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Review

Connection between Endometriosis and Vitamin D – True or False?

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Abstract: Endometriosis is a serious health problem characterized by the persistence and growth of vascularized tissue at various ectopic sites such as ovaries, bowel, or bladder. Despite decades of intensive research, we are not making significant progress toward the etiology or treatment of this disease. The question of risk factor is similarly unclear, with one possible factor being diet-particularly the intake of vitamin D. In addition, as endometriosis has some similarities and clear connections to cancer, where vitamin D is heavily studied, this relation started to be a subject of intensive research in this field, too. The overall aim of this study is to review possible links between vitamin D intake and endometriosis.

Keywords: Endometriosis, Vitamin D, Receptor, Ovaries, Female

Introduction

Endometriosis is a chronic disease with estimated prevalence of 10% (Missmer and Cramer, 2003). Despite the seriousness and long-term research interests, the etiology of endometriosis is still poorly understood. However, immunological aspects are gaining more and more attention (Kralickova and Vetvicka, 2015) and the search for reliable markers is still ongoing, with few clearly defined markers (Kralickova and Vetvicka, 2016). The question of risk factor is similarly unclear, with one possible factor being diet-particularly the intake of vitamin D.

Vitamin D

Vitamin D is an essential steroid pro-hormone playing an important role in maintenance of phosphate and calcium homeostasis. Despite the "vitamin" name, its source is not completely dietary and over 85% is generated in the skin following exposure to ultraviolet light. For detailed description of chemistry and biological effects of vitamin D, see an excellent review by Nandi *et al.* (2016). Besides the principal role in bone homeostasis, vitamin D is involved in additional biological processes such as modulation of cell growth, immune functions and reduction of inflammation. In addition, vitamin D affects *in vitro* insulin and follicle-stimulating, hormone-induced secretion of progesterone (Smolikova *et al*., 2013). Vitamin D is also heavily involved in human reproduction, from fertility outcome to semen quality (for review, Anagnostis *et al*., 2013). Proposed roles of vitamin D in women's reproduction are summarized in a report by Grundmann and von Versen-Hoynck (2011).

A clinical study found small and nonsignificant increase in 1,25-hydroxyvitamin D levels in patients with endometriosis with a slight trend towards higher levels according to the severity of the disease (Somigliana *et al*., 2007). Later, a prospective cohort study of 70,556 women with endometriosis, evaluated over the period of 14 years, investigated whether the plasma 1,25-hydroxyvitamin D levels were associated with the disease. The results suggested that greater plasma levels of vitamin D and higher intake of dairy foods are clearly associated with decreased risk of endometriosis (Harris *et al*., 2013). This study, which estimated serum values of 1-α,25-hydroxyvitamin D3 and calculated variables such as race, age, physical activity or alcohol intake, showed inverse association between 1-α,25-hydroxyvitamin D3 values and endometriosis and women with the highest levels had

24% lower risk of endometriosis (Harris *et al*., 2013). On the other hand, a recent study found 1-α,25-hydroxyvitamin D3 levels significantly lower in serum of patients with severe endometriosis (Miyashita *et al*., 2016), further confusing the question of whether vitamin D levels are important.

The importance of 1-α,25-hydroxyvitamin D3 levels was confirmed using experimental model of rats with endometriotic implants. Animals with 1-α,25-hydroxyvitamin D3 showed significantly lesser symptoms, leading to the conclusion that this molecule resulted in regression via altering implant levels of VEGF, TIMP-2 and MMP-9 (Yildirim *et al*., 2014). Human clinical trials will be needed to confirm the possibility of treatment. An interesting observation by Agic *et al.* (2007) of very high metabolism of vitamin D in the endometrium suggested possible paracrine action of vitamin D. This hypothesis was supported by findings that Elocalcitol, a vitamin D receptor agonist, can reverse endometriotic implants in animal models (Mariani *et al*., 2012).

An in vitro study focusing on the possible effects of 1-α,25-hydroxyvitamin D3 on human endometriotic stromal cells isolated from ovarian endometrioma demonstrated that the addition of 1-α,25-hydroxyvitamin D3 resulted in reduction of IL-1β- and TNF-α-induced inflammatory responses and reduction of numbers of viable stromal cells (Miyashita *et al*., 2016). If these results are confirmed, supplementation with vitamin D might represent a novel strategy. Another hypothesis suggested that endometriosis is an autoimmune disease. With the known autocrine/paracrine action of vitamin D and established relation between autoimmune diseases and vitamin D, Peterlik and Cross (2005) focused their attention on vitamin D as an immunomodulator. The problems with any clear relations result from the fact that endometriosis is associated with normal or elevated levels of 1-α,25-hydroxyvitamin D3 and not with any deficiency. The only possibility would be local effects, which would be missed on fluid evaluation such as serum. Additional hypotheses about vitamin D and endometriosis are summarized in a recent review (Sayegh *et al*., 2014).

