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Evaluation of the Anti-Inflammatory Impact of Vitamin D on Polycystic Ovary Syndrome and Endometriosis

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ABSTRACT

Objective: Although numerous studies demonstrate the link between vitamin D and its anti-inflammatory effects, the correlations could not be fully explained. Platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) are investigated as biomarkers for diagnosis and follow-up in various obstetrics and gynecological studies. We aimed to evaluate the correlation between the anti-inflammatory effect of vitamin D and inflammatory parameters NLR and PLR in women with polycystic ovary syndrome (PCOS) and endometriosis.

Materials and Methods: Serum 25-hydroxy vitamin D (25(OH)D) levels, complete blood count (CBC) parameters, NLR, PLR, Vitamin B_{12}, and thyroid stimulating hormone (TSH) levels of 140 patients who applied to the Department of Obstetrics and Gynecology between 2010-2019 were evaluated. In our study, the levels of 25(OH)D, TSH, vitamin B_{12} and CBC measurements were analyzed simultaneously. SPSS 22.0 Windows version software was utilized in the data analysis, and $p<0.05$ was accepted as statistical significance level.

Results: There were significant differences in NLR (p=0.026) and lymphocytes count between PCOS and endometriosis groups (p=0.010). When we examined PCOS and endometriosis patients as a patient group; according to 25(OH)D vitamin levels, we found that NLR was significantly higher in the group with 25(OH)D vitamin levels below 20 ng/ml (p=0.017), vit B_{12} levels were significantly lower (p=0.034). Bivariate correlation analysis showed that vitamin D was negatively correlated with NLR (r=-0.196, p=0.050) in the patients with PCOS but not with endometriosis.

Conclusion: This retrospective study assessed the association between vitamin D levels and the new inflammation biomarkers in patients with PCOS and endometriosis. The CBC and neutrophil/lymphocyte ratios are accessible and easily measurable biomarkers, therefore, evaluating the anti-inflammatory effect of vitamin D together with NLR is valuable for both PCOS and endometriosis.

Keywords: Vitamin D insufficiency, inflammation, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, PCOS, endometriosis

INTRODUCTION

Vitamin D has a crucial role in maintaining the calcium and mineralization balance of the skeletal system and has anti-inflammatory and antimicrobial properties in reducing the production of T helper 1 (Th1) cells and in the formation of inflammatory interleukins (1, 2).

It has a strong anti-inflammatory impact on account of directly restricting the production of interleukin-2 and gamma interferon (IFN-y). Even though it is accepted that vitamin D is potent for the immune system, especially through the T-helper pathway, the principal mechanisms have not been explained until now. Considering the significance of inflammation, especially in the prognosis of the disease, vitamin D deficiency is thought to be responsible for this inflammation (3).

Vitamin D deficiency may affect disrupt placentation, decrease placental blood flow, and increase the inflammatory

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response (4). Vitamin D is also essential for the ovary and testis function in both females and males, respectively (5).

Polycystic ovary syndrome (PCOS) is one of the endocrine disorders characterized by chronic ovulation and androgen elevation widespread at approximately 5-10% of the women's period of reproductive age. Many studies have highlighted that chronic inflammation in the uterus with PCOS may lead to pregnancy complications (6). Studies have shown elevated inflammatory ingredients such as ferritin, C-reactive protein, interleukin (IL)-6), IL-8, tumor necrosis factors (TNFs) (7) and leukocyte levels in women with PCOS (8).

Studies have suggested that androgen elevation in women with PCOS may be responsible for the increase in leukocyte count and the development of inflammation (9).

Endometriosis is a multifactorial estrogen-dependent chronic inflammatory disease that affects women of reproductive age, especially between the ages of 25 and 35, with a prevalence of 5-10% (10). The immune system as well as the genetic and environmental factors have an effective role in the etiology of endometriosis (11). The study indicated that endometriosis elevated inflammatory cytokines, neutrophils, macrophages, and TNFs in the peritoneal fluid (12).

Regarded as inflammation markers, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are also the potential biomarkers for follow-up in the gynecology and perinatology disorders as in the other chronic diseases and cancer (13,14). Increased leukocyte counts have been found to be a marker and prognostic factor in the development of inflammation and atherosclerosis (15).

Easily measurable and easily accessible biomarkers that can reflect the severity of systemic inflammation in obstetrics and gynecology patients in whom inflammation is important in the etiology will greatly relieve the clinician and the patient. Therefore, whole blood cell counts can reflect the immune system response and the inflammation in endometriosis and PCOS.

