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REVIEW ARTICLE

Association between vitamin D and endometriosis: a systematic review

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Abstract

Background Endometriosis is one of the most common gynecological diseases of reproductive age, with a prevalence of 5–10% and grave consequences for quality of life and fertility. Vitamin D (vit D), a classic regulator of plasma calcium concentration and skeleton mineralization, is also an effective modulator of the immune system. Several studies suggest that immunologic properties attributed to vit D along with vit D receptor (VDR) expression in reproductive tissues may be involved in the pathogenesis of endometriosis.

Objective To systematically review the literature for the association between components of vit D metabolism and endometriosis.

Materials and methods A systematic review of the literature published in the Medline and Cochrane Central databases was conducted for original research articles on humans, published in any language.

Results Twenty-one studies were included in the systematic review. Among them, 12 examined the relationship of endometriosis with vit D metabolites, eight with vit D–binding protein (VDBP), three with VDR polymorphisms, and two with vit D regulatory enzymes. There are discrepancies between the outcomes of the available literature publications.

Conclusions This is a systematic attempt to collect, evaluate, and present the known data on the association between vit D and endometriosis. Given the heterogeneity and the diversity of the present studies, more research is required to elucidate the association between vit D and endometriosis.

Keywords Vitamin D · Vitamin D–binding protein · Vitamin D receptor · 1α-hydroxylase · 25α-hydroxylase · 1,25$(OH)_2$D · 25(OH)D · 25$(OH)D_3$ endometriosis

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Introduction

Endometriosis is an estrogen-dependent chronic inflammatory condition, which mainly affects women of reproductive age. Its prevalence is 5–10%, while most affected women are between 25 and 35 years of age [1]. Typical symptoms include dysmenorrhea, dyspareunia, irregular uterine bleeding, chronic pelvic pain, and infertility [2, 3]. The etiology of endometriosis, which is considered to be multifactorial, has not as yet been completely elucidated; nevertheless, genetics, environmental factors, and immunity have been reported to be implicated in its pathogenesis [4]. Chronic inflammation also seems to play an important role in the pathogenesis of endometriosis. Many studies have reported increased inflammatory cytokines, neutrophils, macrophages, and tumor necrosis factor-a in peritoneal fluid of patients with endometriosis. The variation in the mechanisms of inflammation between the major phenotypes of endometriosis (peritoneal endometriosis, ovarian endometrioma, and deep infiltrating endometriosis) could be both the cause of the pathophysiology and the reason for the discrepancies concerning pain and infertility between the major phenotypes [5].

Vitamin D (vit D), traditionally known as a regulator of plasma calcium concentration and skeleton mineralization, has also been shown to be an effective modulator of the immune system [6]. The vit D metabolic pathway is depicted in Fig. 1. Vit D suppresses lymphocyte proliferation and immunoglobulin synthesis and inhibits the action of proinflammatory transcription factors and the production of cytokines [7]. Most of the biologic activities of vit D are mediated by a high-affinity receptor that acts as a transcription factor. The coding gene of vit D receptor (VDR) is located on chromosome 12 [8]. Various cell types involved in immunologic reactions (monocytes, Langerhans cells, and T and B lymphocytes) express VDR [9]. These immunologic properties attributed to vit D, along with VDR expression in reproductive tissues, including the uterus, ovary, and placenta, have led to the hypothesis of a possible association between endometriosis and the vit D system [10, 11]. The aim of this systematic review was to critically appraise and qualitatively synthesize the results of individual studies that have examined the association between vit D and endometriosis.

Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12, 13].

Literature search and inclusion criteria

Two databases (Medline and Cochrane Central) were searched by two reviewers (DK and IL) independently for relevant articles published until September 21, 2019. The search