Vitamin D-Binding Protein

Vitamin D-binding protein (also called Gc-globulin or DBP) is a multifunctional protein deeply involved in transport of vitamin D sterols and in modulation of inflammation and defense reactions. Due to the suspected role of inflammation and several immune aspects in the development of endometriosis, this protein was also evaluated in women with endometriosis. However, the levels of this protein both in serum and in peritoneum were not significantly different between control and endometriosis groups (Borkowski *et al*., 2008).

2-D electrophoresis was used for evaluation of DBP levels in peritoneal fluid and plasma. One isoform (DBPE) showed lower levels in sampled peritoneal fluid, but when the patients were treated with oral contraceptive, the levels of DBPE returned to normal (Ferrero *et al*., 2005), making the possibility of DBP involvement even more confusing.

Using proteomics, elevated levels of vitamin D-binding protein were found in urine of women with endometriosis (Cho *et al*., 2012), suggesting that urine samples might be utilized in further investigations and that this protein might play a role in endometriosis. A different experimental approach, combining 2-DE gel electrophoresis with mass spectrometry, was later used to compare endometrial protein in ectopic endometrial tissue and normal endometrial tissue. Among fifteen other proteins, levels of vitamin D-binding protein were found to be significantly increased in ectopic endometrium, suggesting that this protein can have a direct role in the progression of this disease (Hwang *et al*., 2013).

Human cycling endometrium has been shown to express vitamin D receptor (Vigano *et al*., 2006). This receptor is a nuclear ligand-inducible transcription factor and in complex with vitamin D, it regulates expression of more than 900 different genes (Carlberg, 2003).

A comparative histological study showed strong staining for vitamin D receptor in endometriosis and endometrial cancer, with the strongest staining in epithelial cells. In addition, these samples also showed stronger expression of vitamin D 1α-hydroxylase (Agic *et al*., 2007). The authors hypothesized that vitamin D might affect local action of immune cells and/or secretion of cytokines involved in development of endometriosis.

Elocalcitol, a selective vitamin D receptor agonist, reduced endometriosis development in mouse model via inhibition of peritoneal inflammation (Mariani *et al*., 2012), demonstrated by inhibition of macrophage influx and inhibition of secretion of inflammatory cytokines.

Genetic alterations in the Vitamin D Receptor (VDR) gene might lead to biologically relevant defects in gene activation with subsequent changes in immune functions. Detailed analysis of vitamin D receptor gene polymorphism in women suffering from endometriosis revealed no changes between patients and controls, strongly demonstrating that VDR polymorphism is not involved in endometriosis (Lima Vilarino *et al*., 2011).

Proteolytic analysis of serum found 3x higher level of vitamin D-binding protein in patients with

endometriosis. Subsequent analysis of specific allele products showed that the most commonly expressed protein is GC*2 allele product. As this product is not converted to a macrophage-stimulating factor, the authors hypothesize that the inability to stimulate macrophages to optimally phagocytose-invading material results in allowing the endometriotic tissue to seed the peritoneal cavity (Faserl *et al*., 2011).

Gene Level

Endometrium is a target of 1-α,25-hydroxyvitamin D3 actions via regulation of specific genes, most probably HOXA10 gene expression. This gene is cyclically expressed in adult endometrium in response to estrogens. 1-α,25-hydroxyvitamin D3 can induce HOXA10 transcription through VDR binding to its responsive elements in the HOXA10 gene 5 region, which might subsequently induce differentiation of endometrial cells to decidual cells (Du *et al*., 2005). Lower expression of this gene was found in the eutopic and ectopic endometrium of endometriosis (Deng *et al*., 2011). However, a study evaluating VDR polymorphism found no association between this polymorphism and endometriosis or infertility (Villarino *et al*., 2011). Another vitamin D-regulated gene is osteopontin gene, with higher expression in eutopic endometrium (Cho *et al*., 2009).

The 1α-hydroxylase (enzyme necessary to catalyze the synthesis of 1-α,25-hydroxyvitamin D3) mRNA is expressed in ectopic endometrium and its levels are increased in proliferative phase cultures derived from women with endometriosis. These data suggested that cycling endometrium might be included among the extrarenal sites able to synthesize vitamin D (Vigano *et al*., 2006).

Conclusion

Endometriosis was first described more than 150 years ago (Von Rokitansky, 1860), but the causes and treatments remain enigmatic and the search for responsible molecules is still ongoing. Numerous studies suggest some kind of vitamin D involvement in the pathogenesis of endometriosis, but direct proof is still elusive. Several studies have found altered levels of vitamin D in patients suffering from endometriosis; however, no clear benefits from supplementation with vitamin D have been established. On the other hand, despite intensive research, we are not closer to understanding the pathogenesis of endometriosis than we were decades ago and there is still a need to fully confirm or disprove the functional role of the vitamin D system at the endometrial level. The hopes that vitamin D will represent the Golden Fleece seem to be unsubstantiated.

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Author's Contributions

Milena Kralickova: Designed the article, wrote the manuscript.

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Conflicts of Interest

There are no conflicts of interest.

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