	%	N	%
Age (yr)				
≤20	0	0	0	0
21-30	6	26,1	8	34,8
31-40	16	69,6	15	65,2
≥41	1	4,3	0	0
WHR				
<0,85	8	34,8	21	91,3
≥0,85	15	65,2	2	8,7
BMI				
Underweight	0	0	2	8,7
Normoweight	6	26,1	17	73,9
Overweight	4	17,4	2	8,7
Obese	13	56,5	2	8,7

Table 1: Characteristic of participants

	VITAMIN D levels (ng/ml)		p*
	Mean	SD	
PCOS	25,25	7,55	
Without PCOS	36,30	8,19	< 0,001
**) t test-independent*			

Table 2: Vitamin D levels in women with and without PCOS.

Serum concentration of 25(OH)D was measured. Vitamin D deficiency were indicated as ≤ 20 ng/ml, insufficiency as 21 – 29 ng/ml and sufficiency was defined as ≥ 30 ng/ml.

All statistical analyses were carried out using software package used for statistical analysis (SPSS) version 16.

3. Results and Discussion

A total of 46 participants were assesses based on age, waist-to-hip ratio and body mass index (Table 1).Based on the age, most of PCOS women were at 31-40 years (69.6%). Similarly, in the control group, mostly at 31-40 years (65.2%).Based on the waist-to-hip ratio, women with PCOS most commonly found in the ratio> 0.85 (65.2%). While in the control group, most in the ratio <0.85 (91.3%)Based on body mass index, women with PCOS mostly in the obese group (56.5%), while the control group mostly were normoweight (73.9%).

Based on Table 2, vitamin D levels is higher in control group (women without PCOS). Independent t-test indicated a significant association between the incidence of PCOS and the vitamin D levels statistically (p value < 0.05).

This is consistent with previous research which claimed the tendency of decreasing of vitamin D levels in PCOS women. Wehr et al previously found a deficiency of vitamin

PCOS	Vitamin D levels (ng/ml)			p*
	n	Mean	SD	
Underweight	0			
Normoweight	6	32,83	4,31	
Overweight	4	26,68	8,90	0,003
Obese	13	21,31	5,54	

Table 3: Vitamin D levels in PCOS Women Based on BMI.

BMI	Diagnose		p*
	PCOS	Without PCOS	
Underweight	0	2	0,001
Normoweight	6	17	
Overweight	4	2	
Obese	13	2	
*) chi square test			

Table 4: Association of Body Mass Index and PCOS.

D in women with PCOS [3]. Several studies have reported that low vitamin D levels in women with PCOS, with average of 25(OH)D levels between 11 and 31 ng/ml, with the most were <20 ng/ml (67-85%) [10]. In this study, the average vitamin D levels were 25.25 ng/ml. This level is higher than a previous study conducted by Wehr et al This is probably caused by the intensity of exposure to UVB rays that occur throughout the year in Indonesia. As discussed earlier, that the intensity of ultraviolet exposure is important in the production of vitamin D also depends on location [11]. Although there is no consensus regarding the optimal level of 25(OH)D, a level of 30 ng/ml or greater can be considered to indicate sufficient vitamin D [3]. In this study, women with PCOS showed an average level below the recommended one.

We found a decrease in vitamin D levels with the increased of body mass index (Table 3). The lowest vitamin D level was in obese women. Using ANOVA test this difference was statistically significant at $p < 0.05$.

When compared between the women with and without PCOS (Table 4), there were significant association with a p-value of 0.001.

	VITAMIN D Levels					
	PCOS			Without PCOS		
	Normal	Insufficiency	Deficiency	Normal	Insufficiency	Deficiency
Underwight	0	0	0	2	0	0
Normal	5	1	0	15	1	1
Overweight	2	0	2	2	0	0
Obese	2	4	7	1	0	1

Table 5: Distribution of Vitamin D Levels in Women with and without PCOS based on BMI.

WHR	VITAMIN D Levels (ng/ml)		p*
	Mean	SD	
<0,85	31	5,09	
≥0,85	22,18	6,90	0,005
*) t test-independent			

Table 6: Vitamin D levels in PCOS Women Based on Waist-to-Hip Ratio.