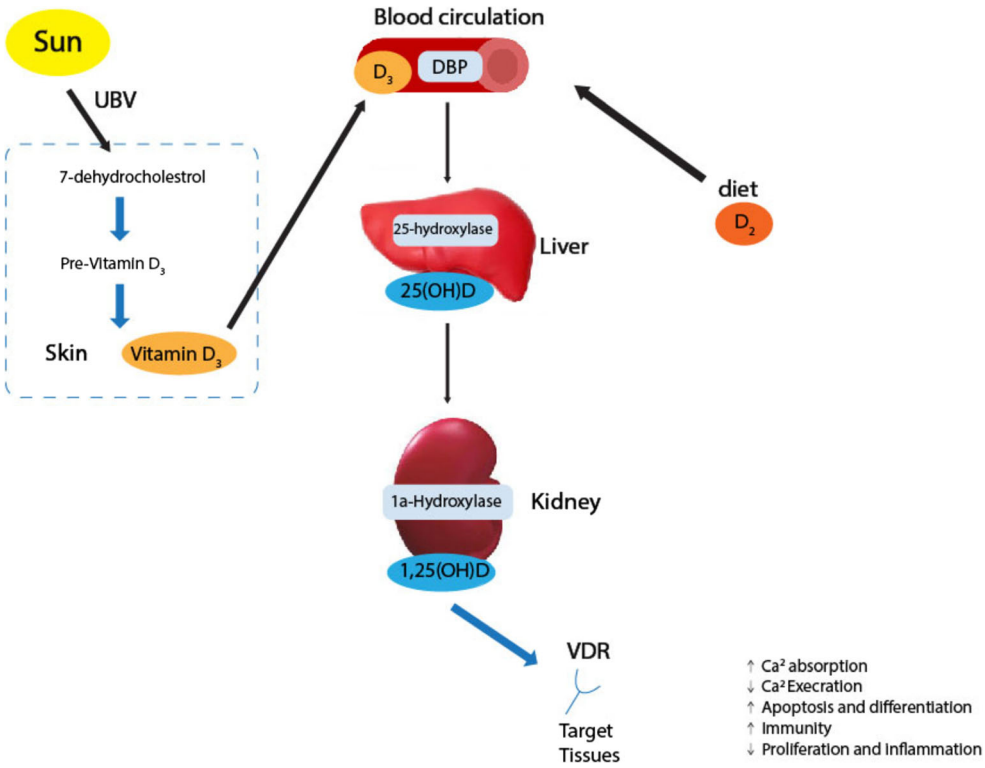

Fig. 1 Vitamin D metabolic pathway

algorithm for Medline contained the following keywords in all possible combinations: vitamin D; calcitriol; endometriosis; calcium; $25(OH)D_3$; 25(OH)D; 1,25(OH)D; $1,25(OH)_2D_3$; vitamin D binding protein; and vitamin D receptor. The references of all the included studies were also searched manually in order to locate additional publications potentially missed by the search strategy.

All of the following inclusion criteria had to be fulfilled in order for a paper to be considered eligible: (a) studies which compare the concentration of vit D metabolites, VDBR, VDR, and vit D key enzymes between endometriosis and control groups (studies with vit D supplementation were excluded); (b) articles published in any language; (c) original research articles (reviews, letters to the editor, systematic reviews, and meta-analyses were excluded); and (d) studies reporting evidence in humans (animal studies and in vitro studies were excluded). When there was a disagreement between the two reviewers (DK and IL) about the eligibility of a study, a third reviewer (FA) was involved in order to reach consensus.

Data extraction

Data were extracted independently by two reviewers (DK and FA). When there was disagreement between the two, a third reviewer (IL) was involved in order to reach consensus. A standardized extraction form was used on an Excel spreadsheet. The following data were extracted for each study: first author, country, study design, age, endometriosis classification, type of tissue used for the study (blood, endometrial tissue, etc.), vit D and metabolites concentrations, vit D–binding protein (VDBP), VDR and its polymorphisms, and 1α-, 24-, 25-hydroxylase concentrations.

Quality assessment

Risk of bias assessment of the included studies was performed by two investigators (DK and IL), and any discrepancies were resolved by consensus. The assessment of the risk of bias in the included studies was completed based on the QUIPS (Quality in Prognosis Studies) tool for predictive studies. Studies were assessed as low, moderate, or high risk of bias according to the following domains: study participation; study attrition; prognostic factor measurement; outcome measurement; study confounding; and statistical analysis and reporting (Table 1).

Results

Study selection

The literature search, after exclusion of duplicates, returned 240 studies. Non-human studies and reviews were excluded, leaving only 22 studies, all of which were reviewed as full texts. After exclusion of a randomized control trial examining supplementation of vit D in patients with endometriosis [14], 21 studies were included in the systematic review. A detailed flow diagram is presented in Fig. 2.

Study characteristics

Demographic characteristics and general information about the included studies are presented in Table 2. All included studies were "real-world" studies: 15 case controls, two retrospective cohort, two prospective cohort, and two cross-sectional studies. The included studies were published between 1990 and 2019. Of the above studies, 14 were conducted in Europe and seven outside Europe. Twelve studies presented data on the association between vit D metabolites and endometriosis, eight were on VDBP, three were on VDR gene polymorphisms, and two studied the association between vit D key enzymes and endometriosis. Two of the above studies, additionally to vit D metabolites, also examined VDBP [15, 16], while one examined vit D metabolites, VDR, and vit D key enzymes [17].

This systematic review included 2835 endometriosis patients and 71,049 controls. Individual study sample size ranged from 19 [18] to 70,556 participants [19]. Five studies did not report data on endometriosis stage classification [16, 17, 19–21]. Different tissues were used, including urine, plasma, eutopic and ectopic endometrial tissue, endometrioma tissue, and peritoneal fluid. The main findings of the included studies are reported in Table 2.

Vit D metabolites and endometriosis

Three studies report findings on the association between serum $1,25(OH)_2D_3$ concentrations and endometriosis [20, 22, 23]. One of them indicated higher serum $1,25(OH)_2D_3$ in the endometriosis group in comparison with the control group [20]. The above outcome could not be confirmed by the other two studies [22, 23]. Three studies also addressed the association between serum $25(OH)D_3$ and endometriosis. One of these indicated lower levels of $25(OH)D_3$ in the endometriosis group than in the control group [23], while another study found higher serum $25(OH)D_3$ concentrations in the endometriosis group [22]. The third study with single ovarian endometriomas reported that 85.7% of the women of this group had hypovitaminosis D [24]. As far as the association between total 25(OH)D and endometriosis is concerned, four studies revealed no significant difference [17, 20, 25, 26], while four other studies showed significantly lower levels in the endometriosis group [15, 16, 19, 21]. Last but not least, only Pagliardini et al. showed significantly higher levels of

Table 1 Risk of bias assessment (QUIPS Tool)

