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The Supplemental Effect of Vitamin-D3 and Omega-3 on Induced Endometriosis in Rat Model to Investigate the Inflammatory Response

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ABSTRACT

Background & Objective: The endometriosis treatment was critical due to complications associated with current drug delivery system. The present study was conducted with aim to compare the curative effect of Vitamin D3 (VTD3) and Omega–3 (OG3) with Diphereline during the treatment of endometriosis.

Materials & Methods: In this study, endometriosis was induced in different groups containing 60 adult female rats. The rat model was categorized into 6 groups untreated and treated (Olive Oil (solvent), VTD3 (42 mcg/kg/day), OG3 (450 mg/kg/day), VTD3+OG3, Diphereline (3 mg/kg/day)). The suspension containing combination of Diphereline and supplements was injected and treated for 4 weeks to analyze the effect of supplements. The interleukin -6 (IL-6) and Tumor necrosis factor – alpha (TNFα) inflammatory responses were measured from the serum samples while endometrial implants was dissected and histopathological investigation was done.

Results: At the end of four weeks, pathologic score decreased significantly with simultaneous measurement of inflammation score of endometriotic lesion, size of implant area, IL-6, TNFα response and compared with untreated female rat. No significant different was observed in groups undergoing treatment of VTD3, OG3 and Diphereline. The combined effect of VTD3+OG3 has similar responses with Diphereline treated endometrial implants.

Conclusion: treatment of VTD3 deficiency and making a change in dietary habits of high-risk population for endometriosis from adolescence may also play a preventative role in adulthood.

Keywords: Vitamin-D3, Omega-3, Diphereline, Endometriosis, Rat Model, Cytokine

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Introduction

Endometriosis is one of the most common chronic diseases in women. It occurs when the endometrial glands and stroma present in ectopic locations including ovaries, fallopian tubes, cul-de-sacs, and pelvic cavity **(1, 2)**. The signs and symptoms of the disease are dysmenorrhea, dyspareunia, chronic pelvic pain, irregular uterine bleeding, and/or infertility **(3, 4)**. Endometriosis is a chronic multifactorial estrogen-dependent gynecological disease affecting about 15% of all women of reproductive age and has been found in 30-50% of infertile women **(3, 5)**. Immune cells in the peritoneal fluid of a patient with endometriosis secrete cytokines as well as some growth and angiogenic factors that stimulate implantation and proliferation of misplaced endometrium which has local angiogenesis and inflammation. Different types of cytokines -TNFα, VEGF, IL1, IL6, and IL10- are enhanced in the peritoneal fluid of a patient with endometriosis **(6)**. In the histopathological evaluation, inflammation (as a common feature) **(7)**, reduced apoptosis, and increased angiogenesis have been detected in favor of survival and development of endometriotic tissue **(1)**. The etiology of endometriosis is ambiguous; however, diet may play an important

role in the improvement of endometriosis. It acts via affecting the immune response, smooth muscle contractility, and estrogenic properties **(8)**. Common medical treatments of this disease such as gonadotropin-releasing hormone analog (GnRHa), have severe secondary adverse effects like preventing pregnancy that cannot be administered over an extended period **(9)**. Diphereline belongs to GnRHa medications which is commonly used in the treatment of endometriosis **(10)**. Some researchers reported that Diphereline has some side effects on the function of the liver and kidneys that may lead to osteoporosis **(11)**.

Endometriosis is a chronic disease which needs long-term treatment **(12, 13)**, therefore, development of new alternative effective medications with limited side effects is necessary for treatment of endometriosis. Some previous studies have reported that serum vitamin D3 levels were lower in severe endometriosis than normal controls or patients with mild endometriosis **(14)**. Vitamin-D3 may change the ratios of T-helper cells leading to the alteration of cell-mediated immunity in women suffering from endometriosis **(5)**. Vitamin-D3 strongly modulates the immune response by affecting the proliferation and differentiation of normal and malignant cells **(15)**. A comparative study indicated that the expression of 1α-hydroxylase increases in the endometrium of patients with endometriosis compared to the healthy controls **(16)**. Vitamin-D3 increases anti-inflammatory cytokines **(17-20)** and cell apoptosis; on the other hand, it suppresses the angiogenesis in vitro and in vivo environments **(21-24)**. Omega-3 (another possible treatment of endometriosis) is a polyunsaturated fatty acid which has Vitamin-D3-like properties, including antiangiogenic, anti-inflammatory, anti-apoptotic, and anti-proliferative effects **(25, 26)**. Endogenous production of Omega-3 may protect against the development of endometriosis **(27)**. Furthermore, it is suggested that omega-3 has beneficial therapeutic potentials for the endometrial hyperplasia **(28)**.