The aim of our study was to evaluate the correlation between the anti-inflammatory effect of vitamin D and the inflammatory parameters NLR and PLR in women with PCOS and endometriosis.

MATERIALS AND METHODS

Research Plan, Data Collection, and Methods

Our study retrospectively analyzed 140 females, 39 diagnosed with endometriosis and 101 diagnosed with PCOS between 2010 and 2019 applied to the Department of Obstetrics and Gynecology. Gaziantep University Faculty of Medicine Ethics Committee approved our research with the order dated 23.09.2020 (reference numbered 2020/290).

Outcomes of simultaneous achieved measurements of 25(OH) D levels, thyroid-stimulating hormone (TSH) levels, vitamin B_{12} levels, and complete blood count (CBC) were recorded.

CBC was measured by fluorescent flow cytometry method on a Sysmex XN-9000 fully automatic blood count device (Sysmex XN-9000 automated analyzers, Kobe, Japan).

Serum vitamin B_{12} levels, 25(OH)D levels and TSH levels of patients were measured by chemiluminescence assay Beckman Coulter Access Unicel DXI 800 (UniCelDXi 800 immunochemical assay, Beckman Coulter, Fullerton, CA, USA) tool.

Serum vitamin D levels were measured with the most sensitive and specific method as chemiluminescence immunological 25(OH)D test (Beckman Coulter Access Total 25(OH)D).

25(OH)D level below the 20 ng/mL is defined as vitamin D deficiency and 25(OH)D level upper 20 ng/mL is defined as vitamin D sufficient (16).

Statistical Analyses

The data was analyzed using the SPSS 22.0 Windows version software system. The Shapiro Wilk test was used to determine whether numerical variables were suitable for standard dispersion. The student's t-test was used to compare the normal distribution parameters of the two groups. The Mann-Whitney U test was used to compare the not normally distributed parameters between the two groups. The Spearman rank correlation coefficient was used to examine the association between improperly distributed numerical parameters. $p<0.05$ was considered significant.

RESULTS

The main characteristics and laboratory data of the endometriosis and PCOS disease groups are given in Table I. There was a significant difference in age between the PCOS and the endometriosis groups (p=0.001). After the results in the patient group were adjusted according to age, the results were not changed. NLR and lymphocyte count had a significant difference between the PCOS and the endometriosis group (p=0.026 and p=0.010; respectively) (Table 1).

When patients were classified into two groups based on 25(OH)D levels (25(OH)D < 20 ng/mL group; 25(OH)D > 20 ng/mL group), there were significant differences in NLR and in vitamin B_{12} (respectively; p=0.017 and p=0.034). NLR was higher in the insufficient vitamin D group than in the sufficient vitamin D group (p=0.017). Vitamin B_{12} levels were correlated with sufficient 25(OH)D levels (p=0.034; Table 2).

Bivariate correlation analysis showed that vitamin D was negatively correlated with the NLR (r=-0.196, p=0.050) in the patients with PCOS but not with endometriosis. The anti-inflammatory impact of 25(OH)D levels on NLR was a weak negative relation in the PCOS patient group but not in the endometriosis group (Table 3).

Table 1. The characteristics of demographic and laboratory in women with PCOS and endometriosis.

	Endometriosis	PCOS	p-value
Age (year)	31 [24-39]	23 [19-27]	0.001
Platelet (K/µL)	273 [248-356]	308 [270-355]	0.115
Neutrophil (/mm^3)	4.33 [3.52-5.23]	4.3 [3.36-5.27]	0.480
Lymphocytes (/mm^3)	2.19 [1.81-2.67]	2.63 [2.16-3.12]	0.010
PLR	128.96 [93.2-169.68]	117.13 [99.2-143.64]	0.269
NLR	1.87 [1.51-2.54]	1.52 [1.28-2.18]	0.026
25(OH)D level (ng/mL)	15.11 [10-25.31]	16.88 [11.63-23.9]	0.532
Vitamin B_{12} level (ng/mL)	219.5 [174.5-265.5]	215 [158-307]	0.722
TSH level (µIU/mL)	1.79 [1.31-2.36]	1.86 [1.4-2.64]	0.464

All values presented as median (25%-75%)

Table 2. The comparison of data based on vitamin D levels in the group consisting of PCOS and endometriosis.