ID	Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis	Overall assessment
Vitamin D metabolites								
1.	Hartwell et al. 1990	L	L	L	L	L	L	L
2.	Agic et al. 2007	L	L	L	L	M	L	L
3.	Somigliana et al. 2007	L	L	L	L	M	L	L
4.	Harris et al. 2012	L	L	L	L	L	L	L
5.	Pagliardini et al. 2015	L	L	L	L	L	L	L
6.	Miyashita et al. 2016	L	L	M	L	L	L	L
7.	Dressler et al. 2016	L	L	L	L	L	L	L
8.	Ciavattini et al. 2017	L	L	L	L	L	L	L
9.	Anastasi et al. 2017	L	L	L	L	M	L	L
10.	Buggio et al. 2018	L	L	L	L	L	L	L
11.	Baek et al. 2019	L	L	L	L	M	L	L
12.	Cho et al. 2019	L	L	L	L	L	L	L
VDBR								
1.	Ferrero et al. 2005	L	L	L	L	M	L	L
2.	Borkowski et al. 2008	L	L	L	L	M	L	L
3.	Ferrero et al. 2009	M	L	L	L	M	L	M
4.	Faserl et al. 2011	L	L	L	L	M	L	L
5.	Cho et al. 2012	L	L	M	L	L	L	L
6.	Hwang et al. 2013	L	L	L	L	M	L	L
7.	Baek et al. 2018	L	L	L	L	M	L	L
8.	Cho et al. 2019	L	L	L	L	L	L	L
VDR								
1.	Agic et al. 2007	L	L	L	L	M	L	L
2.	Vilarino et al. 2011	L	L	L	L	L	L	L
3.	Szczepanska et al. 2015	L	L	L	L	M	L	L
Vitamin D key enzymes								
1.	Viganò et al. 2006	L	L	L	L	M	L	L
2.	Agic et al. 2007	L	L	L	L	M	L	L

L low risk, *M* moderate risk, *H* high risk, *VDBR* vitamin D–binding protein, *VDR* Vitamin D receptor

25(OH)D in the endometriosis group in comparison with the control group [27] (Table 3).

VDR and endometriosis

The only study that reported quantitative results on VDR mRNA and protein in both epithelial and stromal cells of the endometrium observed that in patients with endometriosis, the levels were higher than in the healthy controls [17]. Concerning VDR polymorphisms, two studies were found [28, 29]. Only one of the latter studies [29] supported the notion that the A-T BmsI/FokI VDR haplotype is a significant risk factor for endometriosis-associated infertility [odds ratio (OR) 1.659 95% confidence interval (CI) 1.122–2.453, $p = 0.011$]. Apart from that, no significant differences were observed between the two studies (Table 3).

VDBP and endometriosis

This review includes eight studies with regard to the potent contribution of VDBP to endometriosis pathogenesis. Two studies reported a significant increase of VDBP, in serum and urine respectively, in women with endometriosis compared with women without the disease [30, 31]. Another study showed higher concentrations of VDBP in ectopic endometrium tissue of women with endometriosis than in normal endometrial tissue of controls [18]. Three studies found no difference of VDBP in serum [15, 16, 32]. Borkowski et al. showed in addition no difference of VDBP concentration in peritoneal fluid [32]. Another study found lower expression of VDBP isoform in the peritoneal fluid compared with controls, and the same group later found that VDBP concentrations in peritoneal fluid in patients with endometriosis under therapy with