Previous study conducted by Li et al reported an inverse association between levels of 25 (OH)D and BMI [10]. Wehr et al also found an inverse association between 25(OH)D and BMI [3]. In this study, we also found an inverse association between the levels of 25(OH)D and BMI, although the average levels in obese women have not yet reached the levels of vitamin D deficiency. Obesity can lower 25(OH) in circulation by trapping vitamin D on adipose tissue [3,6,7]. Wortsman et al compared the vitamin D levels in obese and non-obese group after exposure to UVB light in a specific amount for 24 hours. Although the obese group had a body surface area greater for exposure and therefore are expected to produce more vitamin D than the non-obese group, this has not happened. The levels of 25(OH)D after exposure to the whole body, were 57% lower in the obese group compared with the non-obese group. The obesity does not affect the capacity of the skin to produce vitamin D, but may alter the release of vitamin D from the skin into the circulation. Subcutaneous fat, which is the storage of vitamin D, trapping vitamin D in the skin because there is more fat available to this process [3,12].

Obesity is often associated with hypovitaminosis D, due to increased storage of 25(OH)D in adipose tissue, or reduction in exposure to sunlight [13]. In PCOS women, the low 25(OH)D levels were associated with obesity, metabolic and endocrine disorders [14].

Table 6 showed a decrease in vitamin D levels by the increasing of waist-to-hip ratio. With t-test independent, this difference was significant ($p < 0.05$).

Waist-to-hip ratio (WHR) is a way to determine the degree of obesity of the top and the bottom of body, where the ratio was accurately predict the amount of intraabdominal fat [15].

International Diabetes Federation (IDF) in 2005 stated that central obesity (as determined by waist circumference) as an essential component of the metabolic syndrome [2]. Faraji et al in a previous study suggested a link between the increase in WHR with decreased levels of vitamin D. Waist-to-hip ratio of 0.85 or more shows the distribution of fat in the body that lead to hyperinsulinemia, glucose intolerance, diabetes mellitus and increased androgen [16].

Table 7 shows the association of vitamin D with PCOS. In PCOS women group, we also found vitamin D levels are still normal in 9 samples. A total of 5 samples with vitamin D insufficiency and 9 samples with deficiency of vitamin D. In women without PCOS group, we found the vitamin D levels were sufficient. Although we found that normal levels of vitamin D in the PCOS group and found vitamin D deficiency and insufficiency

VITAMIN D Levels (ng/ml)	DIAGNOSE		p*
	PCOS	Without PCOS	
Deficiency (≤ 20)	9	2	*0,004*
Insufficiency (21-29)	5	1	
Sufficiency (≥30)	9	20	
(*) chi square test			

Table 7: Association of Vitamin D Levels and PCOS.

in non-PCOS group, this is still meaningful statistically. This shows that not all incidents of vitamin D deficiency is associated with PCOS.

The study by Yilmaz et al stated that the levels of 25(OH)D lower in overweight and normoweight women with PCOS compared to controls with normal weight. Levels of 25(OH)D lower in overweight women with PCOS than normoweight women with PCOS, although the difference was not significant [17].

4. Conclusion

Women with PCOS most commonly found in the reproductive age, 30-41 years, with WHR ≥ 85 and increased body mass index. Most commonly found in obese women. There are significant differences between the vitamin D levels in PCOS women and in the control group. In PCOS women, we found a significant decrease in vitamin D levels with an increased body mass. In PCOS women, we found a significant decrease in the levels of vitamin D by the increasing of the waist-to-hip ratio. We found vitamin D deficiency and insufficiency was significant in PCOS cases.

5. Limitations

Limitations or weaknesses of this study is that the sample is not homogeneous. We do not do the matching between cases and controls. If the matching is done well, the various types of variables that may contribute to the incidence of PCOS can be likened, in order to get a stronger relationship between the variables studied.

6. Suggestion

In PCOS cases, it is necessary to check the Vitamin D levels to support the therapy. With the many roles of vitamin D on reproductive function, it is necessary to conduct further research on the effects of vitamin D on reproductive function in PCOS.

