Correlation between 25-(OH) vitamin D level and autoimmune thyroid disease in polycystic ovary syndrome

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ABSTRACT: Background: Low 25(OH) vitamin D levels have been associated with several autoimmune diseases and recently with autoimmune thyroid diseases (AITD). **Objective:** To investigate the association of AITD with 25(OH) vit D levels in women with polycystic ovary syndrome (PCOS). **Materials and Methods:** Fifty women with PCOS were enrolled in this study. Routine health checkups were done which included measurement of 25(OH) vit D, anti-thyroid peroxidase (TPO-Ab), anti-thyroglobulin (TG-Ab) antibodies, FT3, FT4 and TSH selecting 50 nmol/L as cut-off point. **Results:** Low 25(OH) vit D levels were detected in 24 of 50 patients (48%). AITD was diagnosed when TPO-Ab, levels exceeding 80 U/ml and/or TG-Ab levels exceeding 70 U/ml. ATTD was detected in 12 of 50 patients (24%). The level of 25(OH) vit D were significantly lower in women with PCOS and AITD when compared to women with PCOS and without AITD ($P = 0.02$). I woman with AITD no correlation was found between 25(OH) vit D and TG-Ab (r = 0.48); $P = 0.16$), IPO-Ab (r = 0.43; $P = 0.21$), TSH (r = 0.38; $P = 0.27$), FT3 (r = -0.4; $P = 0.25$) and FT4 levels (r = -0.54; $P = 0.10$). These findings suggest that low levels of 25(OH) vit D were significantly associated with AITD in women with PCOS. **Conclusion:** Low 25(OH) vit D levels were associated with AITD in PCOS women. So, supplementation of vit D could represent a promising therapeutic approach to prevent or improve the development of AITD in these women.
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1. Introduction

Polycystic ovary syndrome (PCOS) is a complex syndrome characterized by reproductive and metabolic complications [(1)].

PCOS is characterized by chronic anovulatory, oligomenorrhea, or amenorrhea and signs of hyperandrogenism and it is currently considered the most common cause of infertility in women in reproductive age [(2)].

Several risk factors for cardiovascular disease (CVD), including obesity, diabetes, insulin resistance, hypertension, dyslipidemia, increased serum plasminogen activator inhibitors are frequent in PCOS [(3)].

The exact pathogenesis of PCOS is still debated although it is considered as a heterogeneous disorder with both genetic and environmental components. Recently, vitamin D deficiency has been considered as novel risk factor that could take part to the pathogenesis of PCOS. Vitamin D has been hypothesized to have a role in AMH production pattern in ovarian granulosa cells and to blunt FSH sensitivity, probably playing a role in ovarian follicle development. An inverse association between vit D status and metabolic disturbance has been reported in PCOS patients [(4)].

Existence of vit D receptors in the female reproductive system including the uterus, endometrium, ovaries and placenta, represent important role of vit D in female fertility [(5)]. Further studies have suggested that vitamin D deficiency is associated with some female reproductive abnormalities especially gestational diabetes, endometriosis, PCOS, bacterial vaginosis, premature labor pains and preeclampsia [(6)]. Vit D deficiency has been found to be associated with an increased risk to develop thyroid autoimmunity [(7)]. The latter has been found to be very common in PCOS patients [(8)]. Thus, vit D deficiency may be associated to increase risk to develop autoimmune diseases; providing scientific evidence on the association between vitamin D deficiency and thyroid autoimmune disease (AITD) could represent a promising therapeutic approach to improve and/or prevent AITD in women with PCOS[(9)].

So, the aim of this study was to investigate the association of AITD with low 25(OH) vitamin D level in women with PCOS.

2. Materials and methods:

Fifty women with PCOS attending Al-Hussein and Bab El-Sharia University hospitals during the period from June 2015 to January 2016 were enrolled in this study. Explanation of the study procedures was done and informed consent was taken. The diagnosis of PCOS was based on Rotterdam criteria

that required two out of three of the following criteria to fulfill the diagnosis (oligo-and/anovulation; clinical and/or biochemical signs of hyperandrogenism and transvaginal ultrasound. Hyperandrogenism was defined by the clinical presence of hirsutism (Ferriman-Gallwey Score > 8, acne or alopecia and/or related androgen levels).

Exclusion criteria:

Age < 18 or > 40 years, body mass index (BMI) higher than 30 and lower than 18, pregnancy, diabetes mellitus, hypothyroidism, hyperprolactinemia, previous use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic or antiobesity drugs, or other hormonal drugs within previous 6 months. Any medical disorders (i. e., renal respiratory hepatic,… etc.) were also excluded from this study.

After fasting overnight for 10-12 hours, blood samples were collected during the early follicular phase (3rd day) of spontaneous cycle, for the following assays: FSH, LH, testosterone, androstendione, 17-hydroxyprogesterone, DHEAS, 25(OH) vit D, FT3, FT4, TSH, TG-Ab and TPO-Ab. Serum levels of 25(OH) D were determined by chemiluminescence immunoassay (CLIA; Diasorin, liaison) (intra-and inter-assay) coefficient of variations were 5.8 and 7.85, respectively). All hormones concentrations(FSH, LH, testosterone, androstendione,17-hydroxyprogesterone, DHEAS, TSH) were determined using the same commercial RIA kits (Diagnostic Los Angeles, CA).