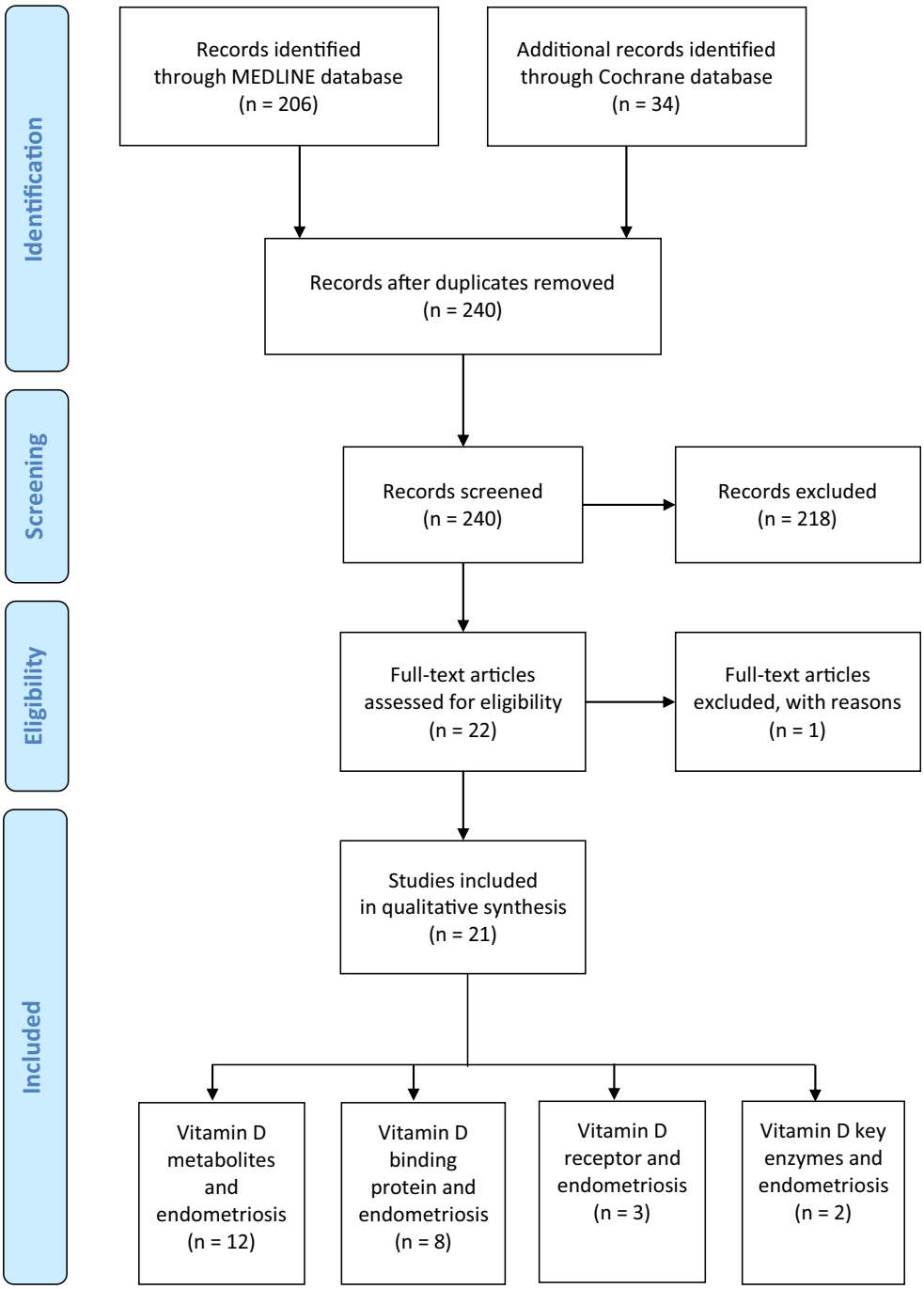

Fig. 2 Study flow chart

GnRH-analogs were lower than those in patients without treatment [33, 34] (Table 3).

Vit D key enzymes and endometriosis

Two studies measured vit D key enzyme levels in endometrial tissue [17, 35]. Both studies observed an increase of 1α-hydroxylase in mRNA and protein levels (Table 3).

Discussion

Vit D metabolites and endometriosis

Three studies referred to the association between $1,25(OH)_2D_3$ serum concentrations and endometriosis. Hartwell et al. [20], after comparing 42 endometriosis patients with 113 healthy women, found higher serum $1,25(OH)_2D_3$ in the endometriosis group. Somigliana et al. [22] and Miyashita

Table 2 Main findings of the studies included in the qualitative synthesis

ID	Study	Main findings
Vitamin D metabolites and endometriosis		
1.	Hartwell et al. (20)	• Higher serum $1,25(OH)_2D_3$ ($p < 0.001$) but not 25(OH)D in endometriosis group
2.	Agic et al. (17)	• Similar serum 25(OH)D ($p = 0.31$) in both groups
3.	Somigliana et al. (22)	• Higher serum $25(OH)D_3$ ($p = 0.05$) in endometriosis group • Similar serum $1,25(OH)_2D_3$ between the groups.
4.	Harris et al. (19)	• Predicted plasma 25(OH)D concentration is negatively correlated with endometriosis
5.	Pagliardini et al. (27)	• Higher serum 25(OH)D ($p = 0.01$) in endometriosis group
6.	Miyashita et al. (23)	• Lower serum $25(OH)D_3$ in severe ($p = 0.05$) and mild ($p = 0.01$) endometriosis groups • Similar serum $1,25(OH)_2D_3$ between the groups.
7.	Dressler et al. (25)	• Similar serum 25(OH)D ($p = 0.40$) in both groups
8.	Ciavattini et al. (24)	• 85.7% of patients with a single ovarian endometrioma had hypovitaminosis D • Negative correlation between serum $25(OH)D_3$ and the diameter of ovarian endometriomas ($r = -0.3$, $p = 0.03$)
9.	Anastasi et al. (21)	• Deficiency/insufficiency of 25(OH)D more frequent in endometriosis group (80% vs. 33.3%; $< p$ 0.001) • The presence of any type of pain ≥ 5 at VAS scale is associated with the deficiency of 25(OH)D (odds ratio = 4.4; 95% CI = 1.12–16.84; $p = 0.033$)
10.	Buggio et al. (26)	• Similar serum 25(OH)D ($p = 0.46$) in group with and without endometriosis and in endometriosis subgroups ($p = 0.14$)
11.	Baek et al. (15)	• Serum levels of total 25(OH)D tended to show a negative relationship with the severity of endometriosis, but this relationship was not statistically significant across the three groups • Total 25(OH)D in the advanced endometriosis group were significantly lower than in the healthy control group ($p = 0.001$)
12.	Cho et al. (16)	• Total serum 25(OH)D levels in the endometriosis patients were significantly lower than in the control group ($p = 0.017$)
Vitamin D binding protein (VDBP) and endometriosis		
1.	Ferrero et al. (33)	• Lower expression of a VDBP isoform (VDBPE) in the peritoneal fluid ($p < 0.05$) in endometriosis group • No difference in VDBPE expression in plasma • Endometriosis and oral contraceptives groups had higher VDBP concentrations both in plasma ($p < 0.05$) and in peritoneal fluid ($p < 0.05$) compared with untreated endometriosis group
2.	Borkowski et al. (32)	• No difference in VDBP concentration in both serum ($p = 0.49$) and peritoneal fluid ($p = 0.63$) • No difference when endometriosis group subdivided according to the severity of disease
3.	Ferrero et al. (34)	• VBDP concentration in peritoneal fluid of endometriosis group significantly downregulated ($p < 0.001$) during treatment with GnRH-a compared with untreated endometriosis group
4.	Faserl et al. (30)	• Higher expression of serum VDBP ($p < 0.02$) and VDBP GC2 allele product ($p = 0.006$) in endometriosis group
5.	Cho et al. (31)	• Higher urinary VDBP concentrations ($p = 0.001$) in endometriosis group • Limited value as diagnostic marker for endometriosis alone (sensitivity 58%, specificity 76%) or in combination with CA-125
6.	Hwang et al. (18)	• Higher expression of VDBP in ectopic endometrial tissue compared with normal endometrial tissue ($p < 0.01$)
7.	Baek et al. (15)	• No significant difference in serum VDBP concentration between the control group and endometriosis groups ($p = 0.241$)
8.	Cho et al. (16)	• No significant difference in serum VDBP concentration ($p = 0.323$) and polymorphisms of VDBP coding gene between the endometriosis and control groups.
Vitamin D receptor (VDR) and endometriosis		
1.	Agic et al. (17)	• Higher VDR mRNA in endometrium of endometriosis group in isolated epithelial cells compared with stromal cells ($p < 0.01$); this trend was not statistically significant in control group • Higher VDR mRNA expression in both epithelial ($p < 0.01$) and stroma cells ($p < 0.01$) of endometriosis group • The observed differences in VDR mRNA concentrations were maintained at the protein level (Western blot analysis)
2.	Vilarino et al. (28)	• No differences in VDR gene polymorphisms between the two groups
3.	Szczepanska et al. (29)	• Correlation between A-T haplotype of VDR and endometriosis-associated infertility ($p = 0.011$) • No other associations between VDR haplotypes and endometriosis
Vitamin D key enzymes and endometriosis		
1.	Viganò et al. (35)	• Higher 1α-hydroxylase ($p = 0.03$) in endometrium of endometriosis group in both mRNA and protein levels • Higher 25α-hydroxylase mRNA in ovarian tissue of endometriosis group in comparison with ovarian cancer group ($p < 0.01$)
2.	Agic et al. (17)	• Higher 1α-hydroxylase ($p < 0.05$) in proliferative phase endometrium of endometriosis group in both mRNA and protein levels