The hypothesis of the present study was that Vitamin-D3, Omega-3, and their combination might be possible candidates for endometriosis treatment because they are placed among the most frequently cited nutrients in terms of the immunomodulatory, anti-angiogenic, and anti-proliferative effects. This study was conducted with aim to compare the efficacy of Vitamin-D3 and Omega-3 with Diphereline as an effective treatment of induced endometriosis in rat models based on clinical and histopathologic findings.

Methods

The protocol of the study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.032). Female rats were provided from the animal holding space of Shiraz University of Medical Sciences, Iran. Formalin, Omega-3, diethyl ether, hematoxylin, and eosin dyes were all purchased from Merck Company, Germany. TNF-α and IL-6 enzyme-linked immunosorbent assay (ELISA) kits were supplied from Hangzhou Eastbiopharm, China. Diphereline and Vitamin-D3 were purchased from Ipsen Pharma Biotech, France and OSVE from Pharmaceutical Co., Iran. In this experiment, 60 female Sprague Dawley rats were included. The animals were kept in special cages with a steel mesh roof and the floor was covered with sawdust and wood chips under a temperature-controlled environment (22±2°C and humidity 55±3 %) with 12 hours light/dark cycles. The animals were handled according to the standard international guidelines for the care and use of laboratory animals.

Endometriosis was induced according to the approach previously presented by Vernon and Wilson **(29, 30)**. Rats were anesthetized through intraperitoneal injection of ketamine hydrochloride (80 mg/kg, Alfasan, Netherlands) and xylazine 2% (5 mg/kg, Al-fasan, Netherlands). Their abdominal surfaces were shaved and disinfected to be prepared for the laparotomy. Their abdomen was also opened by a 4 cm incision. A biopsy was taken from one of the uterine horns of each rat, immersed into warm sterile normal saline, and then longitudinally incised into four equal 5×5 mm pieces. The dissected tissues (implants) were ligated onto the anterior abdominal surface using polyglactin suture. Finally, the abdomen incision was closed using a 4-0 suture. Four weeks after the first surgery, a second look laparotomy was carried out and the endometrial implants' viability was proved by observing good vascular supply and pinkish colored tissue in contrast to seen necrosis and fibrosis.

A total of 60 female rats were divided into 6 groups (10 rats in each group). The control group (endometriosis group without treatment) received 0.5 ml of saline 0.9%/day, the second group received pure olive oil (42 µg/kg/day) as the solvent of Vitamin-D3, the third group took Vitamin-D3 (42 µg/kg/day), the fourth group received Omega-3 (450 mg/kg/day), the fifth group received Vitamin-D3 (42 µg/kg/day) + Omega-3 (450 mg/kg/day) for the next 4 weeks. All the treatments of these groups were administered by oral gavage. The sixth group received a single IM injection of diphereline S.R. 11.25 mg (3 mg/kg, Ipsen, France). Four weeks after the treatments, the rats were sacrificed and endometrial implants were evaluated (Figure 1).

