

The Biological Effects of Vitamin D on the Development of Uterine Fibroids: A Literature Review

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Abstract

Uterine Fibroids (UFs), also known as uterine leiomyomas or myomas, are benign tumors derived from smooth muscle tissue. Vitamin D deficiency is one of the many factors involved in the development and growth of UFs. Many studies have shown that vitamin D supplementation decreases the size of fibroids despite a poorly understood pathogenesis. The activity of vitamin D against UF cells has mainly been supported by various in vitro and in vivo studies. For this review, we conducted in-depth research of published literature on vitamin D's biological and pathophysiological effects on UFs. We searched on Google Scholar and PubMed using common keywords and selected 23 studies from the search results. The literature chosen from the past ten years was read and analyzed thoroughly. However, because of the limited research on the effects of vitamin D on UFs and the different inclusion criteria, the clinical efficacy of vitamin D on women with UFs remains unclear. More extensive, well-organized studies on the specific effects of vitamin D on the growth of UFs would prove efficacious in establishing treatments.

Keywords: Uterine fibroids, vitamin D, biological effects, leiomyoma, fibroid tumors, molecular vitamin D.

Introduction

Uterine Fibroids (UFs) are the most common benign gynecological tumors, often presenting in women of reproductive age. Specifically, they originate from smooth muscle cells of the myometrium. The incidence of UFs ranges between 30% and 70% in women of reproductive age [1]. Studies have shown that by the age of 50, their prevalence is around 70% in the African American (AA) population [2]. The actual incidence of UFs is assumed to be much higher than reported because most patients remain asymptomatic. Although UFs are commonly benign, they are associated with significant morbidity, where 25-50% of women present with severe and chronic symptoms [2]. Some symptoms include menometrorrhagia, anemia, bladder pressure, gastrointestinal problems, and menstrual complications [2]. Furthermore, UFs are associated with multiple obstetrical complications, such as infertility and early pregnancy loss. Several risk factors

of UFs include older age, obesity, family history, race, and vitamin D deficiency.

Among these risk factors, vitamin D deficiency is a significant risk factor contributing to the development of uterine fibroids. Vitamin D is one of the essential nutrients for the human body, and it is involved in regulating several biological functions [1]. Its deficiency has become a significant public health concern worldwide, most commonly from low vitamin D consumption in diet or an inability to absorb it [2]. Vitamin D deficiency affects almost 50% of the population worldwide, which is an estimated 1 billion people worldwide [3].

Research has shown that active vitamin D can inhibit cell growth in vitro. One study in 2016 found a strong connection between UF pathology and vitamin D deficiency on a genetic level. Results showed that vitamin D might potentially inhibit significant pathways involved in the biology of UFs [3]. Another research in 2012 was conducted on the Eker rat animal model. It was found that vitamin D treatment significantly decreased the size of UFs in the rat through suppression of cell proliferation [3]. Achieving optimal vitamin D levels may be very important in patients with UFs. Additionally, screening, treatments, and public health strategies for women deficient in vitamin D with UFs or at high risk of developing UFs might also be of interest.

In this review, the development of UFs and their association with vitamin D is carefully researched with the aid of literature and published works. This review aims to summarize and understand the effects of vitamin D deficiency on the development of UFs on a biological level, as not many studies have investigated this relationship upon review of the literature. This review aims to raise awareness of this relationship among clinicians and leaders in women's health and build an evidence base for better treatment.

Methods

A thorough literature search was conducted on PubMed and Google Scholar for relevant published studies using the following keywords: uterine fibroids, vitamin D, biological effects, and vitamin D deficiency. The search was then narrowed down by using "AND," as recorded in Table 1. We collected and reviewed articles written in

the English language from 2012 to 2022. The articles studied both animal and human subjects included in clinical trials, meta-analyses, randomized control trials, and systematic review case reports. We excluded articles that were without full-text options. No systematic review guidelines, such as Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA), were used as this was for a traditional review article.

The study was designed as a literature review, so no statistical analysis was conducted.