Table 3 Characteristics of studies included

Study				Endometriosis			Controls		Results			
Name	Year	Design	Country	n	Stage	Age (years)	n	Age (years)	Tissue	Outcome	Endometriosis	Controls
Cho (16)	2019	Case control	Korea	16	NA	34.0 (29.8–4-1.3)	16	35.5 (27.8–3-7.8)	Serum	25(OH)	25(OH)D 9.55 ng/ml	25(OH)D: 16.48 ng/ml
										VDBP	(IQR 3.00–24.41) VDBP 173.06 μg/mL (IQR 76.39–265.08)	(IQR 8.36–26.00) VDBP 158.58 μg/mL (IQR 112.68–224.08)
Baek (15)	2019	Case control	Korea	16	I–II: 9	I–II: 35.44 (7.20)	16	37.31 (6.35)	Serum	25(OH)D	I-II	25(OH)D 16.96 (4.71) ng/ml
					III–IV: 7	III–IV: 32.57 (6.95)				VDBP	25(OH)D: 14.17 (7.62) ng/ml VDBP: 161.25 (53.09) μg/mL III–IV 25(OH)D: 8.91 (1.67) ng/ml VDBP 198.34 (42.54) μg/mL	VDBP: 169.20 (36.31) μg/mL
Buggio (26)	2018	Case control	Italy	217	Ovarian endometrioma: 127 Deep infiltrating endometriosis: 90	34.2 (6.5)	217	33.2 (6.5)	Serum	25(OH)D	17.9 (7.0) ng/ml	18.4 (7.6) ng/ml
Anastasi (21)	2017	Case control	Italy	135	NA	34.7 (6.3)	90	NA	Serum	25(OH)D	21.3 (8.9) ng/ml	32.3 (2.7) ng/m
Ciavattini (24)	2017	Retrospective cohort	Italy	49	Singleton ovarian endometrioma	41.8 ± 7.1	NA	NA	Serum	25(OH)D3	women with singleton ovarian endometrioma ($n = 49$) 22.0 (8.9) ng/ml Hypovitaminosis ($n = 42$) 19.4 (5.7) ng/ml Normal vitamin D ($n = 7$) 37.5 (9.7) ng/mll	NA
Miyashita (23)	2016	Case control	Japan	35	I–II: 17	I–II: 35.4 (1.64)	371	32.8 (1.0)	Serum	25(OH)D3	I–II	25(OH)D3 21.8 (1.3) ng/ml
					III–IV: 22	III–IV: 34.6 (1.53)				1,25(OH)2D3	25(OH)D3 21.5 (1.4) ng/ml 1,25(OH)2D3 NA III–IV 25(OH)D3 17.2(1.1) ng/ml 1,25(OH)2D3 NA	1,25(OH)2D3: NA

Table 3 (continued)