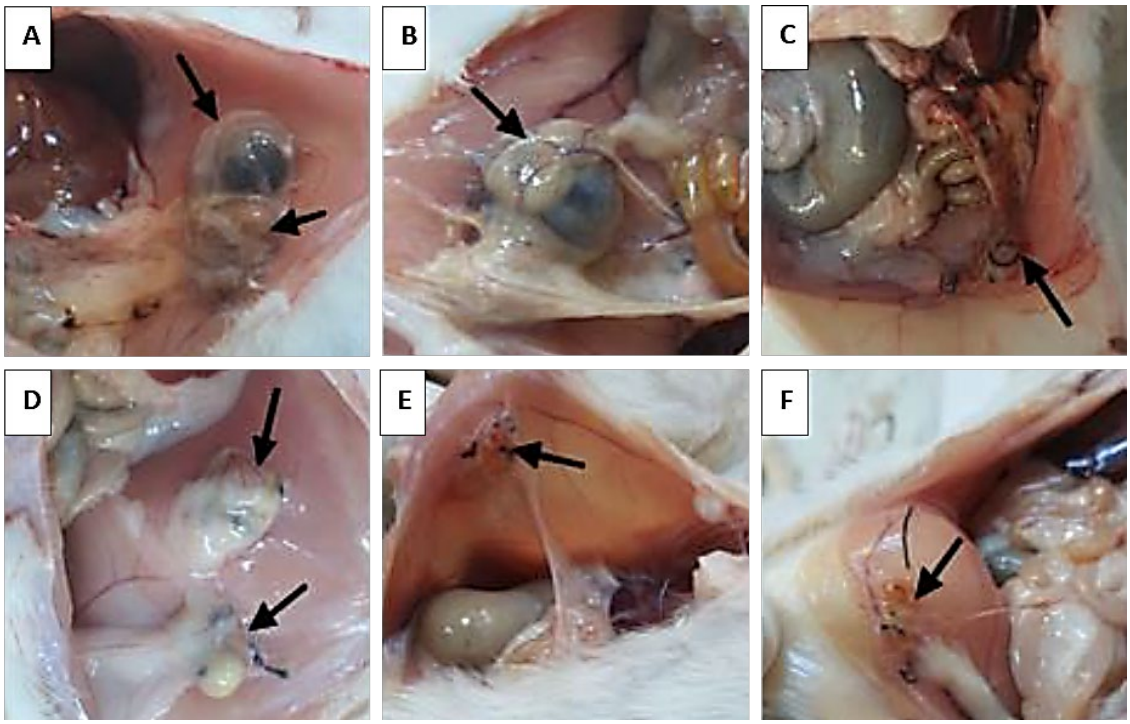


Figure 1. Endometrial implants in various groups **A)** Endometriosis group (large size). **B)** olive oil receiving group (large size and the surrounding blood vessels). **C)** Vit D receiving group (small size). **D)** Omega 3 receiving group. **E)** Vit D+Omega 3 receiving group (small size as well as its lack of growth). **F)** diphereline receiving group (small size as well as its lack of growth).

Blood samples were obtained from the rats and the sera were separated by centrifugation (3500 rpm/10 min). The levels of IL-6 and TNF-α were quantified by ELISA, based on the manufacturer's instruction. The researcher who performed the test was not aware of the intervention done on the rats.

Prepared animals were placed in a jar and anesthetized by ether and then sacrificed based on ethical scarifying guidelines. The endometrial implants were dissected from the rats, washed with physiological serum, and put into 10% formalin to be prepared for the tissue blocks. Using a tissue processor, the samples were dehydrated, embedded in paraffin, and cut into 5-µm sections. The sections were stained with hematoxylin and eosin and evaluated using a light microscope by a single experienced pathologist. The samples rendered to the mentioned pathologist (who evaluated the main histopathological findings) were blinded and the pathologist was not aware of the intervention done on rats.

Data were analyzed using SPSS software (version 25) and parametric one-way ANOVA followed by Tukey HSD (honestly significant difference) test for assessing the IL-6 and TNF-α concentration as well as implants' size. Non-parametric Mann-Whitney test was used for measuring pathologic and inflammation scores. Data are presented as Mean ± SD (standard deviation). $P<0.05$ was considered statistically significant.

Results

The level of IL-6 and TNF-α in the endometriosis and different treated groups are shown in Table 1. The level of serum IL-6 after 4 weeks of treatment was significantly decreased in the Vitamin-D3, Vitamin-D3 + Omega-3 and diphereline receiving groups compared to the endometriosis group ($p<0.05$). All treated groups were compared with the diphereline group as a proven treatment for endometriosis. Interestingly, the findings indicated that the level of this cytokine was significantly diminished in the Vitamin-D3 + Omega3 receiving group compared to the diphereline group ($p=0.04$).