Database	Date searched	Search term	Total studies
PubMed	October 12, 2022	Uterine fibroids	1,419
PubMed	October 12, 2022	Vitamin D	6,446
PubMed	October 12, 2022	Uterine fibroids AND vitamin D	17
PubMed	October 12, 2022	Uterine fibroids AND vitamin D AND biological effects	2
PubMed	October 12, 2022	Uterine fibroids AND vitamin D deficiency	9
Google Scholar	October 12, 2022	Uterine fibroids AND vitamin D AND biological effects	3,580
Google Scholar	October 12, 2022	Leiomyomas AND vitamin D	1000
Google Scholar	October 12, 2022	Uterus fibroid tumors	4,720

Table 1: Literature search results

Discussion

Uterine Leiomyomata

Uterine Leiomyomas, also known as UFs, are women's most frequent benign tumors. In the United States alone, 42 per 10,000 women are hospitalized annually due to UFs [4]. They arise from the uterine smooth muscle tissue (myometrium), where its growth is dependent on estrogen and progesterone. Their incidence is even higher in some ethnic groups [1]. They can be detected in up to 80% of women by the age of 50 years [5]. Interestingly, UFs can undergo spontaneous regression after menopause. Although almost half of women with UFs are asymptomatic, their quality of life is often impaired by symptoms such as bladder pressure, rectal pressure (constipation), dyspareunia, or pelvic pressure [5]. The most common

symptom, however, is abnormal uterine bleeding, usually excessive and in the form of clots. More importantly, increasing evidence shows that UFs negatively impact fertility [1].

A few risk factors that affect the risk of UFs include radiation of the pelvis, obesity, increasing age, vitamin D deficiency, and African descent [5]. African American women have three times the risk of developing UFs compared to white women; they are more likely to be diagnosed at an earlier age and have larger and more rapidly growing fibroids [4]. A study done on Nigerian women included 100 participants, where fifty of them had UFs and the remaining fifty did not have UFs [6]. The serum vitamin D levels were measured in all of the women and found to be insufficient. The study concluded that many factors may have contributed to low vitamin D levels in this population, specifically the abundant melanin on the black skin which absorbs ultraviolet rays and decrease the synthesis of vitamin D [6]. More importantly, it was also found that although the vitamin D levels were insufficient in both groups of women, the levels were significantly lower in the group of women with uterine fibroids.

The development of uterine fibroids has been found to be associated with Chinese women as well; however, it is not as common in this population as it is in the African American population. In a study with 546 women, 279 of them had UFs and the remaining participants did not have fibroids [7]. Similar to the previous study on Nigerian women, this study resulted in lower serum vitamin D levels in Chinese women with UFs versus Chinese women without UFs [7]. Another study on an Indian population of premenopausal women and the association of their serum vitamin D level and UFs also showed a significant relationship [8]. Studies on UF development and vitamin D development have been limited on Asian populations compared to the black and white populations.

Even though the exact cause of UFs remains unclear, genetic, and epigenetic factors continue to influence their risk of development. Clinicians consider UF location, number, and size in designing the proper treatment for symptomatic patients. Because there is minimal concern for malignancy in women with UFs, the preferred management is usually watchful waiting. Additionally, enlarging UFs is not an indication for removal because the natural course of fibroids involves growth and regression [5].

Biology and Metabolism of Vitamin D

Vitamin D is a fat-soluble prohormone endogenously synthesized from the skin naturally after exposure to ultraviolet (UV) light or dietary sources. The two major isoforms of vitamin D include ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) [9]. Some major sources of vitamin D are egg yolks, fatty fish, yogurts, and cod liver oil [2]. However, its conversion to the skin is still the main source of vitamin D. Vitamin D has a powerful effect on many organs in the human body,

including bones, intestines, kidneys, skin, liver, and reproductive tissues. Its receptors are expressed in many tissues of the endocrine system, muscles, and immune system cells.

One of the most important public health concerns worldwide is vitamin D deficiency. Deficiency can result from low consumption of vitamin D in diet, low sun exposure, inability to absorb it in the intestine, and the inability of the kidneys and the liver to activate it [2]. One of the most important and accurate ways to measure vitamin D serum levels is the 25-hydroxyvitamin D blood test [2]. The metabolism of vitamin D is illustrated in Figure 1.

