The Gynecologist

ISSN: 2688-9366

Review Article

Impact of Exogenous or Sun-Induced Vitamin D on Endometriosis-Related Cellular and Molecular Processes

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Abstract

Hundreds of articles have unsuccessfully attempted to delineate the effect of the sunlight-induced vitamin D (vitD) on endometriosis, endometriosis-born pain and/or infertility. Numerous studies have failed to conclude in a positive or negative way on the role of vitD in this inflammatory disease that has a quite rich etiology ranging from environmental to immunologic and from infectious to gene-promoted causes. We here review a number of cellular and molecular aspects of the disease that may be influenced by this bioactive compound known to have an anti-inflammatory and immunomodulating action on a variety of bodily systems. We, thus, compare its effect on the disease using a literature-based search using as a measure high and low sun-exposed European cities, using as reference Athens, Greece and Helsinki, Finland, respectively, that belong to the same time zone but are separated by a South to North road distance of 3,431 kilometers. Analyses show that, despite the individual action of vitD on a number of important endometriosis-related process, the prevalence and/or risk of the disease does not change regardless of the route of vitD uptake, i.e., induction through sun or food fortification, although evidence for and against vitD's contribution is equally distributed by the literature reviewed.

Keywords: Vitamin D (vitD); Sunlight, Endometriosis; Vitamin D deficiency; Dioactive compounds; Genes; BrCA, VEGF; CD44

Endometriosis

Endometriosis is a common gynecologic syndrome of multifactorial etiology and pathogenesis having a rather unexpected, due to reasons analyzed in this review, stable worldwide prevalence of approximately 1:10. Importantly, it is a pathologically benign disease behaving, however, in a manner similar to that of a malignant tumor without having the potential to metastasize. It is generally accepted that the condition is a result of the implantation of exfoliated endometrium, deposited in the peritoneal cavity following retrograde menstruation [1,2]. Growth factors and inflammatory mediators produced by peritoneal leukocytes have been shown to participate in the pathogenesis of the disease. Angiogenic factors released from peritoneal macrophages also play a role in the development of this disease, whereas gene participation also completes the number of puzzle pieces required to form the complete picture that, nevertheless, remains sketchy. It is well known that endometriosis is often associated with infertility, dysmenorrhea and pelvic pain, while characterized by the presence of ectopic endometrial implants. Although our concepts as to its identity have changed over the years, endometriosis has generally been considered a local pelvic disorder in the domain of gynecology. However, since the beginning of the 1980s, an increasing body of evidence has linked endometriosis with changes in immune function. Growth factors and inflammatory mediators produced by peritoneal leukocytes have been identified to participate in the pathogenesis of endometriosis. Additionally, the presence of Vascular Endothelial Cell Growth Factor (VEGF) in ectopic and eutopic endometrium has well been demonstrated [1], while in a case of familial endometriosis circulating levels of Human Lukocyte Antigens (HLA) and VEGF in two generations of a single family (mother and three daughters) are markedly expressed [2,3]. Moreover, in the same family, a possible correlation between a breast cancer type 1 (BrCA1) mutation and soluble HLA expression appears to exist [4].

Finally, as endometriosis has been shown to be an estrogen-dependent disease, the impaired estrogen and progesterone signaling over-activates the wingless-related integration site (Wnt)/β-catenin pathway in endometriotic patients giving an insight on the effectiveness of endometrial cells' invasion [5].

All these parameters will be discussed in detail below, always in relation to vitD potential action.

Role of Vitamin D in Healthy and Endometriotic Subjects

Vitamin D (vitD) is an essential nutrient known for its role in bone health, which is often addressed as the "sunshine vitamin" as it is produced endogenously in the skin on exposure to solar ultraviolet B radiation, whereas only a small proportion derives from food sources rich in vitD (fatty fish, cod liver oil) [6]. However, a variety of factors can impair cutaneous production of vitD in people living in cities/countries with high sunlight levels, such as higher melanin content of the skin, use of sunscreens, limited outdoor activity, etc [7]. Vitamin D is a well-known steroid hormone whose activated form is the result of the conversion of 7-dehydrocholesterol in the skin, under the influence of ultraviolet B light. To become active, it

Citation: Vassiliadis S, Vlachos A. Impact of Exogenous or Sun-Induced Vitamin D on Endometriosis-Related Cellular and Molecular Processes. Gynecologist. 2020; 2(1): 1012.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Mar 31st, 2020

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requires two hydroxylation steps: a (i) 25-hydroxylation occurring mainly in the liver, leading to 25-hydroxyvitamin D3 (25-OHD3) and (ii) 1α-hydroxylation occurring in the proximal tubules cells of the kidney, leading to 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) [8,9].

According to the European climate data site, Athens, the capital city of Greece, records high sunlight levels ranging from 2,700 to 2,800 hours yearly; 2,773 hours to be exact [10]. This fact would suggest, as sunlight exposure produces and maintains serum 25(OH)D levels, that 25(OH)D deficiency should be limited to places with lower sun exposure. Nonetheless, an adequate number of studies from countries with high sunlight levels demonstrate a serious vitD deficiency [7,11]. Considering that a S-25(OH)D status of 25-80 ng/mL is sufficient without the need of external supplementation [12], Buggio et al. [13] has reported levels of 18.4 ng/mL for women without endometriosis *vs.* 17.9 ng/mL for women with endometriosis.