Study				Endometriosis			Controls		Results			
Dressler (25)	2016	Retrospective cohort	Germany	55	NA	NA	143	NA	Serum	25(OH)D	50.9% vitamin D deficiency	NA
											NA	NA
Szczepanska (29	2015	Case control	Poland	154	I 85 II: 69	33 (20–42)	347	33 (19–39)	Plasma	VDR genotype	NA	NA
Pagliardini (27)	2015	Cross sectional	Italy	75	NA	NA	175	NA	Serum	25(OH)D	NA	NA
Hwang (18)	2013	Case control	Korea	13	II: 1 III: 4 IV: 8	27–40	6	25–48	Endometrial tissue	VDBP	NA	NA
Harris (19)	2012	Prospective cohort	USA	1385	NA	25–42	69,171	25–42	Plasma (predicted)	25(OH)D intake	NA	NA
Cho (31)	2012	Case control	Korea	57	I–II: 5 III–IV: 52	34.2 (6.9)	38	32.7 (10.3)	Urine	VDBP	106.1 (74.6) ng/ml	58.7 (60.8) ng/ml
Vilarino (28)	2011	Case control	Brazil	132	I–II: 72 III–IV: 60	35.1 (3.9)	133	39.7 (3.2)	Plasma	VDR	NA	NA
Faserl (30)	2011	Cross sectional	Austria	56	I–II: 20	18–49	20	18–49	Plasma	VDBP	NA	NA
Ferrero (34)	2009	Case control	UK /Italy	107 Gn-RHI	I–II: 4 III–IV: 6 no GnRH 97 I–II: 38 III–IV: 59	GnRH 32.1 (3.7)	NA	NA	Peritoneal fluid	VDBP	GnRH 0.209 (0.028) %vol No GnRH 0.507 (0.023) %vol	NA
Borkowski (32)	2008	Case control	Poland	26	I–II: 11 III–IV: 15	21–50	17	21–50	Serum Peritoneal fluid	VDBP	Serum 449.4 (24.4) μg/ml Peritoneal fluid 387 (24.7) μg/ml	Serum 424.5 (23.5) μg/ml Peritoneal fluid 408 (23.1) μg/ml
Agic (17)	2007	Case control	Germany	46	NA	NA	33	NA	Endometriotic tissue Ovarian tissue	25(OH)D VDR 1α-hydroxylase 24α-hydroxylase 25α-hydroxylase	Endometrium 25(OH)D 25.7 (2.1) ng/ml VDR 857.3 (298.7) 1α-hydroxylase: 1.318 (0.488) 24α-hydroxylase 203.5 (123.8) 25α-hydroxylase: 48.02 (15.57) Ovaries VDR 843.0 (206.6)	Endometrium 25(OH)D 22.6 (2.0) ng/ml VDR 341.3 (101.2) 1α-hydroxylase 0.317 (0.092) 24α-hydroxylase 24.62 (9.65) 25α-hydroxylase 30.39 (5.52) Ovaries

Table 3 (continued)

Study				Endometriosis			Controls		Results			
												1α-hydroxylase 1.560 (0.205)
											1α-hydroxylase 1.979 (0.320)	1α-hydroxylase 1.560 (0.205)
											24α-hydroxylase 37.99 (17.33)	24α-hydroxylase 2.232 (1.110)
											25α-hydroxylase 4518 (779.7)	25α-hydroxylase 7051 (1505)
Somigliana (22)	2007	Prospective cohort	Italy	87	I–II: 13	33.3 (5.3)	53	34.1 (6.8)	Serum	25(OH)D3	I-II	25(OH)D3: 20.4 (11.8) ng/ml
					III: 39					1,25(OH)2D3	25(OH)D3 23.4 (14.1) ng/ml	1,25(OH)2D3 48.9 (17.5) ng/ml
					IV: 35						1,25(OH)2D3 47.2 (12.9) ng/ml	
											III	
											25(OH)D3 23.6 (13.3) ng/ml	
											1,25(OH)2D3 51.6 (15.8) ng/ml	
											IV	
											25(OH)D3 27.0 (16.8) ng/ml	
											1,25(OH)2D3 55.9 (20.6) ng/ml	
Viganò (35)	2006	Case control	Italy	27	I: 4	NA	50	NA	Endometrial tissue	1α-hydroxylase	NA	NA
					II: 5					25α-hydroxylase		
					III: 11							
					IV: 7							
Ferrero (33)	2005	Case control	Italy/UK	105	No COC	No COC 32.1 (5.3)	40	32.6 (6.2)	Plasma	VDBP	Plasma 0.568 (0.034) %vol	Plasma 0.563 (0.047) %vol
					I–II: 36	COC 32.4 (5)			Peritoneal fluid		Peritoneal fluid 0.576 (0.026) %vol	Peritoneal fluid 0.911 (0.022) %vol
					III–IV: 52							
					COC							
					I–II: 7							
					III–IV: 10							
Hartwell (20)	1990	Case control	Denmark	42	NA	19–43	113	19–43	Plasma	25(OH)D	25(OH)D: 32.2 (0.1) μg/l	25(OH)D: 30.5 (27.9–33.1) μg/l
										1,25(OH)2D3	1,25(OH)2D3 42.2 (1.9) ng/l	1,25(OH)2D3 35 (33.2–37.4) ng/l

et al. [23] indicated that the difference between the two groups was not significant.