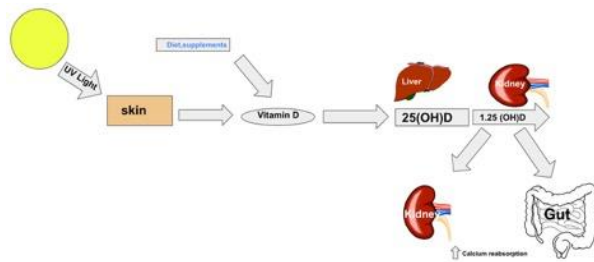


Figure 1: Vitamin D metabolism

UV: Ultraviolet, 25(OH)D: 25-hydroxylase vitamin D, 1,25(OH)D: 1,25-hydroxylase vitamin D

Vitamin D has also shown some benefits in clinical symptoms of various infections, including Coronavirus-19 (COVID-19). A small cohort study has shown that vitamin D as well as other minerals have protective effects against the clinical deterioration of acute respiratory tract infections from COVID-19 [10]. However, other studies have not shown any relationship between the role of vitamin D against respiratory tract infections. Thus, it is vital that randomized controlled trials and cohort studies are necessary for more information on this hypothesis.

Uterine fibroids and Diet

Among the many risk factors for the development of UFs, vitamin D deficiency has been found to be the most important. Different ethnic groups have been affected by low levels of serum vitamin D. In one study by Xu et al., premenopausal Han Chinese women were reported to have lower vitamin D levels in those with UFs compared to age-matched samples of women without UFs [11]. Lower vitamin D levels in African American and Chinese women are essential to note because it serves as evidence of the role of this deficiency in UF development across populations.

Traditionally, estrogen was thought to play a major role in the development of UFs. However, new studies have shown that progesterone and its receptors played a greater role [2]. Food and dietary habits have been studied, and evidence indicates a link with a high risk of uterine myoma [12]. A Japanese study claimed that the consumption of eggs, butter, margarine, and oil does

not influence the risk of UF development [12]. Additionally, omega-3 fatty acids have been shown to lead to membrane architecture remodeling and the expression of genes involved in signaling in leiomyoma cells. This finding indicates a potential preventative or therapeutic option for developing UFs [12].

Dietary fruit and vegetable intake [12] has demonstrated an impact on UF risk. The Black Women's Health Study (BWHS) found that women who have four fruit or vegetable servings per day have a lower risk of developing UFs than women who have less. A case-control study by He et al. showed that fruit and vegetables also had a protective role in the pathogenesis of UFs in Chinese premenopausal women. Interestingly, strawberry extract in another study has shown an increased percentage of apoptotic and dead cells and high reactive oxygen species in leiomyoma cells [12]. Moreover, these studies, and many more, have proven the possible role of fruit and vegetable in UF formation and the possibility of their formation through dietary phytochemicals [12].

Vitamins are bioactive compounds with many physiological functions; however, their relationship with myoma risk and prevalence has not been adequately investigated. Through a cross-sectional study of 887 women aged 20 to 29 years, the BWHS reported a statistically significant relationship between vitamin A and the occurrence of UFs [12]. Additionally, current literature has shown no relationship between vitamin C, folate, and vitamin E on UF development. Maintaining sufficient vitamin D levels has been associated with a low risk of all-cause mortality and diseases. More importantly, the regulation of biological processes, including immune response, reduced cell proliferation, and increased apoptosis, are a few of the important functional effects of vitamin D [13].

Pathophysiology of Uterine Fibroids and Vitamin D

The causes and pathogenesis of the development of UFs have not been fully established. Based on recent data, myometrium stem cells that carry the antigens CD32, CD45, and glycoprotein A are involved in the development of UFs [14]. Although UFs are known to frequently appear spontaneously, there is a heritability component as well and the development of UFs through this component ranges between 8% to 70% [15]. Understanding all the mechanisms behind the development of UFs through cellular characteristics could allow for the discovery of specific pathways that provide a better comprehension of the molecular insights on UFs.

Vitamin D has been found to have numerous functions other than bone health and calcium homeostasis during the last decade. Vitamin D receptors (VDRs) are an important factor in the biological actions of vitamin D. These receptors interact with specific regions of DNA, which eventually work to recruit coactivators for the regulation and transcription of target genes, cell proliferation, differentiation, and immune response

[16]. VDRs are expressed in different organs, one of which includes reproductive tissues. Several studies, many of which involved animal models, have demonstrated that the ovary is one of the reproductive organs for vitamin D activity. For many years, trials done on female knockout mice with vitamin D deficiency show their inability to reproduce due to defects in uterine development [9].