	25(OH)D<20(ng/mL)	25(OH)D>20(ng/mL)	p-value
Age (year)	24 [21-30]	24 [21-33]	0.941
Platelet (K/µL)	292.5 [262-359]	312 [252-350]	0.879
Neutrophil (/mm^3)	4.41 [3.36-5.3]	4.06 [3.4-5.16]	0.453
Lymphocytes (/mm^3)	2.47 [1.82-2.97]	2.64 [2.16-3.01]	0.153
PLR	126.31 [98.95-160.67]	118.18 [90.35-135.9]	0.104
NLR	1.78 [1.41-2.34]	1.45 [1.27-1.87]	0.017*
Vit B_{12}(ng/mL)	212.5 [157.5-257]	277 [177-348]	0.034*
TSH (µIU/mL)	1.89 [1.38-2.58]	1.73 [1.28-2.65]	0.912

All values presented as median (25%-75%); statistical significance is shown with *: p<0.05

Table 3. Correlation analysis between 25(OH)D levels and complete blood count parameters in women with PCOS and endometriosis.

			Platelet (K/µL)	Neutrophil (/mm^3)	Lymphocytes (/mm^3)	PLR	NLR
Endometriosis	25(OH)D (ng/mL)	r	-0.124	-0.239	0.050	-0.088	-0.196
		p	0.464	0.153	0.767	0.596	0.232
		n	37	37	37	39	39
PCOS	25(OH)D (ng/mL)	r	0.018	0.021	0.167	-0.154	-0.196
		p	0.865	0.846	0.113	0.124	0.050*
		n	91	91	91	101	101

*: p<0.05

DISCUSSION

This retrospective study assessed the association between vitamin D levels and the new inflammation biomarkers NLR and PLR in women with PCOS and endometriosis.

We obtained three significant findings as the results of our study. Firstly, NLR, the inflammatory parameter of CBC, has importantly higher in the patient group with insufficient 25(OH) D levels. Secondly, the anti-inflammatory action of 25(OH) D levels on NLR has a weak negative correlation in the PCOS group. Finally, the observed correlation between vitamin B_{12} and vitamin D represents that vitamin B_{12} levels should also be controlled in the insufficient 25(OH)D levels.

Vitamin D insufficiency is still a widespread and important global health problem (17). Vitamin D insufficiency has been originated to be related to severe pregnancy results such as repeated pregnancy losses and the possibility of preeclampsia (18). T cells, B cells, and antigen-presenting cells provide vitamin D synthesis via signaling (19), suggesting that vitamin D deficiency may be responsible for the inactive immune system.

Although numerous studies demonstrated the relationship between vitamin D and its anti-inflammatory effects, their correlations could not be completely explained (20).

$1,25(OH)_2D_3$'s *in vivo* suppression mechanism of autoimmune diseases, namely its anti-inflammatory effect, involves inhibiting the development and function of Th1 cells and increasing IL-4 production from Th2 cells (21).

The ratio of neutrophil to lymphocyte is considered as an easy and rapidly measurable parameter of systemic inflammation in severe diseases (22).

In this study, we found vitamin D levels to be significantly lower in the PCOS and endometriosis patient groups. We observed that plasma 25(OH)D level and NLR, which are accepted as inflammatory markers, and lymphocyte count increased in PCOS and endometriosis patients. The low 25(OH)D levels may support a pro-inflammatory environment in PCOS and endometriosis (3).

Numerous studies suggest that increased inflammation in PCOS patients affects obesity and insulin resistance (23) and that there is an association between high androgen concentration and leukocytes (15).

Administration of a synthetic vitamin D derivative to experimental animals has been shown to result in the development of endometriosis and reduction of peritoneal inflammation, indicating the immunomodulatory effect of vitamin D (24). Harris et al. found an opposite correlation between plasma 25(OH) D levels and endometriosis (25). Also, we indicated a negative correlation between plasma 25(OH)D levels and PCOS, but no negative correlation could be demonstrated between endometriosis and vitamin D.

A study in 2018 examining the relationship between vitamin levels and low-grade inflammation in overweight and obese individuals reported that serum vitamin D and vitamin B_{12} increased together, while serum C-Reactive Protein (CRP), the parameter indicating inflammation, decreased (26). A negative correlation was detected between both vitamin B_{12} and vitamin D levels and autoimmune disease (27).

We observed a direct proportional association between vitamin B_{12} levels and 25(OH)D levels because vitamin B_{12} levels were also insufficient in the group with inadequate vitamin D.

As the limitations of our study, since it is a retrospective study, data such as season, obesity, and BMI that may affect vitamin D levels could not be evaluated. Also, we consider that the correlation of vitamin D with inflammation through the immune system should have been explored at the cellular and molecular levels.

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