References

[1] B. N. Kalro, T. L. Loucks, and S. L. Berga, Neuromodulation in polycystic ovary syndrome, *Infertility and Reproductive Medicine Clinics of North America*, **14**, no. 4, 529–555, (2003).

[2] L. Speroff and MA. Fritz, Chronic Anovulation and The Polycystic Ovary Syndrome, in *Clinical Gynecologic, Endocrinology and Infertility*, 495–533, 2011, 8th ed.

[3] E. Wehr, S. Pilz, N. Schweighofer, A. Giuliani, D. Kopera, T. R. Pieber, and B. Obermayer-Pietsch, Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome, *European Journal of Endocrinology*, **161**, no. 4, 575–582, (2009).

[4] E. Wehr, O. Trummer, A. Giuliani, H.-J. Gruber, T. R. Pieber, and B. Obermayer-Pietsch, Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome, *European Journal of Endocrinology*, **164**, no. 5, 741–749, (2011).

[5] M. F. Holick, Medical progress: Vitamin D deficiency, *New England Journal of Medicine*, **357**, no. 3, 266–281, (2007).

[6] L. Wamberg, T. Christiansen, S. K. Paulsen, S. Fisker, P. Rask, L. Rejnmark, B. Richelsen, and S. B. Pedersen, Expression of vitamin D-metabolizing enzymes in human adipose tissue - The effect of obesity and diet-induced weight loss, *International Journal of Obesity*, **37**, no. 5, 651–657, (2013).

[7] S. M. Kabadi, B. K. Lee, and L. Liu, Joint effects of obesity and vitamin D insufficiency on insulin resistance and type 2 diabetes: Results from the NHANES 2001-2006, *Diabetes Care*, **35**, no. 10, 2048–2054, (2012).

[8] P. Anagnostis, S. Karras, and D. G. Goulis, Vitamin D in human reproduction: A narrative review, *International Journal of Clinical Practice*, **67**, no. 3, 225–235, (2013).

[9] M. Grundmann and F. Versen-Hoynck, Vitamin D-roles in womens reproductive health? *Reprod Bio and Endocrinol*, (2011).

[10] R. L. Thomson, S. Spedding, and J. D. Buckley, Vitamin D in the aetiology and management of polycystic ovary syndrome, *Clinical Endocrinology*, **77**, no. 3, 343–350, (2012).

[11] D. Bikle, J. Adams, and S. Christakos, Vitamin D: Production, Metabolism, Mechanism of Action, and Clinical Requirements, *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism: Seventh Edition*, 141–149, (2009).

[12] J. Wortsman, L. Y. Matsuoka, T. C. Chen, Z. Lu, and M. F. Holick, Decreased bioavailability of vitamin D in obesity, *American Journal of Clinical Nutrition*, **72**, no. 3, 690–693, (2000).

[13] A. Bellia, C. Garcovich, M. D'Adamo, M. Lombardo, M. Tesauro, G. Donadel, P. Gentileschi, D. Lauro, M. Federici, R. Lauro, and P. Sbraccia, Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects, *Internal and Emergency Medicine*, **8**, no. 1, 33–40, (2013).

[14] E. Lerchbaum and B. Obermayer-Pietsch, Mechanisms in endocrinology - Vitamin D and fertility: A systematic review, *European Journal of Endocrinology*, **166**, no. 5, 765–778, (2012).

[15] L. Speroff and MA. Fritz, Obesity, in *Clinical Gynecologic, Endocrinology and Infertility, 8th ed*, 2011.

[16] R. Faraji, SH. Sharami, Z. Zahiri, et al., Evaluation of Relation between Anthropometric Indices and Vitamin D Concentrations in Women with Polycystic Ovarian Syndrome, *Journal of Family and Reproductive Health*, **8**, no. 3, 123–129, (2014).

[17] SA. Yilmaz, SO. Altinkaya, A. Kebabcilar, et al., The relationship between polycystic ovary syndrome and vitamin D levels, *J Turk Soc Obstet Gynecol*, **1**, 18–24, (2015).