

Comparative, literature-based, analysis of the effect of vitamin D/sunlight in endometriosis between Greece and Finland

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Abstract

This is a literature-based comparative analysis for the delineation of the role of sunshine in vitamin D (vitD) synthesis and its impact on endometriosis, an immune, inflammatory disease. The findings, between high (Greece) and low (Finland) sun exposed countries show that the prevalence of endometriosis does not change in the general population and that vitD supplementation through sun and/or vitD food fortification does not lower the disease's risk, thus pointing to a scientific myth that has to be either re-examined or abandoned after thorough further research.

Introduction

Background concerning vitamin D in healthy subjects

Vitamin D is produced in the skin between March and October, with the highest quantities being produced in the summer months. The intake of vitD both through the skin and from dietary sources is described as the vitD level in the blood, or serum 25 hydroxy vitD (25(OH)D) concentration. Vitamin D is classified as a pro-hormone which exists in circulation in two major forms, 25(OH)D: 25(OH)D₂ (ergocalciferol) and 25(OH)D₃ (also known as cholecalciferol) [1,2]. These precursors bind to a binding protein (VDBP) to transit in the blood and reach the liver where they are modified into calcidiol (25-OH cholecalciferol) then metabolized a second time by the kidney to generate calcitriol (or 1,25 dihydroxycholecalciferol), the active form of vitD [3]. Vitamin D levels are positively associated with bone mineral density [4] and several studies have reported a link with muscle mass and strength [5]. There exists evidence that vitD insufficiency and/or deficiency in elderly people, especially women, leads to secondary hyperparathyroidism and, consequently, to increased bone turnover and, finally, bone loss [6].

Greece is considered a country of high sunlight levels according to the Hellenic National Meteorological Service (2,600 to 2,800 hours yearly) [7]. Based on the important contribution of sunlight exposure to the production and maintenance of serum 25(OH)D levels, one might consider that 25(OH)D deficiency may be a problem limited to countries located at higher latitudes. Nevertheless, numerous studies from countries with high sunlight levels, Greece included, have shown that vitD deficiency is a common occurrence and a global health problem [8-10]. A 2016 state-of-the-art review article by Holick, a pioneer in the field of vit D synthesis, concisely outlines all the biological effects of sunlight, ultraviolet radiation, visible light and infrared radiation on vitD production and benefits for health [11]. The vitD status within different European countries shows a high variation. A serum 25(OH)D lower than 25nmol/L has been monitored in 2 to 30% of adults [12].

In Finland, a country where, according to the Finnish Meteorological Institute standards, there are seasons of high (summer (1 June-30 August) autumn (1 September-31 October)) and low sunlight (winter (1 November-31 March) and spring (1 April-31 May)), it has been observed that low sunlight exposure period (*versus* high) is associated positively with 25(OH)D₂ and negatively with 25(OH)D₃ concentrations [13]. The vitD status of the Finnish adult population has been shown to improve considerably due to food fortification, especially of fluid milk products, and increased vitD supplement use. Other factors, such as the difference in the ultraviolet radiation index may, to a certain extent, explain the rise in vitD concentration. When consuming vitD sources, based on nutritional recommendations, vitD status appears sufficient [S-25(OH)D \geq 50 nmol/L] and, thus, supplementation is generally not needed [14]. Analytically, the mean increase in S-25(OH)D in daily fluid milk consumers among supplement non-users is reported at 20 nmol/L, which is 6 nmol/L higher than non-consumers. In total, 91% of non-users who consumed fluid milk products, fat spreads and fish, based on Finnish nutrition recommendations, reached S-25(OH)D concentrations $>$ 50 nmol/L at the end of a study that took one year to complete [14].

Background concerning vitamin D and endometriosis

Vitamin D influences the functioning of the female reproductive system and has been associated with polycystic ovary syndrome (PCOS), uterine leiomyomas, endometriosis and outcome of *in vitro* fertilization

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(IVF) [15]. However, this does not appear to be the case since, in terms of infertility, there are no definitive results despite the fact that a high prevalence of vitD deficiency among PCOS women exists [16]. The same sketchy results have been obtained in the IVF practice [17]. Similarly, when it comes to endometriosis *per se*, dysmenorrhea and/or pelvic pain reduction, both related to the disease, vitD does not exhibit any significant effect [18], although Harris et al. [19] claim that the greater predicted plasma 25(OH)D levels and higher intake of dairy foods are associated with a decreased risk of endometriosis. This view is being contradicted by a recent 2019 systematic review where the Authors cannot reach a positive conclusion [20]. Conflicting results also appear in an older publication where it is stated that endometriosis is associated with higher serum levels of vitD [21]. A biological plausibility for a role of vitD, as an immunomodulator and anti-inflammatory agent, in the pathogenesis and treatment of endometriosis has been suggested since long-term vitD deficiencies have been linked to a weakened immune system and to chronic inflammation [22]. Comparing, however, two countries with high (Greece) and low (Finland) sunshine periods, in relation to vitD synthesis, it appears that there is no change in the prevalence of the disease, which, and this has to be noted, is similar in the two countries (approximately, 1 in 10 females) [10,23]. External supplementation of vitD does not also appear to affect the outcome of the disease as the prevalence of vitD deficiency is extremely high in both population samples and particularly in subjects with chronic diseases [24]. Vitamin D uptake *via* dairy or fat fish supplementation, through food fortification programs, is evident in the serum of the Finnish patients but this increase does not correlate with a lower risk of endometriosis and, thus, a cause-effect relationship is still missing [14].

Discussion / Conclusions

According to the knowledge acquired thus far, vitD deficiency in the Greek population, under an average sunshine exposure of 2,700 hours yearly, constitutes an absolute paradox that matches that of the Finnish population, with an average sun exposure time of 1,300 hours per year, respectively.

In terms of endometriosis, there is no solid evidence that vitD lowers the risk of the disease, as anticipated, while increased levels of serum vitD through food fortification do not appear to ameliorate the patients' status and/or disease's prevalence.

Endometriosis is an immune, inflammatory disease and vitD, as an immunomodulator and anti-inflammatory agent, is expected to have an -at least- corrective, if not, restorative action. The above-described literature-based data, however, point to a null correlation between endometriosis and role of vitD or insinuate unknown yet mechanisms required to trigger the proper biochemical reactions towards a positive result. Therefore, the synergistic actions of other dietary bioactive compounds should be studied in order to elucidate whether vitD can be activated beneficially towards endometriosis or whether this theory has to be abandoned.

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