Results concerning total 25(OH)D were controversial. Four studies showed no difference in serum 25(OH)D concentrations between groups [17, 20, 25, 26]. Pagliardini et al. [27] concluded that serum 25(OH)D concentrations were positively associated with a history of endometriosis. Harris et al. [19], who studied 1385 cases of laparoscopically confirmed incidental endometriosis, indicated that predicted plasma 25(OH)D based on intake of dairy products was negatively correlated with endometriosis. Another study from Italy [21] including 135 surgical and histological cases of endometriosis and 90 controls also reported that levels of 25(OH)D were significantly lower in the endometriosis group, and that insufficient levels are correlated with the presence of moderate or severe pelvic pain. In concordance with the last study, a small study from Korea [16] found significantly lower total 25(OH)D in the endometriosis group. Baek et al. noted a negative association between severity of endometriosis and serum levels of total 25(OH)D, although this association was not significant [15].

Three studies include measurements of serum $25(OH)D_3$. Somigliana et al. [22] observed higher levels of $25(OH)D_3$ in the sera of 87 women with endometriosis compared with 53 women without endometriosis and, additionally, higher $25(OH)D_3$ in women with more advanced stages of the disease. On the other hand, Miyashita et al. [23] observed that serum $25(OH)D_3$ levels in women with severe endometriosis (rASRM III-IV) were significantly lower than in controls and in women with mild endometriosis (rASRM I-II). Finally, Ciavattini et al. [24], who examined 49 women with single endometrioma, reported a negative correlation between serum $25(OH)D_3$ and the diameter of ovarian endometriomas; of these women, 85.7% had hypovitaminosis D.

Vit D has been shown to have immunomodulatory actions relevant to endometriosis. A recent experimental study in a mouse model of endometriosis [36] resulted in reduction of endometriosis development and peritoneal inflammation after the administration of elocalcitol, a synthetic derivative of vit D. Regression of endometriosis after treatment with vit D was also observed in two other animal studies [37, 38].

Given that inflammatory cytokines are involved in the pathogenesis of endometriosis, two studies examined the effects of $1,25(OH)_2D_3$ on cytokine production by human endometriotic stromal cells. Miyashita et al. [23] examined the in vitro effects of $1,25(OH)_2D_3$ on human endometriotic stromal cells, isolated from ovarian endometriomas. Use of $1,25(OH)_2D_3$ reduced IL-1 induced IL-8 mRNA expression ($67.4 \pm 9.4\%$ vs. $72.1 \pm 1.7\%$, $p = 0.05$), prostaglandin activity, viable endometrial stromal cell numbers, and DNA synthesis, but it did not affect apoptosis in comparison with controls. Furthermore, Delbandi et al. [39] demonstrated that vit D in vitro increases cell adhesion and decreases invasion and proliferation of ectopic and eutopic endometrial stromal cells, by reducing the production of IL-6, Bcl-2, Bcl-xL, and VEGF-α.

A RCT from Iran [14], which examined vit D as a therapy for endometriosis, found no differences in severity of pelvic pain ($p = 0.24$) and dysmenorrhea ($p = 0.45$), 24 weeks after surgical treatment. The 39 patients (50,000 IU vit D weekly, $n = 19$; placebo, $n = 20$) were diagnosed and treated with laparoscopy and had scores ≥ 3 for dysmenorrhea and/or pelvic pain at 8 weeks after surgical treatment. The high prevalence of vit D deficiency in Iran and the small sample size were two limitations of this study.

In summary, although vit D has beneficial effects on endometrial tissues in animal models and in vitro studies, clinical studies provide inconclusive evidence as to its role in the diagnosis and treatment of endometriosis. Additional studies are necessary to reach safe conclusions. In addition, due to the complexity of endometriosis and the multiple phenotypes, including ovarian, peritoneal, and deep infiltrating endometriosis which could present different pathogenesis, the association between vit D and the subtypes of endometriosis has to be examined for every subtype separately. More randomized control trials including supplementation of vit D in women with endometriosis are required in order to determine whether vit D could be used as a therapeutic option for endometriosis.

VDR and endometriosis

This report includes three studies on the association between VDR and endometriosis. Agic et al. [17] showed that VDR mRNA levels in both epithelial and stromal cells in the endometrium of patients with endometriosis were greater than in healthy controls, which was also confirmed at a protein level by Western blot analysis. As far as VDR polymorphisms are concerned, Szczepanska et al. [17, 29] examined 154 infertile women with endometriosis and 347 fertile controls and reported that the A-T BmsI/FokI VDR haplotype constituted a risk factor for endometriosis-associated infertility. However, no further correlation between VDR haplotypes and endometriosis was demonstrated.

The genomic pathway mainly responsible for vit D antiproliferative and anti-neoplastic activity is regulated by the VDR [40]. The latter is expressed in endometrial [41] and ovarian tissue, in placenta-decidua tissues [42], in endometriosis [17] and in a large number of tumors [43–45]. Data from Agic et al. indicate that VDR expression in women with endometriosis, in both the endometrium and ovaries, lies between the levels seen in oncological patients and healthy controls. A question to be answered is whether the increased VDR expression is a cause or an effect of endometriosis. The role of VDR polymorphisms and their transcriptions is not to date clear, the most thoroughly examined being BsmI and FokI [46, 47].

In summary, given that present studies cannot draw firm conclusions, it is clear that further research is warranted to understand the role of VDR in the pathogenesis of endometriosis.