At the same time zone as Athens, 3,431 kilometers apart, Helsinki, the capital city of Finland, has an average time of sunshine of 1,858 hours per year [14], which appears optimal compared to the city of Kuopio in central Finland at 383.54 kilometers North of Helsinki, with a yearly average time of sunshine of 1,518 hours. Studies of the temporal changes in vitD status in the Finnish adult population with the use of standardized S-25(OH)D concentrations show considerable improvements in vitD status in both men and women, thus providing evidence of the benefits of the vitD food fortification policy the country has adopted [15,16]. However, prevalence and risk of endometriosis is not being modified as the 1:10 ratio remains stable. In addition, although vitD influences the functioning of the female reproductive system does not apparently act on endometriosis and its consequences, i.e., pelvic pain, dysmenorrhea and infertility, with vitD deficiency remaining an issue [17-19], despite numerous reports claiming that higher intake of dairy and/or fat foods are associated with a decreased risk of the disease and/or accompanying symptoms [20]. Such claims, however, cannot be supported due to conflicting results released in the literature [21,22].

Impact of Vitamin D on Growth Factors, Inflammatory Mediators, as well as Genes in Relation to Endometriosis

Vitamin D is an immunomodulator and anti-inflammatory agent. Endometriosis, on the other hand, is, inter alia, an immune and inflammatory disease. Therefore, since long-term vitD deficiencies have been linked to a weakened immune system and to chronic inflammation [23], one might consider that use of vitD would ameliorate the status of endometriotic patients. This hypothesis, however, has never been validated as there is no change in the prevalence of the disease. This is true for countries of both high and low yearly sun exposure times with the disease's ratio being stable worldwide [15,24], regardless of use of vitD-enriched foods or supplements [16].

The pathogenesis of endometriosis has been shown to be affected by growth factors and inflammatory mediators produced by peritoneal leukocytes. One case is the presence of Vascular Endothelial Cell Growth Factor (VEGF) in ectopic and eutopic endometrium [1]. Vitamin D supplementation improves multiple clinical parameters in VitD-deficient women with Polycystic Ovary Syndrome (PCOS) and decreases VEGF levels in several other pathologic conditions [25], endometriosis included [26]. However, lower VEGF levels do not correlate with a remedial outcome of the disease or its accompanying symptoms such as pain, dysmenorrhea and infertility. Additionally, in a case of familial endometriosis, circulating levels of Human Leukocyte Antigens (HLA) in two generations of a single family (mother and three daughters) are markedly expressed [3]. The concept of a vitD-HLA interaction, however, is not novel. Weiss [27] reported in 2014 a PubMed search identifying 239 articles on the relationship between vitD and HLA. Again, when it comes to soluble HLA molecules and endometriosis, vitD, although acting at an individual level on soluble HLA, appears unable to modify the route of the disease towards a positive outcome.

Another important aspect in the above case of familial endometriosis is a correlation between a stage-independent BrCA1 mutation and soluble HLA expression that seemingly influences the secretion of both classes I and II antigens, which are totally absent from the serum of only one family member [4]. However, although 1α,25-dihydroxyvitamin D3 is a potent inhibitor of breast cancer growth [28], studies on the influence of vitD on circulating HLA levels and/or BrCA1 expression, always in relation to endometriosis, are missing and, therefore, a conclusion cannot be reached.

It is also worth of mentioning that, since, endometriosis is an estrogen-dependent disease, the impaired estrogen and progesterone signaling over-activates the Wnt/β-catenin signaling pathway in endometriosis patients, thus explaining the increased invasion potency of endometrial cells derived from the endometrium of women with endometriosis [5,29]. The regulatory effects of vitD on the Wnt/β-catenin pathway have already been demonstrated. Ample evidence from many biological systems shows that inhibition of Wnt/β-catenin pathway is one of the mechanisms of vitD action. As 1,25(OH)2D3 regulates gene expression *via.* binding to the vitD receptor (VDR), it has been found that 1,25(OH)2D3 has a repressive action on several β-catenin/T-cell factor (TCF; transcription factor) target genes one of which is CD44 that, according to gene prioritization method among Wnt target genes, is in high ranking in relation to endometriosis [29]. However, in this apparently very complex system of cellular interactions, vitD supplementation does not impair the effectiveness of endometrial cells to invade ectopic tissues, thus allowing endometriosis to proceed.

Conclusion

Despite literature's conflicting results about the role of vitD on endometriosis, it is absolutely clear that this anti-inflammatory and immunomodulating agent does have a positive impact on a number of cellular and molecular processes at an individual level. However, these processes - when related to endometriosis- are not being affected by this bioactive compound since the disease per se, characterized by ectopic invasion of endometrial cells, pelvic pain, dysmenorrhea or infertility are not being ameliorated. Thus, in terms of endometriosis, there is no solid evidence that vitD, alone or *via.* sunlight exposure or through the cellular and genetic pathways discussed herein, lowers the risk of the disease as anticipated. By the same token, increased levels of serum vitD through food fortification do not appear to improve the patients' status and/or disease's prevalence and/or risk. This negative result, however, does not, by any means, suggest that vitD cannot be a beneficial modulator of endometriosis. Its vast range of actions and individual impact on a large number of cellular and biochemical processes forms an intriguing basis for further investigating possible synergistic actions between vitD and other bioactive compounds that may positively regulate the above described pathways for offering a curative outcome. Therefore, further and copious research should be undertaken in order to delineate any possible links that could be promising towards the disease.

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