The level of TNF-α was decreased in all treated groups ($p\leq0.01$), except for olive oil treatment. Moreover, the Vitamin-D3, Omega-3 and, Vitamin-D3 + Omega-3 were demonstrated no significant differences in comparison with diphereline group.

Table 1. The level of serum IL-6 and TNF-α

	IL6 (pg/ml)			TNF-α (pg/ml)		
Groups	Mean ± SD	P val 1	P val 2	Mean ± SD	P val 1	P val 2
Endometriosis	254.80 ± 30.10	------	------	430.23 ± 87.21	------	------
Olive oil	244.85 ± 29.17	0.55	0.003	417.01 ± 76.23	0.77	< 0.001
Vitamin D3	180.40 ± 27.59	0.001	0.89	246.42 ± 23.75	0.003	0.187
Omega3	201.04 ± 38.07	0.02	0.39	275.04 ± 70.61	0.01	0.98
VitaminD3 + Omega3	138.28 ± 37.12	< 0.001	0.04	229.08 ± 35.45	< 0.001	0.71
Diphereline	182.57 ± 37.31	0.002	-------	221.01 ± 43.41	< 0.001	-----

P val 1: P-value based on comparison between Endometriosis and other groups; P val 2: P-value based on comparison between Diphereline and other groups

The surface area of the endometriotic implants, pathologic and inflammation scoring of the endometrial implants are shown in Table 2.

Table 2. Size and pathologic features of the endometrial implants

	Endometrial implants' size			Pathologic score			Inflammation score		
Groups	Mean ± SD	P val 1	P val 2	Mean ± SD	P val 1	P val 2	Mean ± SD	P val 1	P val 2
Endometriosis	48.33 ± 5.39	------	----	2.83 ± 0.40	------	----	2.83 ± 0.40	------	-----
Olive oil	50.42 ± 6.90	0.56	< 0.001	2.57 ± 0.53	0.33	< 0.001	2.57 ± 0.53	0.34	< 0.001
Vitamin D3	19.71 ± 5.82	< 0.001	0.01	1.28 ± 0.75	0.001	0.11	1.14 ± 0.69	< 0.001	0.07
Omega3	30.00 ± 6.20	0.001	0.002	2.20 ± 0.83	0.13	0.003	2.00 ± 0.70	0.03	0.001
VitaminD3 + Omega3	15.66 ± 3.66	< 0.001	0.03	0.66 ± 0.51	< 0.001	0.99	1.00 ± 0.63	0.001	0.16
Diphereline	12.11 ± 2.02	< 0.001	------	0.66 ± 0.70	< 0.001	------	0.55 ± 0.52	< 0.001	-----

The size of the implants was significantly decreased after the treatment even though diphereline was more effective than other ones and there are significant differences between the current treatments and diphereline (Figure 1) with notice to the endometrial size). Specimens of the treated groups stained by hematoxylin-eosin (scale bar: 40 μm) are demonstrated in Figure 2.