In vitro and ex vivo studies have shown the strong relationship between vitamin D and fibroid pathobiology [17]. Beyond physiology, evidence has also shown the effects of vitamin D on endometrial pathologies such as endometriosis and endometrial cancer [18]. Endometriosis is the presence of active endometrial tissue, glands, and stroma in ectopic sites of the reproductive system. It presents with abnormalities on a structural and functional level, thus affecting proliferation, cytokine production, and the presence of immune components [9].

Vienonen et al. were the first to demonstrate the presence of vitamin D receptors in the endometrial tissue of humans. They studied the different expressions of transcription factors on a nuclear level [19]. They focused on evaluating the uterine samples of three premenopausal women who had undergone hysterectomy and found a notable difference in expression levels between the women. However, the levels did not differ between the proliferative and secretory phases of the cycle. Linda Giudice's group conducted a study in 2012 comparing the expression of different nuclear receptors in various stages of the endometrial cycle. Their result showed downregulation of VDRs in the mid-secretory phase compared to earlier [20]. A further study by Bergada et al. took tissue samples in various stages of the endometrial cycle were taken from 60 women. Their ages ranged from 25 to 55. The samples were embedded in paraffin blocks, and tissue microarrays were analyzed and showed a low expression of VDRs in the proliferative endometrium compared to the secretory phase [21]. Arjeh et al. had a recent study that tested high-dose vitamin D in a randomized clinical trial for 12 weeks. Results showed that this treatment had no impact on the volume of lesions, but it inhibited further growth of UFs. The placebo group, on the other hand, showed an increase in the number of UFs [22].

More recently, research has come out on the coexistence of anemia and hypovitaminosis D in the development of UFs in premenopausal women. In one study, sixty premenopausal women with UFs were enrolled in the study [23]. Thirty of the women had anemia and the remaining thirty did not have anemia. It was determined based on the results that low ferritin levels were associated with vitamin D deficiency in the women with UFs [23]. Additionally, serum ferritin levels significantly affect serum vitamin D levels in a fibroid uterus in women with anemia [23]. More research should be done on the positive correlation between serum ferritin and vitamin D levels in women with microcytic hypochromic anemia.

Although the mentioned results are controversial, using different techniques could explain them. Some of these techniques included immunohistochemistry analysis of tissue or contamination of tissue samples. These studies' differences in age and control patients may have also affected the results. The association between vitamin D and endometrial cancer risk is controversial as there is a need for a better investigation of the potential molecular mechanisms involved that could be of value in understanding this better.

Genetic and Molecular basis of Vitamin D deficiency in the Pathogenesis of Uterine fibroids

Many genetic studies have demonstrated that UFs are monoclonal tumors originating from myometrial stem cells. These stem cells undergo many molecular changes, eventually proliferating and differentiating later under specific steroid hormones [22]. Regardless of ethnicity, recent studies have shown a negative correlation between vitamin D levels and the presence of UFs, where lower levels of vitamin D in the blood serum of women were more commonly associated with UFs [24]. Interestingly, the authors also found that exposure to the sun was associated with a lower risk of UF development.

The actions of vitamin D on the development of UFs were found to be associated with a significant reduction in the effects of transforming growth factor beta 3 (TGF- β 3) on a molecular level [9]. More importantly, an increase in cell proliferation and deposition of extracellular matrix (ECM) contributes to the growth of UFs. Ultimately, the abnormal deposition of ECM components plays a vital role in the pathogenesis of UFs [9].

In one study, research showed an antifibrotic effect of vitamin D on UFs via the reduction of TGF- β 3-induced ECM protein expression, including collagen and fibronectin in the cells of UFs [25]. The same group of researchers did two studies in 2011 and 2015. In 2011, Sharan et al. demonstrated that vitamin D inhibited the cell growth of UFs through the downregulation of proliferating cell nuclear antigen and cyclin-dependent kinase 1, as well as catechol-O-methyltransferase expression. Additionally, vitamin D regulates the expression and activity of matrix metalloproteinases (MMPs), enzymes that play a role in ECM remodeling [24]. In 2015, these researchers demonstrated that vitamin D presented antiprogesterone and antiestrogenic activities [24]. Ultimately, vitamin D treatment significantly reduced the expression of estrogen and progesterone receptors through VDR expression.