TPO-Ab and TG-Ab were determined using a BRAHMS Radioimmunoassay kit (Limburg, Germany). AITD was diagnosed when TPO-Ab level exceeding 80 U/mL and/or TG-Ab levels exceeding 70 U/mL.

Statistical analysis:

Statistical analysis was carried out using SPSS 9.0. Data are expressed as mean ± SD. Kolmogorou-Smirnov test was used to examine for normal distribution of the variables and, where necessary, log transformation, the normal distribution of the variables was checked. Person correlations were used to determine relation between variables. Depending on the distribution of the data, the Student's t test for independent samples and the non-parametric Mann-Whitney U test for independent samples were applied to test for differences between group. Statistical significance was defined as P value lower than 0.05.

3. Results:

Table (1): Clinical and hormonal data stratified according to the presence/absence of AITD

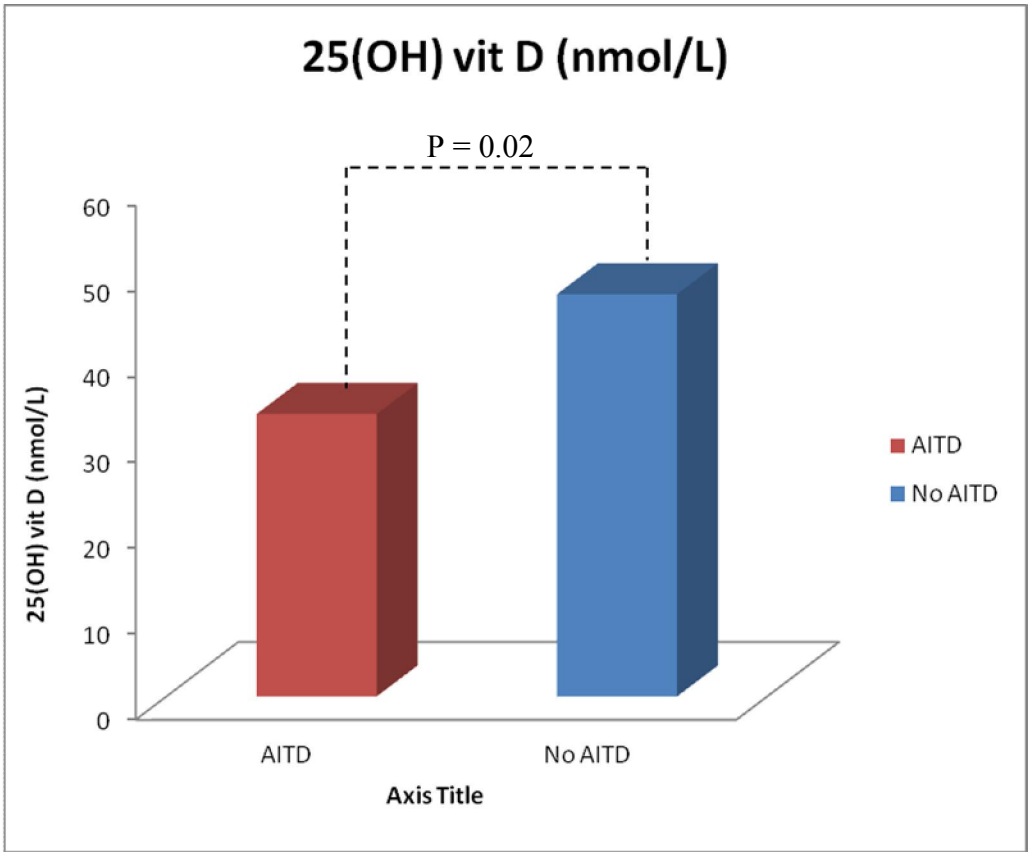
Variables	Total (n = 50)	AITD (n = 14)	No AITD (n = 36)	*P* value
Age (years)	26.7 ± 8.5	25.7 ± 5.3	25.6 ± 8.4	0.47
BMI (kg/m^2)	28.2 ± 7.2	27.9 ± 7.5	28.1 ± 7.0	0.46
Ferriman-Gallwey score	10.7 ± 2.8	10.3 ± 3.0	10.9 ± 3.8	0.37
TSH (mcIU/mL)	2.1 ± 0.9	2.8 ± 1.0	1.9 ± 0.9	0.02
FT3 (Pg/mL)	3.3 ± 0.4	3.5 ± 0.3	3.4 ± 0.4	0.30
FT4 (ng/dL)	1.2 ± 0.1	1.25 ± 0.1	1.26 ± 0.1	0.18
25(OH) vit D (nmol/L)	72.3 ± 51.4	32.0 ± 225	49.6 ± 19.8	0.02
LH (mIU/mL)	10.9 ± 17.6	8.3 ± 3.3	11.8 ± 20.5	0.31
FSH (mIU/mL)	11.3 ± 18.5	6.8 ± 2.5	13 ± 21.6	0.19
Testosterone (ng/mL)	47.9 ± 20.6	49.5 ± 18.1	47.3 ± 21.5	0.36
DHEAS (ng/mL)	232.5 ± 152.3	214.9 ± 128.4	238.9 ± 161.6	0.41
Androstenedione (ng/mL)	4.6 ± 4.6	5.7 ± 5.5	4.1 ± 4.3	0.14
17-OHP (ug/L)	1.1 ± 1.6	1.0 ± 0.4	1.1 ± 1.8	0.44