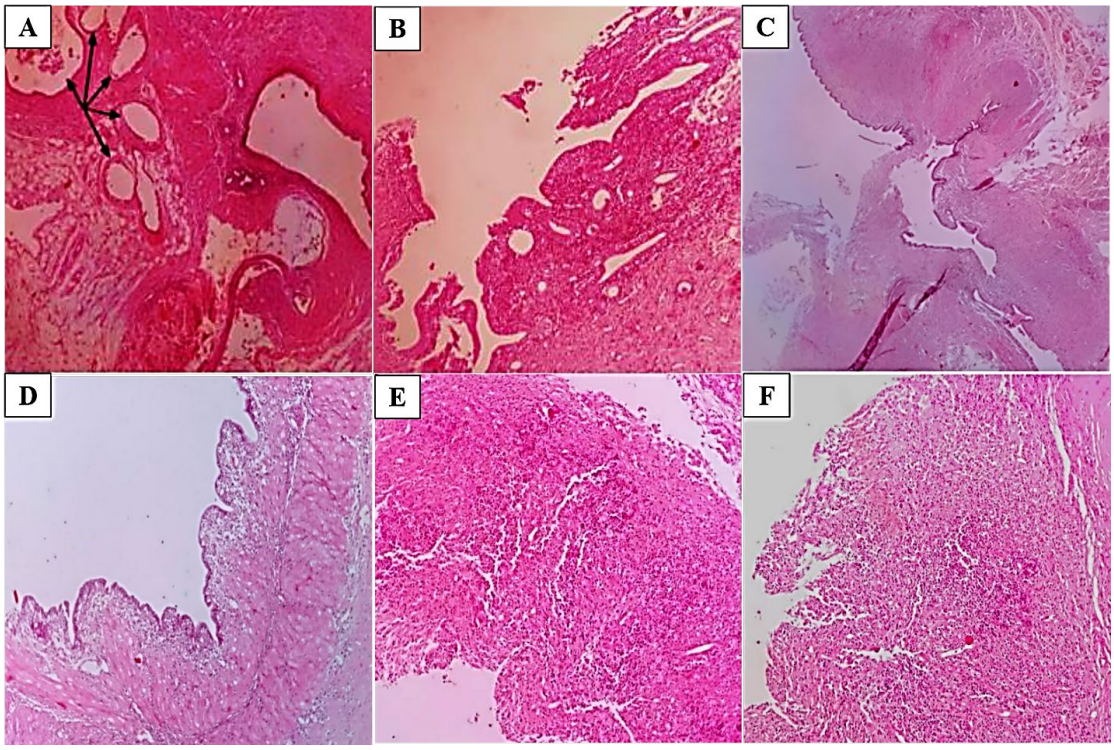


Figure 2. Specimens of the treated groups stained by hematoxylin-eosin (scale bar: 40 µm). A) Endometriosis group, B) Olive oil group. In A and B, severe cystic endometriosis (the arrow) along with the necrosis and the presence of apoptotic cells as well as severe inflammation and the presence of hemosiderin-laden macrophages in different regions was observed. C) Vitamin D group, in this group, the severity of inflammation, as well as the necrosis, was reduced. Cystic endometriosis was also slightly decreased compared to the olive oil receiving group. D) Omega 3 group, in this group, cystic endometriosis, necrosis and inflammation were reduced compared to the endometriosis group. However, hemosiderin-laden macrophages were observed in some regions. E) Vitamin D + Omega 3 group, in this group, cystic endometriosis was sharply reduced; the severity of inflammation and necrosis, as well as the presence of apoptotic cells and hemosiderin-laden macrophages, was decreased in different regions. A significant decrease was also observed in the epithelial layer. F) Diphereline group, like the Vitamin D + Omega 3 group, the severity of cystic endometriosis was reduced in this group. Moreover, a significant decrease was observed in the epithelial layer coverage, inflammation, necrosis, apoptotic cells and hemosiderin-laden macrophages in various regions.

Pathologic score indicated a significant reduction in vitamin D3, vitamin D3 + omega3 and diphereline. Interestingly, the pathologic score in vitaminD3 and vitamin D3 + omega3 groups is close to diphereline group with no significant difference. The inflammation score of the treated group was statistically significant differences compared to the endometriosis group. The vitaminD3 and vitamin D3 + omega3 groups were not significantly different compared to the dophereline group.

Discussion

Endometriosis is a common estrogen-dependent disease and is polygenic and multifactorial **(31, 32)**. Although estrogen lowering drugs lead to the decrease of endometriosis symptoms, they have revealed to possess some side effects. New treatments of endometriosis include anti-inflammatory drugs, anti-angiogenesis agents and statins **(33)**, which lead to the reduction of the growth rate of endometriosis by influencing angiogenesis, inflammation, and activity of metalloproteinase **(34)**. This investigation aimed to evaluate the role of Vitamin-D3 and Omega-3 as anti-inflammatory and anti-angiogenetic drugs in the improvement of endometriosis. As the results of the present study showed, the administration of Vitamin-D3 decreased the development of endometriosis which might be attributed to the reduction of inflammation, angiogenesis, and prevention of extra-cellular matrix destruction **(34)**. Previous studies demonstrated that dysfunction of the immune response such as poor activation of T lymphocytes and natural killer cells, decrease of cytokine secretion by T helper lymphocyte and decrease of antibody secretion by B lymphocyte are associated with endometriosis **(35, 36)**.