VDBP and endometriosis

This systematic review included seven comparative studies on VDBP concentration in blood, endometrial and endometriosis tissues, peritoneal fluid and urine in women with endometriosis and controls. Apart from its role as a major transport protein of vit D and its metabolites, VDBP has also been identified as a precursor of the potent macrophage activation factor Gc-MAF [11]. The three major phenotypes of VDBP (GC1S, GC1F, and GC2), differ by two amino acids at positions, 416 and 420, and, consequently, in their glycosylation state, during which the macrophage-activating function is regulated [48, 49]. GC1 allele products are glycosylated at a total rate of 10–30%, whereas the GC2 allele product is glycosylated at a rate of 1–5% [50]; thus, the form of VDBP which is encoded by the GC1 allele is much more readily converted to Gc-MAF than that encoded by GC2.

Faserl et al. [30] conducted a proteomic analysis of serum of women with and without endometriosis, demonstrating higher expression of VDBP in women with endometriosis as compared with the control group ($p < 0.02$), especially the VDBP GC2 allele product ($p = 0.006$), suggesting a potent implication of this polymorphism in the pathogenesis of endometriosis. Ferrero et al. [33] showed that patients with endometriosis had significantly lower expression of a VDBP isoform (VDBPE) in the peritoneal fluid when compared with controls, but not in plasma, which could indicate a potent local conversion of VDBP at the site of inflammation to macrophage-activating factor (MAF). The role of macrophages in endometriosis was the subject of multiple studies demonstrating that the absolute number of peritoneal macrophages is increased in women with endometriosis, although these macrophages may not be competent scavengers of ectopic endometrial cells [51, 52]. Thus, the inability to adequately activate macrophages via VDBP due to overexpression of the GC2 allele in women with endometriosis may allow the survival and implantation of ectopic endometrial tissue in the peritoneal cavity.

Another case-control study demonstrated no difference in VDBP concentration in both serum and peritoneal fluid between women with endometriosis ($n = 26$) and a control group of women without endometriosis ($n = 17$) [32]. Cho et al. with 32 participants (16 endometriosis patients and 16 healthy controls) found no difference in serum VDBP concentrations between the two groups [16]. Moreover, Baek et al., after comparing patients with different stages of endometriosis with a control group, found no difference in the concentrations of serum VDBP [15]. Hwang et al. [18] observed that the expression of VDBP in ectopic endometrial tissue compared with normal tissue is higher, and that a positive correlation exists between the stage of the disease and the expression of the above protein. Last but not least, urine concentration of VDBP corrected for creatinine (VDBP-Cr) was higher in the endometriosis group than in controls; nevertheless, VDBP-Cr has limited value as a diagnostic marker for endometriosis (sensitivity 58%, specificity 76%), even when combined with serum Ca-125 [31]. Despite the small number of patients with minimal to mild stages of endometriosis and the imprecise way of determining VDBP excretion in urine, this marker, alone or in combination with other markers, could be the future to non-invasive diagnosis of endometriosis.

Two studies from the same group, included in this systematic review, found an increase of VDBP concentrations in the endometriosis group after treatment with oral contraceptives [33] and a decrease after treatment with GnRH analogs [34]. These findings are in accordance with those of Hashimoto et al., which reported decreased serum VDBP after menopause and increased after administration of estrogens [53].

In summary, the above studies revealed that the VDBP genotype potentially plays a role in the pathophysiology of endometriosis, although further studies are required to arrive at safe conclusions.

Vit D key enzymes and endometriosis

The elevation of 1α-hydroxylase in patients with endometriosis [17, 35] suggests local production of the active form of vit D, $1,25(OH)_2D_3$, which might mitigate endometriotic cell growth. High expression of vit D key enzymes in the endometrium of patients with endometriosis underlines the potential for local autocrine or paracrine responses rather than the classic endocrine effects of vit D.

25-hydroxylase expression in ovaries of patients with endometriosis and healthy controls was higher than in ovaries of patients with ovarian cancer [17]. These results are not in concurrence with Friedrich et al. [45], who reported an upregulation of 25-hydroxylase in ovaries of ovarian cancer patients. It is likely that the expression and distribution of 25-hydroxylase in different tissues may not be fully reflected in the quantitative levels of mRNA transcripts. Nevertheless, more studies are required to reach safe conclusions.

Strengths and limitations

To the best of our knowledge, the present systematic review is the first systematic demonstration of the role of vit D and its metabolites in endometriosis, which critically evaluates the results of the available studies.

The main limitation was the quality of the studies included. In all studies, the control groups were not representative of the

general population but were extracted from women who attended a hospital or infertility clinics or were included in cohorts. Our search strategy did not exclude studies in which cases had clinically confirmed endometriosis, but most of these enrolled only women with surgically confirmed endometriosis as cases. Another limitation is the small number of studied patients, given the needs for performing laparoscopy for endometriosis staging and histologic confirmation of the disease. Moreover, most of the results from the logistic regression models suffered from considerable imprecision; the 95% confidence intervals were substantially wide, an implication of heterogeneous populations. Endometriosis is a disease with many faces and possible variations related to its pathophysiology and histopathologic characteristics. The majority of included endometriosis groups included in this systematic review consisted of patients with a not clearly specified subtype of endometriosis. In addition, several crucial parameters of vit D metabolism were available only for a limited number of participants, such as race, ethnicity, use of sun blockers, and outdoor activity. Last but not least, due to the different laboratory methods of measurement of vit D and VDBP, the results of the above studies are not comparable.

Conclusions

The present systematic review is the first examining specifically the association between vit D and endometriosis. Given the heterogeneity and the diversity of the present studies, additional research on the association between different phenotypes of endometriosis (peritoneal, ovarian, and deep infiltrating endometriosis) and vit D is warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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