Clinical and biochemical variables of the all women with PCOS and AITD (study group) and controls are shown in table 1. The mean age was 26.7 ± 8.5 years and the mean BMI was 28.2 ± 7.2 in the all women with PCOS. Selecting 50 nmol/L as cut-off point of vit D deficiency [10]. Low 25(OH) vit D levels were detected in 24 women (48%) of all patients. Twelve women (24%) with PCOS were affected by AITD. We compared the serum 25(OH) vit D levels between patients with PITD and control group. 25(OH) vit D levels were significantly lower in women with AITD when compared to the control group (32.0 ± 22.5 vs 49.6 ±19.8 nmol/L; *P* = 0.02) (Fig. 1).

Although thyroid hormones were within normal range (TSH: 0.35-5.50 mIU/mL); FT3: 2.3-4.2 pg/ml; FT4: 0.89-1.76 ng/dL). Women with AITD have higher levels of TSH compared to women without AITD (2.8 ±1.0 vs 1.9 ± 0.9 mcIU/mL; *P* = 0.02).

Whereas there was no difference regarding FT3 (3.5 ± 0.3 vs 3.4 ± 0.4 pg/mL; *P* = 0.30) and FT4 levels (1.24 ± 0.1 vs 1.26 ± 0.1 ng/dL; *P* = 0.25).

Similarly, no difference was found in terms of TSH (2.7 ± 1.1 vs 2.8 ± 1.1 mcIU/mL; *P* = 0.7), FT3 (3.5 ± 0.2 vs 3.1 ± 0.3 pg/mL; P = 0.06), and FT4 levels (1.2 ± 0.1 vs 1.0 ± 0.07 ng/dL; p = 0.06) between women with AITD and vit D deficiency (25(OH) vit D < 50 nmol/t) and women with AITD without vit D deficiency, respectively. In women with AITD Pearson coefficient analysis revealed no correlation between 25(OH) vit D and TG-Ab (r = 0.48; *P* = 0.16) TPo=Ab (r = 0.43; *P* = 0.21), TSH (r = 0.38; *P* = 0.27) FT3 (r = -0.40; *P* = 0.25) and FT4 levels (r = -0.54; *P* = 0.10).



4. Discussion

Our study found that women with PCOS and AITD have significantly lower 25(OH) vit D concentrations compared to women with PCOS without AITD. So, both AITD and low 25(OH) vit D concentration has been associated with PCOS [11].

In our study, the incidence of AITD in women with PCOS was 24% and this was in agreement with a study performed by Jannsen *et al.*[12] that reported a prevalence of around 25% of AITD in women with PCOS. Although, the pathogenesis of the association of PCOS with AITD is not clear, one of the possible hypotheses could be the defective progesterone secretion with leads to imbalance between estrogen and progesterone. Estrogen could increase the expression of interleukin-6 in I cells and lack of inhibitory action of progesterone may cause an overestimation of the immune system, thus, leading to an increased prevalence of autoimmune disorders in these patients [13]. However, the development of autoimmune disease could be determined by several risk factors. Recently, vit D deficiency has been identified as an environmental trigger of AITD [13].

Lower 25(OH) vit D levels have been found in patients with AITD compared to healthy subjects by Obrach *et al.*[14]. This finding was subsequently confirmed by Tamer *et al.*[15], who demonstrated an increased prevalence of vit D deficiency [25(OH) vit D ≤ 10 ng/mL] in patients with AITD. Vit D deficiency has been reported to increase the risk to develop metabolic derangements in women with PCOS [11]. In our study, the prevalence of vit D deficiency in PCOS was (48%) and this was in agreement with a study performed by Li *et al.*[16] reporting a prevalence of (47%) in women with PCOS. The degree of vit D deficiency has been reported to have a tight relationship with antibody levels and with thyroid hormones. Thus, suggested that vit D levels may have a direct role in determining

the severity of autoimmune disease and of the consequent hypothyroidism [17].

In conclusion, our study shows that low 25(OH) vit D levels were associated with AITD in PCOS. Further, study after study has reported that adequate vit D levels are substantially associated with a lower risk of developing AITD. So, supplementation with vit D could represent a promising therapeutic approach to prevent or improve the development of AITD. This is of crucial importance in PCOS; as well known, PCOS is characterized by metabolic derangements and AITD may contribute to further worsen metabolic dysfunction in these women. Thus, future longitudinal cohort studies along with prospective interventional trials may contribute to better clarify the role of vit D in the pathogenesis of AITD in women with PCOS.

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