In the present study, TNF α and IL-6 concentrations significantly decreased in the Vitamin-D3, Vitamin-D3 + Omega-3 and diphereline receiving groups compared to the endometriosis group without treatment. Vitamin-D3 is a strong immune modulator influencing the division and proliferation of normal and malignant cells **(12)**. The Vitamin-D3 receptor and its metabolizing enzymes were found in the endometrium and may act through autocrine and paracrine manner in the immunologic environment **(3)**. The results of the present study indicated that the pathologic scores

significantly decreased in the Vitamin-D3 + Omega-3 and diphereline groups than in the Omega-3 group. Furthermore, a significant decrease was observed in the inflammation score of the diphereline group compared to the Omega-3 group. Previous studies reported the anti-inflammatory, anti-angiogenesis, anti-proliferative, and anti-apoptotic roles of Omega-3 (25, 26). Ruggiero et al. showed that Omega-3 decreased the production of pro-inflammatory cytokines -TNFα, IL-1, IL-6- and prevented the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (nuclear factor-κβ).

It is hypothesized that Omega-3 can have a role in the treatment of autoimmunity dysfunctions and malignancies **(36)**. Since endometriosis share some similarities with systemic inflammation and malignancies in terms of immune impairment, cytokine generation, and angiogenesis, this agent can be useful for the treatment of endometriosis **(12)**. Similar to the results of the present study, Tomio, et al. **(26)** found that endogen Omega-3 and exogen eicosapentaenoic acid have a protective role against peritoneal endometriosis **(26)**. Akyol, et al. **(10)** showed that Vitamin-D3 and Omega-3 improved the endometriosis by decreasing the endometrial histopathology implants volume and parameters as well as decreasing the IL6, TNFα, and VEGF. These results are in agreement with the findings of the current research. Contrary to the results, the decrease in the implant volume was not significant in the Akyol, et al. **(10)** study. It was probably due to the treatment duration which was lower than that in the present study **(10)**. In the present research, the pathologic scores, the inflammation score and implant area increased in the endometriosis without treatment and in the endometriosis + olive oil groups compared to the Vitamin-D3, Vitamin-D3 + Omega-3 and diphereline receiving groups. Similarly, Abbas, et al. **(9)** reported that peritoneal administration of Vitamin-D3 led to the decrease of the implant area in rats with endometriosis **(9)**. Gonadotropin-releasing hormone agonists such as diphereline cause inactivation and degeneration of the endometrial implant through suppression of the hypothalamic-pituitary-gonad axis **(37)**. Similar to the findings of the present study, Namavar Jahromi, et al. **(28)** demonstrated that diphereline decreased the volume and area of the endometrial implant and significantly decreased the inflammation and pathologic parameters compared to the control **(28)**.

Conclusion

As shown by the findings of the current research, the co-administration of Omega-3 and Vitamin-D3 was more effective than used alone. This combination acts in a manner similar to diphereline. On the other hand, administration of Vitamin-D3 had more favorable results than the Omega-3 treatment for the improvement of endometriosis. According to the public health perspective, more detailed and long-term experimental studies are required to be conducted to clarify the association between Vitamin-D3 and Omega-3 with the improvement of endometriosis. This will also give more understanding about the valuable properties of these nutritional agents by identifying the alternative treatments for endometriosis.

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Authors' Contribution

Z.S.: Conceptualization, idea, design and writing. F.N., M.A., E.A., T.P., N.T., S.R., G.S., N.M., D.P., S.S., C.C.: investigation and editing.

Conflict of Interest

The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval

This study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.032).

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