Halder et al. demonstrated the ability of 1,25(OH) $_2$ D $_3$ to reduce UF growth via modulation of the expression and activity of MMP-2 and MMP-9, both of which are involved in the degradation of the ECM [6]. These studies present that disturbances in the degradation of ECM could be essential for developing fibroids. Ali et al.

showed that vitamin D suppressed UF development by targeting different DNA repair networks [26]. This research proved that this vitamin deficiency could enhance DNA damage in the myometrium. The most recent study in 2019 stated that vitamin D worked as an antiproliferative compound in UFs. This is through cell growth arrest and Wnt/ β -catenin pathway inhibition [27].

Uterine Fibroid Management

Despite the high prevalence of UFs, available medical treatment options are limited. These benign tumors affect up to 80% of women. Although they originate from various pathobiological processes, they are all managed in a standardized symptom-oriented approach that does not consider these diverse processes [28]. Some women with UFs may also suffer from other metabolic diseases, hypertension, or other conditions. Thus, these factors may have different underlying processes and different responsiveness to various treatment options. Moreover, a call for more research to develop new management of UFs with the treatment approach varying depending on the patient's underlying biological processes is essential to reduce the health, social, economic, and psychological burden of these tumors.

Clinical research has shown the cardiometabolic risk factors, including obesity, hypertension, and hyperlipidemia, and their effects on UF development [27]. One research group shows the possible beneficial effects of simvastatin, an anti-hyperlipidemic drug, on UFs [29]. This drug was shown to induce calcium-dependent apoptosis and restore the altered state in UFs. Another controlled study showed that statin use was also associated with a lower risk of UF development [30]. Additionally, a recent study suggests that angiotensin-converting enzyme inhibitors play a role in reducing the incidence of UFs in patients with hypertension [31]. These studies indicate that the underlying pathophysiological process in the development of UFs and the response to treatment options can differ between patients with vitamin D deficiency and those with metabolic syndrome.

The most common and first approach for symptomatic women with UFs includes medical treatments such as hormonal contraceptives, gonadotropin-releasing hormone analogs (GnRHa), and selective progesterone receptor modulators [1]. Surgical approaches include hysterectomy, myomectomy, and uterine artery embolization when medical treatment has failed. More research is needed to develop specific biomarkers that can predict future UF growth and development of symptoms beyond the current work available. More importantly, it is essential to prioritize UF prevention and conduct research to reduce the heavy burden of women suffering from this condition.

Limitations

In this literature review, we were able to review a large number of high-quality articles on the relationship between vitamin D deficiency and UF occurrence however, we had a few limitations. As mentioned earlier, there is much controversy on the impact of vitamin D on the endometrial cycle and insufficient research and data from clinical trials on this; it is challenging to have a solid conclusion on this relationship and understand any potential pathophysiological effects. Additionally, we included studies with a small number of women that portrayed an association between vitamin D and UFs. Another limitation was the lack of full access to a few research papers and articles behind a paywall. Moreover, we reviewed studies from the last ten years, so our criteria limitations have excluded some relevant studies from previous years.

Conclusion

Uterine fibroids are benign tumors originating from smooth muscle cells with a high prevalence in women of reproductive age. Their complete etiology remains largely unknown. Many epidemiological studies have identified low serum concentrations of vitamin D as an essential factor in the etiology of UFs. The reported studies describe the effect of vitamin D and its pleiotropic actions in reducing UF growth and improving symptoms. Additionally, mechanisms by which vitamin D affects UFs are conveyed in research through the regulation of gene expression. Some of the effects of the vitamin are also mediated through intracellular signaling pathways, which suggest that vitamin D is connected to multiple cellular processes, including inhibition of angiogenesis, cell proliferation, and activation of apoptosis. While data suggests that vitamin D causes changes on a molecular level in leiomyoma cells, more data and research is needed on its clinical benefit in women with UFs. More well-designed randomized clinical studies are required to explore and better understand the efficiency of vitamin D in women, of all ethnicities, with these benign tumors. Despite the available data and research on the relationship between vitamin D and UF development, current clinical data are insufficient to support the use of vitamin D as therapy. Thus, more extensive randomized clinical trials may shed light on the role of vitamin D on UF growth in women and eventually provide strong evidence supporting vitamin D as an efficacious therapy.

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